Chromosomal Abnormalities

Chromosome Number	Mutations/Anomalies / Diseases
1	1. **CMM** 1 (**C**utaneous **M**alignant **M**elanoma) is on the chromosome 1 = **Autosomal Dominant**, for dysplastic Nevi (BK moles = BK derived from the initials of two of their patient for cutaneous pigmented lesion which had particular clinical representation). (Page 318). 1) Dysplastic nevus = a nevus exceeding 5 mm in diameter, with irregular, indistinct, or notched borders and mixed tan-to-black and pink-to-red color. Microscopically these are basally nested and scattered intraepidermal melanocytes with hyperchromatic nuclei larger than those of basal keratinocytes. If multiple and associated with a family history of melanoma, these nevi have a high risk of malignant change, but isolated dysplastic nevi in the absence of a family history of melanoma are less frequently premalignant. See: dysplastic nevus syndrome. 2) Malignant mole syndrome = irregularly shaped, variously colored, distinctively melanocytic, 5–10-mm nevi occurring in large numbers (to over 100) primarily on the trunk and extremities, with a high risk of malignancy; probably **autosomal dominant** inheritance. 2. Variegate porphyria (VP)= porphyria characterized by abdominal pain and neuropsychiatric abnormalities, by dermal sensitivity to light and mechanical trauma, by increased fecal excretion of proto- and coproporphyrin, and by increased urinary excretion of δ-aminolevulinic acid, porphobilinogen, and porphyrins; due to a deficiency of protoporphyrinogen oxidase; autosomal dominant inheritance, caused by mutation in the gene for protoporphyrinogen oxidase (PPOX) on chromosome 1q. Syn: South African type porphyria, protocoproporphyria hereditaria. 3. Owren disease= Factor 5 deficiency = Factor V Leiden deficiency = Factor 5 Leiden deficiency = due to mutation of chromosome 1q23= a congenital deficiency of factor V, resulting in prolongation of prothrombin time; **bleeding and clotting times are consistently prolonged**; autosomal recessive inheritance caused by mutation in the F5 gene on chromosome 1q. Factor 5 Leiden deficiency is the most common inherited disorder that causes hypercoagulable state and predisposed to thromboses especially DVT (deep venous thrombosis) of

	lower extremities. Prevalence of factor V deficiency may be as high as 5-6% in the population. **(Note: Factor V Leiden is not the same as factor V deficiency. Factor 5 Leiden causes a hypercoagulable state (=thrombophilia = increase risk of clotting and DVT) whereas factor 5 deficiency causes an increase risk of bleeding).** 4. Uridyl Diphosphate-galactose-4-epimerase deficiency = UDP-galactose-4-epimerase deficiency = Cytogenetic Location: 1p36-p35 . GALE gene is "UDP-galactose-4-epimerase. The GALE gene is located on the short (p) arm of chromosome 1 between positions 36 and 35. The GALE gene provides instructions for making an enzyme called UDP-galactose-4-epimerase. This enzyme enables the body to process a simple sugar called galactose, which is present in small amounts in many foods. Galactose is primarily part of a larger sugar called lactose, which is found in all dairy products and many baby formulas. UDP-galactose-4-epimerase converts a modified form of galactose (UDP-galactose) to another modified sugar (UDP-glucose). Glucose is a simple sugar that is the main energy source for most cells. This enzyme also promotes the reverse chemical reaction, the conversion of UDP-glucose to UDP-galactose. UDP-galactose is used to build galactose-containing proteins and fats, which play critical roles in chemical signaling, building cellular structures, transporting molecules, and producing energy. Galactosemia is caused by mutations in the GALE gene. More than 20 mutations in the GALE gene have been identified in people with a form of galactosemia known as type III or galactose epimerase deficiency. Most of these genetic changes alter a single protein building block (amino acid) in UDP-galactose-4-epimerase, which makes the enzyme unstable or disrupts its usual function. Some GALE mutations severely reduce or eliminate the activity of UDP-galactose-4-epimerase in all of the body's tissues. These genetic changes lead to a severe form of galactosemia type III described as the generalized form. A loss of enzyme activity prevents cells from processing galactose obtained from the diet. As a result, compounds associated with galactose processing can build up to toxic levels in the body. The accumulation of these substances damages tissues and organs, leading to serious complications such as clouding of the lens of the eye (cataract), intellectual disability, and damage to the liver, kidneys, and brain. Other mutations in the GALE gene reduce the activity of UDP-galactose-4-epimerase in red blood cells only. These genetic changes underlie a much milder form of galactosemia type III described as the

peripheral form. Affected individuals may not have any of the complications typically associated with galactosemia and often do not require treatment. Researchers are unclear why the effects of some GALE mutations are restricted to blood cells, while other mutations affect all of the body's tissues and cause severe medical problems. In uridyl diphosphate galactose – 4- epimerase deficiency gets hypotonia and nerve deafness (Peds, p 6).

5. Stargardt Disease= fundus flavimaculatus initiated with atrophic macular lesions, caused by mutation in the ATP-binding cassette transporter, retina-specific gene (ABCR) on 1p.
6. Fucosidosis = A metabolic storage disease characterized by accumulation of fucose-containing glycolipids and deficiency of the enzyme α-fucosidase; progressive neurologic deterioration begins after the first year of life, accompanied by spasticity, tremor, and mild skeletal changes; autosomal recessive inheritance, caused by mutation in the α-1-fucosidase gene on chromosome 1.
7. Mutilating keratoderma= diffuse keratoderma of the extremities, with the development during childhood of constricting fibrous bands around the middle phalanx of the fingers or toes that may lead to spontaneous amputation; there may be congenital deafness; autosomal dominant inheritance, caused by mutation in the gene for loricrin (LOR), a component of the epidermal differentiation complex on 1q. Syn: keratoma hereditarium mutilans, Vohwinkel syndrome.
8. Hyperprolinemia= A metabolic disorder characterized by enhanced plasma proline concentrations and urinary excretion of proline, hydroxyproline, and glycine; autosomal recessive inheritance. Type I hyperprolinemia is associated with a deficiency of proline oxidase and renal disease; Type II hyperprolinemia is associated with a deficiency of Δ-pyrroline-5-carboxylate dehydrogenase, mental retardation, and convulsions and is caused by mutation in the Δ-pyrroline 5 carboxylate gene (P5CD) on 1p.
9. t (2, 13) = alveolar Rhabdomyosarcoma. (Kaplan peds, p218). The most common types of rhabdomyosarcoma (RMS) are alveolar RMS (ARMS), which are characterized by the specific **translocation t (2; 13)(q35; q14)** or its rarer variant, **t (1; 13)(p36; q14)**, producing the fusion genes PAX3-FKHR and PAX7-FKHR, respectively, and embryonal RMS (ERMS), which is characterized by multiple numeric chromosome changes.
10. Multiple epiphyseal dysplasia (EDM)= a disorder

	of epiphyses characterized by difficulty in walking, pain and stiffness of joints, stubby fingers, and often short stature; on X-ray examination, the epiphyses are irregular and mottled, the ossification centers are late in appearance and may be multiple, but the vertebrae are normal. There are at least 3 forms of autosomal dominant inheritance: EDM1 due to mutation in the cartilage oligomeric matrix protein gene (COMP) on chromosome 19p; EDM2, due to mutation in the type IX collagen gene (COL9A2) on 1p; and EDM3, which is linked to an unknown locus. There is also an autosomal recessive form. Syn: dysplasia epiphysealis multiplex 11. Erythrokeratodermia variabilis= a dermatosis characterized by hyperkeratotic plaques of bizarre, geographic configuration, associated with erythrodermic areas that may vary remarkably in size, shape, and position from day to day; hair, nares, and teeth are not affected; onset is usually in the first year of life. Autosomal dominant or recessive inheritance, caused by mutation in the connexin gene encoding gap junction protein beta-3 (GJB3) on 1p. 12. **1p19q codeletion in anaplastic oligodendrogliomas**= Neuronal differentiation in oligodendrogliomas with 1p19q codeletion and support the hypothesis that the cell of origin for gliomas with 1p19q codeletion could be a bi-potential progenitor cell, able to give rise to both neurons and oligodendrocytes. Anaplastic oligodendrogliomas with **1p19q codeletion** have a proneural gene expression profile. A recent study analyzed survival based on chromosomal deletions and the effects of radiation or chemotherapy as treatment, with the following results (both low-grade and anaplastic oligodendrogliomas): 1p/19q deletion with radiation = 121 months (mean), 1p/19q deletion with chemotherapy = over 160 months (mean not yet reached), no 1p/19q deletion with radiation = 58 months (mean), and no 1p/19q deletion with chemotherapy = 75 months (mean). Another study divided anaplastic oligodendrogliomas into the following four clinically relevant groups of histology with the following results: combined 1p/19q loss = median survival was >123 months (not yet reached), 1p loss only = median survival was 71 months, 1p intact with TP53 mutation = median survival 71 months, and 1p intact with no TP53 mutation = median survival was 16 months. 13. Deletion 1p = leiomyosarcoma (pg326). Leiomyosarcoma = A malignant neoplasm derived from smooth (nonstriated) muscle. 14. Nemaline myopathy=congenital, nonprogressive muscle weakness most evident in the proximal muscles; named after

	the characteristic nemaline (threadlike) rods seen in the muscle cells composed of Z-band material. There are two forms, **dominant form** caused by **mutation in the tropomyosin-3 gene (TPM3) on 1q22–q23**, and **recessive form** that are clinically indistinguishable. Syn: rod myopathy. 15. L-Myc 1 = small (L for Little) cell lung carcinoma (pg 82,136). Small Cell lung cancer (=SCLC) is associated with inactivating mutations of other tumor suppressor genes such as Rb (for retinoblastoma) and activating mutations in proto-oncogenes such as Myc. 16. Amaurosis congenita of Leber= a disorder of cone-rod abiotrophy causing blindness or severely reduced vision at birth; autosomal recessive inheritance with at least 3 different loci. Type I is caused by mutation in the gene for retinal guanylate cyclase (GUC2D) on chromosome 17p, type II by mutation in the gene for retinal pigment epithelium-specific 65-kD protein (RPE65) on 1p, and type III by mutation in the gene for photoreceptor-specific homeobox gene CRX on 19q. 17. Van Der Woude syndrome = Autosomal Dominant cleft lip/cleft palate = Van Der Woude syndrome is an autosomal dominant syndrome characterized by a cleft lip or cleft palate, distinctive pits of the lower lips, or both. It is the most common syndrome associated with cleft lip or cleft palate. The degree to which individuals who carry the gene are affected widely varies, even within families (= **variable expression**). These variable manifestations include lower lip pits alone, absent teeth, or isolated cleft lip and cleft palate of varying severity. Hypodontia (absent teeth) has been increasingly recognized as a frequently associated anomaly. Many other associated anomalies have also been described. Most cases of van der Woude syndrome have been linked to a deletion in **chromosome 1q32-q41**; however, a second chromosomal **locus at 1p34** has also been identified. The responsible mutation has been identified in the **interferon regulatory factor-6 (IRF -6) gene**, but the exact mechanism of this mutation on craniofacial development is uncertain. Demonstrating the presence or absence of an IRF-6 mutation can be helpful when distinguishing between uncomplicated cleft lip and/or cleft palate and van der Woude syndrome. A wide variety of chromosomal mutations that cause van der Woude syndrome and are associated with IRF-6 gene mutations have been described. A potential modifying gene has been identified at **17p11.2-p11.1**. 18. Presenilin-2 gene for Alzheimer's disease (pg307)

	19. Gaucher Disease = **mutation of glucocerebrosidase A gene** (GBA) on chromosome 1q. Common in Ashkenazi Jews. Death by age three. Type 1 gaucher is compatible with normal life span = a lysosomal storage disorder due to a **deficiency of glucocerebrosidase** resulting in accumulation of glucocerebroside; high incidence among persons of Ashkenazi Jewish descent; occurs most severely in infants, characterized by **hepatosplenomegaly**, hematologic abnormalities, **bone lesions**, neurological manifestations with ataxia, spastic paraplegia, seizures, and dementia, and presence of characteristic **histiocytes (Gaucher cells = "crumpled-silk" histiocytes)** in the viscera. Get accumulation of **abnormal glucocerebrosides in reticuloendothelial cells in may organs (spleen, liver, bone marrow and brain),** Diagnosis of gaucher disease is confirmed by radiologic studies, which shows **Erlenmeyer flask deformity** of distal femor and bone marrow studies, which shows gaucher cells with **wrinkle paper** appearance ("**crinkled paper" with enlarged cytoplasm**. **Autosomal recessive inheritance** caused by mutation in the glucocerebrosidase A gene (GBA) on chromosome 1q (1st aid CK p 305). There are three main forms: type I, non-cerebral juvenile (type 1 Gaucher= **the adult chronic non-neuronopathic form also give pingueculae and brown skin pigments**); type II, cerebral juvenile; and type III, adult cerebral; the juvenile forms are most severe. Syn: cerebroside lipidosis. In gaucher disease get dilated (congestive) cardiomyopathy (IM, p 150) 20. Pyruvate Kinase Deficiency = autosomal recessive inheritance, caused by mutation in the pyruvate kinase liver and red blood cell gene (PKLR) on chromosome 1 → causes hemolytic anemia, red cell have trouble producing enough ATP to maintain the Ns+/K+ pump on the plasma membrane, secondarily causing swelling and lysis. 21. **Hereditary progressive arthroophthalmopathy**= Stickler syndrome= **Autosomal dominant** inheritance caused by mutation in either the COL2A1 gene on 12q, COL11A1 gene on 1p or COL11A2 gene on 6p. Pierre Robin Syndrome can be a feature of other syndromes; such has Edwards's syndrome and stickler syndrome (=early arthritis, ocular problems). (Kaplan Peds, p 249) 22. Hereditary spherocytosis = Autosomal dominant inheritance, caused by mutation in the ankyrin gene (ANK1) on 8p. However, as with elliptocytosis, there is an autosomal recessive form, caused by mutation in the alpha-spectrin 1 gene (SPTA1) on chromosome 1q.

	23. Hereditary elliptocytosis = A hematologic disorder in which 50–90% of the red blood cells consist of rod forms and elliptocytes; often associated with a hemolytic anemia. There are several autosomal dominant forms, with one form linked to the Rh blood group, caused by mutation in the gene encoding erythrocyte membrane protein band 4.1 (EPB41) on chromosome 1p, while the unlinked form is due to mutation either in the alpha-spectrin gene on 1q, or in the beta-spectrin gene on 14q or the band 3 gene on 17q. There is one autosomal recessive form known. Syn: ovalocytosis. 24. Congenital hypophosphatasia = a rare disorder associated with a low level of serum alkaline phosphatase, hyperphosphaturia, hypercalcemia, skeletal abnormalities, pathologic fractures, craniostenosis, premature loss of teeth, and often early death; eyes may show blue sclerae, lid retraction, band-shaped keratopathy, cataracts, papilledema, and optic atrophy; **autosomal recessive** inheritance, caused by mutation in the liver **alkaline phosphatase gene (ALPL) on chromosome 1p**. 25. Chédiak-Higashi syndrome = A genetic disorder associated with abnormalities of granulation and nuclear structure of all types of leukocytes and with the presence of peroxidase-positive granules, cytoplasmic inclusions, and Döhle bodies; characterized by hepatosplenomegaly, lymphadenopathy, anemia, neutropenia, partial albinism, nystagmus, photophobia, and susceptibilities to infection and lymphoma; death usually occurs in childhood; occurs in mink, cattle, mice, killer whales, and humans; **autosomal recessive** inheritance, caused by mutation in the **Chediak-Higashi gene (CHS)** on **chromosome 1q**. This disorder is due to a **defect in neutrophil chemotaxis** (= phagocytic immunodeficiency disease). CGD presents with **oculocutaneous albinism, neuropathy and neutropenia** (CK p 309). Chediak-Higashi Syndrome (CHS) is caused by mutation in LYST gene (**LYST=Lysosomal Trafficking Regulator (Lyst) Gene) localized to chromosome 1q42-43**. Syn: Chédiak-Steinbrinck-Higashi anomaly, Béguez César disease, Chédiak-Higashi disease, Chédiak-Steinbrinck-Higashi syndrome. 26. Antithrombin III=a plasma α_2-globulin process that inhibits thrombin and has anticoagulant activities. Deficiency is commonly inherited as an autosomal dominant trait, caused by mutation in antithrombin III gene (AT3) or chromosome 1q; this is one of the few known mendelizing disorders from which thrombotic disease occurs.

27. Antithrombin III Deficiency: inherited as an autosomal dominant trait, caused by mutation in antithrombin III gene (AT_3) or chromosome 1q; this is one of the few known mendelizing disorders from which thrombotic disease occurs. (Normal anti-thrombin inhibits thrombin and has anticoagulant activities.). When have Deficiency of ATIII, pt get excessive clotting.
28. **Crigler-Najjar syndrome = Crigler-Najjar disease** = A **deficiency of uridine-diphosphoglucuronate glucuronosyltransferase** is seen in Crigler-Najjar disease. Crigler-Najjar syndrome is a rare defect in ability to form **bilirubin glucuronide due to deficiency of bilirubin-glucuronide glucuronosyltransferase;** characterized by familial nonhemolytic jaundice and, in its severe form, by **irreversible brain damage (= Kernicterus)** in infancy that resembles kernicterus and may be fatal; **autosomal recessive** inheritance, **caused by mutation in the uridine diphosphate glycosyltransferase 1 gene (UGT1) on chromosome 1q.** Get unconjugated hyperbilirubinemia **(=indirect bilirubin, insoluble in water, bound to albumin in blood).** There is an **autosomal dominant form called Gilbert syndrome**, also caused by mutation in the UGT1 gene. **Get unconjugated hyperbilirubinemia (= increase indirect bilirubin in blood) with Gilbert Syndrome and with Crigler-Najjar Syndrome** (Peds, p 15).
29. **Hypokalemic Periodic Paralysis** = a form of periodic paralysis in which the serum potassium level is low during attacks; onset usually occurs between the ages of 7–21 years; attacks may be precipitated by exposure to cold, high carbohydrate meal, or alcohol, may last hours to days, and may cause respiratory paralysis; autosomal dominant caused by mutation in the muscle dihydropyridine (DHP)-sensitive calcium channel α-1-subunit (CACNL1A3) on chromosome 1q, or X-linked inheritance.
30. Epidermolysis bullosa lethalis= Junctional Epidermolysis bullosa = a form of epidermolysis bullosa characterized by persistent and nonhealing perioral and perinasal crusted lesions with bullae often present in the oral mucosa and trachea, but not on the palms and soles, complicated by dermal sepsis and serum protein and electrolyte loss leading to death; autosomal recessive inheritance, caused by mutation in any one of the three distinct polypeptides of laminin-5; alpha-3 (LAMA3) on chromosome 18q, beta-3 (LAMB3) and gamma-2 (LAMC2)

	on 1q or the gene encoding integrin, beta-4 (ITGB4) on 17q. Syn: epidermolysis bullosa, epidermolysis bullosa, junctional type, Herlitz syndrome. 31. Multiple endocrine neoplasia 2 = MEN 2= (= **Sipple syndrome**), RET oncogene mutation on chromosome (10q, 11.2), missense mutations on chromosome 1 (pg263),), (1st aid surgery, p 153) = syndrome associated with pheochromocytoma, parathyroid adenoma and medullary thyroid carcinoma; autosomal dominant inheritance, caused by mutation in the RET oncogene on chromosome 10q. Multiple endocrine neoplasia syndrome, type 2A= multiple endocrine neoplasia, type 2A = an **autosomal-dominant** predisposition to tumors of thyroid C cells (medullary carcinoma), adrenal medulla (pheochromocytoma), and nodular hyperplasia of parathyroid glands. 32. Möbius syndrome = congenital facial diplegia =a developmental bilateral facial paralysis usually associated with oculomotor or other neurological disorders. Möbius syndrome (also spelled Moebius) is an extremely rare congenital neurological disorder, which is characterized by facial paralysis and the inability to move the eyes from side to side. Most people with Möbius syndrome are born with complete facial paralysis, which means they cannot close their eyes or form facial expression. The syndrome is listed as Online Mendelian Inheritance in Man (OMIM) Number 157004, with a **gene map locus of 13q12.2-q13**. Scattered reports have described specific genetic localizations in Möbius syndrome. In 1977, Ziter et al reported a variant of Möbius syndrome co-segregating with a **reciprocal translocation between chromosomes 1 and 13**, i.e., **t(1p34;13q13)**, in at least 7 members of an affected family over 3 generations. In 1991, Slee et al described a 2.5-year-old girl with Möbius syndrome who had a deletion of band q12.2 on **chromosome 13.** Both reports suggested that a gene responsible for Möbius syndrome is located in region 13q12.2-q13. In 1996, Kremer et al described a large pedigree with autosomal dominant Möbius syndrome consisting largely of asymmetric bilateral facial paresis. After exclusion of the candidate region on **13q12.2-13**, they localized a gene to 3q21-22, raising the possibility of genetic heterogeneity of the syndrome. In 1997, Nishikawa et al reported a boy with a Möbius-like syndrome (i.e., facial diplegia and ptosis but with normal extraocular movements and no skeletal anomalies) with a **reciprocal translocation**

between chromosomes 1 and 2 (p22.3, q21.1). A dominantly inherited syndrome (with the clinical features of Möbius syndrome and clubfoot, digital abnormalities, and arthrogryposis) was described in a family with 15 affected members in 2 generations. Because of inconsistency in defining the condition, the role of inheritance in Möbius syndrome remains unclear. Pedigrees with autosomal dominant, autosomal recessive, and X-linked recessive inheritance patterns have been described.

33. Pelger-Huët anomaly (PHA) = **autosomal dominant** due to mutation in **chromosome 1q41-q43**, the region that contains **the lamin B receptor gene (LBR)** . Pelger-Huet anomaly (PHA) is a blood laminopathy associated with the lamin B receptor. It is characterized by a white blood cell type known as a neutrophil whose nucleus is hyposegmented (= **hyposegmented neutrophil = bilobed Neutrophil = Neutrophil with only 2 lobes**). It is a genetic disorder with an autosomal dominant inheritance pattern. Heterozygotes are clinical normal although their neutrophils may be mistaken for immature cells which may cause mistreatment in a clinical setting. Homozygotes tend to have neutrophils with rounded nuclei that do have some functional problems. Pelger-Huet anomaly is an **autosomal dominant** disorder characterized by abnormal nuclear shape and chromatin organization in blood granulocytes. Heterozygotes show hypo-lobulated neutrophil nuclei with coarse chromatin. Presumed homozygous individuals have ovoid neutrophil nuclei, as well as varying degrees of developmental delay, epilepsy, and skeletal abnormalities.. By genome wide linkage scan, mapped the PHA locus to 1q41-q43, the region that contains the lamin B receptor gene (LBR).
34. Dejerine-Sottas disease = a familial type of demyelinating sensorimotor polyneuropathy that begins in early childhood and is slowly progressive; clinically characterized by foot pain and paresthesias, followed by symmetrical weakness and wasting of the distal limbs; one of the causes of stork legs; patients are wheelchair-bound at an early age; peripheral nerves are palpably enlarged and non-tender; pathologically, onion bulb formation is seen in the nerves: whorls of overlapping, intertwined Schwann cell processes that encircle bare axons; usually autosomal recessive inheritance; an autosomal dominant form also exists; both forms can be caused by mutations in the peripheral myelin protein **gene 22** (PMP22) on **17q** or in the myelin protein zero gene (MPZ) on **1q**. Syn: Dejerine disease, hereditary hypertrophic neuropathy, progressive

	hypertrophic polyneuropathy.
2	1. N-Myc for Neuroblastoma, in chromosome 2p (pg82) 2. Duffy blood group, chemokine receptor (DARC), also known as CD234 (Cluster of Differentiation 234), is a human gene. DARC gene is on chromosome 2. Anti- Duffy antibody= is a isoimmunization disease of newborn (hemolytic disease of newborn = HDN. (Tx: give mother RhoGAM injection after delivery)= remember anti-Duffy antibody cause the next baby to be Dead= The Duffy antigen is a protein located on the surface of red blood cells and is named after the patient in which it was discovered. In humans, this protein is encoded by the DARC gene. DARC gene is on chromosome 2. 3. Feingold Syndrome = Oculodigitoesophagoduodenal syndrome = Feingold syndrome (also called oculodigitoesophagoduodenal syndrome) is a rare **autosomal dominant** hereditary disorder. It is named after Murray Feingold, an American physician who first described the syndrome in 1975. Feingold syndrome is marked by various combinations of microcephaly, limb malformations, esophageal and duodenal atresias, and sometimes learning disability or mental retardation, microcephaly ,clinodactyly and shortness of index and little fingers ,syndactyly of 2nd & 3rd and 4th & 5th toe, short palpebral fissures ,esophageal and/or duodenal atresia. Feingold syndrome is caused by mutations in the neuroblastoma-derived V-myc avian **myelocytomatosis viral-related oncogene (MYCN)** which is located on the short arm of **chromosome 2 (2p24.1)**. 4. **t (2, 13) = alveolar Rhabdomyosarcoma** . (Kaplan peds, p218). The most common types of **rhabdomyosarcoma (RMS) are alveolar RMS (ARMS)**, which are characterized by the specific **translocation t(2;13)(q35;q14)** or its rarer variant, **t(1;13)(p36;q14)**, producing the fusion genes PAX3-FKHR and PAX7-FKHR, respectively, and embryonal RMS (ERMS), which is characterized by multiple numeric chromosome changes. A solid variant of ARMS that is morphologically indistinguishable from ERMS has been described recently. We present two cases with an initial histopathologic diagnosis of ERMS in which the combined findings by cytogenetic, **reverse-transcriptase polymerase chain reaction (RT-PCR)**, and comparative genomic hybridization (CGH) analyses demonstrate that both tumors were in fact the solid variant of ARMS. The cytogenetic analysis of patient 1 revealed a t(2;13)(q35;q14) and the RT-

	PCR study detected the corresponding PAX3-FKHR chimeric transcript. In patient 2, the cytogenetic finding of multiple trisomies was compatible with the initial histopathologic diagnosis of ERMS, but the finding of a PAX7-FKHR fusion transcript by RT-PCR pointed to the diagnosis of ARMS. Interestingly, the CGH findings of this case reconciled the molecular and cytogenetic data by detecting, in addition to the trisomies, amplification of chromosomal bands 1p36 and 13q14, where the PAX7 and FKHR genes are located, respectively. Our data indicate that this multimodal genetic analysis could be important for the differential diagnosis of these tumors. Furthermore, our findings and previous studies indicate that there are no apparent genetic differences between solid variant and typical ARMS. Childhood muscle cancer alveolar rhabdomyosarcoma (ARMS) that is driven by the chromosomal translocation product, Pax3:Fkhr. Tumors that closely recapitulate the spectrum of molecular markers and histology seen in human ARMS are exclusively produced in this model. Unexpectedly, expression of Pax3:Fkhr in muscle satellite cells did not produce tumors, but it did in differentiating myofibers. Expression of Pax3:Fkhr in muscle is necessary but not sufficient to initiate tumorigenesis at high frequency. This model offers new insight into the roots of alveolar rhabdomyosarcoma and illustrates the utility of Cre-loxP technology for studying otherwise inaccessible cancers in the mouse. 5. t (2, 13) = clear cell sarcoma = malignant melanoma of soft part arises from soft tissues rather than skin and found usually in tendon of extremities(pg 326) ??? 6. Distal myopathy= myopathy affecting predominantly the distal portions of the limbs; onset is usually after age 40, with weakness and wasting of small muscles of the hands; The infantile form and the Swedish later-onset are autosomal dominant. There is a Japanese late-onset type that is recessive and is caused by mutation in the gene encoding dysferlin on 2p13. 7. Asthma = Linkage to **asthma** on chromosome **2q**. (near the IL-1 family cluster), **6p, 9, and 12q**. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. The search for genes in asthma has now led to several locations on the genome, including genes on **chromosome 5, 11 and 12**. Like the Fc epsilon receptor for IgE on chromosome 11 and the cluster of cytokines on chromosome 5q. 8. Xanthinuria= **1.** Excretion of abnormally large amounts of xanthine in the urine. **2.** A disorder , characterized by urinary

	excretion of xanthine in place of uric acid, hypouricemia, and occasionally the formation of renal xanthine stones. There are two types: type I is due to xanthine dehydrogenase deficiency (XDH), and type II is due to deficiencies of both xanthine dehydrogenase and aldehyde oxidase. Autosomal recessive inheritance, caused by mutation in the XDH gene on chromosome 2p in some cases. Syn: xanthiuria, xanthuria. [xanthine + G. *ouron,* urine] 9. Hypobetalipoproteinemia = Abnormally low levels of β-lipoproteins in the plasma, occasionally with acanthocytosis and neurological signs; autosomal dominant inheritance; caused by mutation in the apolipoprotein B gene (APOB) on 2p. See Also: abetalipoproteinemia 10. Klein-Waardenburg syndrome (WS- III), Type I = mutation in the PAX3 gene on chromosome 2q. 11. Cystinuria =Excessive urinary excretion of **cystine**, along with **lysine, arginine, and ornithine**, arising from defective transport systems for these acids in the kidney and intestine; renal function is sometimes compromised by cystine crystalluria and **nephrolithiasis (Kidney Stones)**. The stone form in acid urine. Cystinuria is due to defect in the renal tubular reabsorption of four amino acids: cystine, ornithine, lysine and arginine (mnemonic COLA).There are at least three forms of cystinuria, which are distinguished by the severity of urinary excretion of cystine in obligate carriers; all with **autosomal recessive inheritance**. Types I and II cystinuria are allelic disorders caused by mutation in the solute carrier family 3 gene (SLC3A1), which is an amino acid transporter gene on **chromosome 2q**. Type III is caused by mutation at a separate locus. Cystinuria leads to formation of cystine stones. These stone are **radiopaque (= can Not be seen in X-ray, need contrast dye to see them**) because of the **sulfur** content of the stones. They are less radio-opaque than calcium stones, however and **appear grayish fuzzy on a plains film**. Hexagonal crystals seen on the urinanalysis are characteristic of cystine crystals. To confirm the diagnosis, a 24-hours urine for cystine and if possible a stone analysis should e done. **Normal cystine excretion is less than 30 mg/day. Patients with cystine stones typically excrete more than 200 mg of cystine in a day**. 12. Waardenburg Syndrome= disorder characterized by lateral displacement of inner canthi (**dystopia canthorum**), broad nasal root, heterochromia iridis, cochlear deafness, white forelock, and synophrys; autosomal dominant inheritance with type I distinguished from type II by the

	presence of dystopia canthorum. Type I is caused by mutation in the PAX3 gene on chromosome 2q while some cases of type II are caused by mutation in the microphthalmia-associated transcription factor gene (MITF) on chromosome 3p. Finding in Waardenburg syndrome include lateral displacement of the inner canthi, severe bilateral deafness, and partial albinism (**white forelock, pale blue eyes**). The eyebrows flare medially, and may meet in the middle. Occasionally, patients exhibit the **cupids' s bow lips**, and may have ventricular septal defect (VSD) or **Hirschsprung**. It is transmitted in an **autosomal dominant** fashion. **Older paternal age (= when father is too old) is reported in fresh mutation.** (Kaplan peds, p 252). There is evidence that advanced paternal age is linked to an increased risk of autosomal dominant mutations. Which lead to diseases such as neurofibromatosis, achondroplasia, Apert Syndrome and Marfan syndrome. Increasing paternal age also may be associated with X chromosome mutations that are transmitted through carrier daughters to affected grandsons. 13. C gene for the Kappa light chain gene is on chromosome 2 14. V-gene for the kappa light chain gene is on chromosome 2 15. Alport syndrome, type 2 = the autosomal recessive form is due to mutation in the collagen type IV alpha-3 gene (COL4A3) or alpha-4 gene (COL4A4) on 2q. **(Don't mix Apert syndrome (chromosome 10q) with Alport syndrome (x-liked, chromosome 2q)** (Kaplan peds, p184). 16. Ehlers-Danlos syndrome (EDS) = a group of connective tissue disorders characterized by hyperelasticity and fragility of the skin, hypermobility of the joints, and fragility of the cutaneous blood vessels and sometimes large arteries due to deficient quality or quantity of collagen. Patient may have blue sclera, a wide nasal bridge, glaucoma, retinal detachment, small stature, kyphoscoliosis, dissecting aortic aneurysm (Kaplan Peds, p 252). The most common types are inherited as **autosomal dominant**, caused by mutation in one of the following genes: the collagen V alpha-1 gene (COL5A1) on chromosome 9q or the collagen V alpha-2 gene (COL5A2) on 2q or COL3A1 gene on 2q. (Kaplan Peds, p 252) 17. Burkitt's Lymphoma = common variant t (8,14) (q24, q32), involving the oncogene myc on chromosome 8 and the heavy immunoglobulin chain on chromosome 14. The other tow variants are t (8,22) (q24, q11) involving myc and the lambda light chain immunoglobulin site and t (2,8)(p12, 24) involving the kappa light chain and myc. Burkitt

	lymphoma is a form of malignant lymphoma reported in African children, frequently involving the jaw and abdominal lymph nodes. Geographic distribution of Burkitt lymphoma suggests that it is found in areas with endemic malaria. It is primarily a B-cell neoplasm and is believed to be caused by Epstein-Barr virus, a member of the family *Herpesviridae*, which can be isolated from tumor cells in culture; occasional cases of lymphoma with similar features have been reported in the United States. 18. Mutations in the CPS1 gene on chromosome 2q35 , cause carbamoyl phosphate synthetase I deficiency . The official name of PS1 gene is "carbamoyl-phosphate synthetase 1, mitochondrial." . Carbamoyl phosphate synthetase = a phosphotransferase catalyzing the formation of carbamoyl phosphate. There are two significant isozymes. Carbamoyl phosphate synthetase I is a mitochondrial enzyme that catalyzes the reaction of 2ATP, NH_3, CO_2, and H_2O to carbamoyl phosphate, 2ADP, and orthophosphate. It is activated by N-acetylglutamate and participates in urea biosynthesis. A deficiency of carbamoyl phosphate synthetase I can result in hyperammonemia. Carbamoyl phosphate synthetase II is a cytosolic enzyme that, under physiological conditions, uses L-glutamine as the nitrogen source (producing L-glutamate) instead of NH_3, is not activated by N-acetylglutamate, and participates in pyrimidine biosynthesis. 19. Primary hyperoxaluria and oxalosis = a metabolic disorder, usually evident clinically in the first decade of life, characterized by calcium oxalate nephrocalcinosis and nephrolithiasis, extrarenal oxalosis, and increased urinary output of oxalic and glycolic acids, leading to progressive renal failure and uremia. Type I is due to a deficiency in alanine-glyoxylate aminotransferase and type II to a deficiency in D-glycerate dehydrogenase; the latter is a milder disease with a better long-term prognosis for renal function. Both types are inherited as **autosomal recessive**, caused by mutation in the alanine-glyoxylate aminotransferase gene (AGXT) on 2q. 20. Oguchi disease= a rare congenital nonprogressive night blindness with diffuse yellow or gray coloration of fundus; after two or three hours in total darkness, fundus resumes normal color; **autosomal recessive inheritance**, caused by mutation in either the arrestin gene (SAG) on 2q or the rhodopsin kinase gene (RHOK) on 13q 21. Cerebrotendinous xanthomatosis= a metabolic

	disorder associated with deposition of cholestanol and cholesterol in the brain and other tissues; plasma cholestanol level is high but plasma cholesterol level is normal; characterized by progressive cerebellar ataxia beginning after puberty, cataracts, spinal cord involvement, premature atherosclerosis, and tendinous or tuberous xanthomata; due to a defect in hepatic mitochondrial sterol 27-hydroxylase in bile acid biosynthesis; autosomal recessive inheritance, caused by mutation in the gene involved in cytochrome P-450 in the C27 position (CYP27) on chromosome 2q. 22. Familial juvenile nephrophthisis=cystic disease of renal medulla characterized by polyuria, polydipsia, anemia, and renal failure. There are two forms: one is inherited as an autosomal recessive , caused by mutation in the NPHP1 gene on 2q13; the other is an autosomal dominant form . 23. Dravet's Syndrome = Severe Myoclonic Epilepsy of Infancy (SMEI) = Epileptic syndrome characterized by infantile onset, multiple seizure types, and progressive cognitive decline. Epilepsies and syndromes undetermined as to whether they are focal or generalized," since the syndrome shows both generalized and localized seizure types and EEG paroxysms. Dravet's syndrome (= is a seizure syndrome) is due to new mutations in the **sodium-channel gene SCN1A.** SCNIA gene for genic mutation that cause epilepsy. The **SCN1A gene** is on **chromosome 2q**. = Known causative **genes are the sodium channel α subunit genes SCN1A and SCN2A on chromosome 2q24-q33 , 2q21-q33 , an associated β subunit SCN1B, and a GABAA receptor γ subunit gene, GABRG2. Penetrance for this disorder is estimated at approximately 60%**. There is a positive **Family history of either epilepsy or febrile convulsions** in people affected with Dravet's syndrome. Severe myoclonic epilepsy begins during the first year of life. Development is normal prior to the onset of seizures. Affected infants develop either generalized or unilateral clonic seizures without prodromal signs. Myoclonic jerks and partial seizures usually appear later. Psychomotor retardation and other neurologic deficits occur in affected children. Psychomotor development stagnates around the second year of life. Missense mutations in the gene that codes for a **neuronal voltage-gated sodium-channel α-subunit (SCN1A) located on chromosome 2q**, were identified in **families with generalized epilepsy with febrile seizures plus (GEFS+)**. GEFS+ is a mild type of epilepsy associated with febrile and afebrile seizures. Both GEFS+ and SMEI involve fever-associated seizures.

	24. Human insulin receptor substrate-1 gene (IRS1): chromosomal localization to **chromosome 2 (2q35-q36.1)** and identification of a simple tandem repeat DNA polymorphism2) The human IRS-1 gene contains the entire 5'-untranslated region and protein coding region in a single exon and was localized on **chromosome 2 q36-37** by in situ hybridization. 3) IRS1 insulin receptor substrate 1 Gene on **Chromosome 13.** 4) The IRS-2 Gene on Murine **Chromosome 8** Encodes a Unique Signaling Adapter for Insulin and Cytokine Action. Insulin receptor substrate-1 = a cytoplasmic protein that is a direct substrate of the activated insulin receptor kinase. Insulin exposure results in its rapid phosphorylation at multiple tyrosine residues. Its phosphorylated sites associate with high affinity to certain cellular proteins. IRS-1 thus acts as an adaptor molecule that links the receptor kinase to various cellular activities regulated by insulin. IRS-1 is also phosphorylated after stimulation by insulinlike growth factor-1 and several interleukins. 25. Achromatopsia, achromatopsy= This is the compete form of achromatopsia, characterized by severe deficiency of color perception, associated with nystagmus, photophobia, reduced visual acuity, and "day blindness"; autosomal recessive inheritance, caused by mutation in the cone photoreceptor cGMP-gated cation channel, alpha-subunit 3 gene (CNGA3) on chromosome 2q. Syn: monochromasia, monochromasy, monochromatism(2), achromatic vision.
3	1. VHL gene (3p25) → Von Hippel Lindau disease, renal cell carcinoma (pg 57,152). **Von Hippel-Lindau syndrome = cerebroretinal angiomatosis = Lindau disease =** a type of phacomatosis, consisting of retinal vascular malformations (retinal vascular hamartomas), which may be multiple and bilateral, associated with hemangioblastomas primarily of the cerebellum and walls of the fourth ventricle, occasionally involving the spinal cord; sometimes associated with renal cell carcinomas or cysts or hamartomas of kidney, adrenal, or other organs, (pheochromocytoma, polycythemia); autosomal dominant inheritance due to mutation in the von Hippel-Lindau gene (VHL) on 3p (CK p 83, 102). Von Hippel- Lindau Syndrome is an autosomal dominant disorder consisting of retinal angiomas, cerebellar medullary angioblastic tumors, pancreatic cysts and renal tumors and cysts. Usually the skin is not involved, although occasionally angiomas may occur in

	the occipitocervical region (Q book3, p 230). 2. Laurence-Moon-Bardet-Biedl Syndrome (LMBBS) = is an **autosomal recessive** genetic disorder characterized by obesity, retinal degeneration, extra digits on the hands and feet, and intellectual impairment. The gene responsible for LMBBS was located on chromosome **16q21** (type 2). Shortly thereafter, another gene on chromosome **11q13** (type 1) was identified. Since then, two others were found on chromosomes **3p12** (type 3) and **15q22** (type 4). The most common form of LMBBS is type 1 and the most rare form is type 3. It is expected, however, that another gene that causes the syndrome also exists because there are identified cases that have none of these four defects. Recently, however, the Laurence-Moon-Bardet-Biedl syndrome (LMBBS) was split into Laurence-Moon (LMS) and Bardet-Biedl (BBS), where LMS is characterized as the cases involving mental retardation and spastic paresis and BBS involved obesity, polydactyly, and learning disabilities. It has been shown that BBS represents the majority of published cases. Characteristics that have been seen in children with LMBBS are as follows, Not all children will exhibit all of these features: Rod-cone dystrophy (retinitis pigmentosa) , Strabismus , Nystagmus ,Myopia, Optic atrophy, Macular dystrophy, Glaucoma ,Cataracts , Polydactyly (extra fingers and toes), Brachydactyly (short, stubby fingers and toes), Syndactyly (webbing of the toes) , **Obesity** (excess weight gain begins around ages 1 to 2 years) (Kaplan peds, p 32) , Learning disabilities, Developmental delay (delay in sitting, standing, and walking) , Speech delay, Behavioral difficulties, Kidney abnormalities, Hepatic fibrosis, Hypertension (likely a consequence of obesity), Diabetes mellitus, Hypothyroidism, Hypogonadism, Small penis (hypogonadism), Undescended testes (cryptorchidism), Infertile males ,Unusually short tooth roots, Short stature, Ataxic gaits, Deep-set eyes, Premature frontal balding in adult males. 3. Ocular albinism with sensorineural deafness= Waardenburg syndrome, type II = some cases of type II are caused by mutation in the microphthalmia-associated transcription factor gene (MITF) on chromosome 3p. see: **Waardenburg syndrome** 4. Klein-Waardenburg syndrome type II = mutation in the microphthalmia-associated transcription factor gene (MITF) on chromosome 3, white forelock, two different eye color (different cornea color = heterochromia irides)

	5. Bart syndrome= a form of epidermolysis bullosa with blistering of the extremities and intertriginous areas, congenital localized absence of skin, erosions of the mouth, and dystrophic nails; there is often spontaneous improvement with no residual scarring; autosomal dominant inheritance, caused by mutation in the collagen type VII gene (COL7A1) on chromosome 3p. 6. Epidermolysis bullosa dystrophica= Dystrophic Epidermolysis Bullosa (DEB) = Epidermolysis bullosa dystrophica = Absence of type 7 collagen = a form of epidermolysis bullosa in which scarring develops after separation of the entire epidermis with blistering; it is inherited as an autosomal dominant (appearing in infancy or childhood) or recessive (present at birth or appearing in early infancy) trait, the latter including lethal and nonlethal types; both dominant and recessive forms are caused by mutation in the gene for type VII collagen (COL7A1) on chromosome 3p. Syn: dermolytic bullous dermatosis, epidermolysis bullosa, epidermolysis bullosa, dermal type. 7. Waardenburg syndrome= disorder characterized by lateral displacement of inner canthi (dystopia canthorum), broad nasal root, heterochromia iridis, cochlear deafness, white forelock, and synophrys; autosomal dominant inheritance with type I distinguished from type II by the presence of dystopia canthorum. Type I is caused by mutation in the PAX3 gene on chromosome 2q while some cases of type II are caused by mutation in the microphthalmia-associated transcription factor gene (MITF) on chromosome 3p. Finding in Waardenburg syndrome include lateral displacement of the inner canthi, severe bilateral deafness, and partial albinism (white forelock, pale blue eyes). The eyebrows flare medially, and may meet in the middle. Occasionally, patients exhibit the cupids' s bow lips, and may have ventricular septal defect (VSD) or Hirschsprung. It is transmitted in an **autosomal dominant** fashion. Older paternal age (= when father is too old) is reported in fresh mutation. (Kaplan peds, p 252). **There is evidence that advanced paternal age is linked to an increased risk of autosomal dominant mutations. Which lead to diseases such as neurofibromatosis, achondroplasia, Apert Syndrome and Marfan syndrome. Increasing paternal age also may be associated with X chromosome mutations that are transmitted through carrier daughters to affected grandsons**.

	8. Alcaptonuria, alkaptonuria = autosomal recessive inheritance; caused by mutation in the homogentisate 1,2-dioxygenase gene (HGD) on chromosome 3q. Accumulation of black homogentisic acid in blood, cartilage (**ochronosis**) and urine. (biochem p255) 9. Ochronosis= autosomal recessive disease characterized by alkapton uria. 10. Familial hypoparathyroidism=inherited isolated hypoparathyroidism characterized by hypocalcemia, hyperphosphatemia, cataracts, intracerebral calcifications, and tetany; all three mendelian forms (sex-linked, autosomal dominant and recessive) of inheritance are known. The autosomal dominant form is caused by mutation in either the parathyroid hormone gene (PTH) on chromosome 11p or the calcium sensing receptor gene (CASR) on 3q. 11. Benign Familial Hypocalciuric Hypercalcemia = FHH= Familial Benign Hypercalcemia = Familial hypocalciuria hypercalcemia (FHH) is an **autosomal dominant** condition caused by mutations in the calcium sensing receptor gene. It is characterized by moderate hypercalcemia, with normal or slightly elevated PTH levels and hypocalciuria secondary to the increased calcium reabsorption at the distal tubule level (→ therefore urine calcium level would be low in patient with FHH). Genetic analysis of the propositus undercovered a **heterozygous mutation in R648X of CASR gene (located in the long arm of chromosome 3). Altered calcium sensing and a bunted PTH feedback loop is the mechanism of hypercalcemia seen in familial hypocalciuric hypercalcemia**. This is a rare autosomal dominant disorder that rarely results in any clinical problems and usually in not treated. Familial hypocalciuric hypercalcemia (FHH) is an autosomal dominant trait comprising hypercalcemia, hypophosphatemia, parathyroid hyperplasia, and unusually low renal clearance of calcium. FHH is autosomally dominantly inherited atypical form of primary hyperparathyroidism (PHPT). 12. Orotic aciduria= Autosomal recessive inheritance, caused by mutation in the uridine monophosphatase synthase gene (MMPS) on 3q13 (biochem p277) 13. Morquio syndrome= an error of mucopolysaccharide metabolism with excretion of keratan sulfate in urine; characterized by severe skeletal defects with short stature, severe deformity of spine and thorax, long bones with irregular epiphyses but with shafts of normal length, enlarged joints, flaccid ligaments, and waddling gait; autosomal

	recessive inheritance; type IVA mucopolysaccharidosis is due to an absence of galactose-1-sulfatase and is caused by mutation in the N-acetylgalactosamine-6-sulfate sulfatase gene (GALNS) on 16q, while type IVB is due to a deficiency of a beta-galactosidase, and is caused by mutation in beta-galactosidase gene (GLB1) on 3p. Syn: Brailsford-Morquio disease, Morquio disease, Morquio-Ullrich disease, type IVA, B mucopolysaccharidosis. 14. Pseudocholinesterase deficiency =an autosomal dominant disorder manifested by exaggerated responses to drugs ordinarily hydrolyzed by serum pseudocholinesterase (e.g., succinylcholine), caused by mutation in the pseudocholinesterase E1 gene (CHE1) on 3q. (also cause atypical pseudocholinesterase).
4	1. Achondroplasia, autosomal dominant (4p16), FGR3 (fibroblast growth factor receptor 3), constant activation of FGR3 inhibits chondrocyte proliferations (pg268) (Kaplan Peds, p251). This chondrodystrophy, characterized by an abnormality in conversion of cartilage to bone, is the most common form of short-limb dwarfism; characterized by short stature with rhizomelic shortening of the limbs, large head with frontal bossing and midface hypoplasia, exaggerated lumbar lordosis, limitation of elbow extension, genu varum, trident hand, characteristic radiographic skeletal findings, and neurologic symptoms complicating hydrocephalus and spinal canal stenosis. Autosomal dominant inheritance with most cases sporadic, caused by mutation in the fibroblast growth factor receptor 3 gene (FGFR3) on chromosome 4p. There is evidence that advanced paternal age is linked to an increased risk of autosomal dominant mutations. Which lead to diseases such as neurofibromatosis, achondroplasia, Apert Syndrome and Marfan syndrome. Increasing paternal age also may be associated with X chromosome mutations that are transmitted through carrier daughters to affected grandsons. 2. Piebaldism= cutaneous albinism = piebaldness= piebald skin = Patchy absence of the pigment of scalp hair, giving a streaked appearance; patches of vitiligo may be present in other areas due to absence of melanocytes; often transmitted as an autosomal dominant trait caused by mutation in the KIT protooncogene on 4q and may be associated with neurologic defects or eye changes. *Cf.* Waardenburg syndrome. (CK p 96) 3. Fraser syndrome = CRYPTOPHTHALMOS WITH OTHER MALFORMATIONS = CRYPTOPHTHALMOS-SYNDACTYLY

	SYNDROME, INCLUDED = Fraser syndrome (cryptophthalmos syndrome) is a rare **autosomal recessive** disorder **FRAS1 gene** or in the **FREM2 gene** located the **Fraser syndrome locus to chromosome 4q21** .1 It combines acrofacial and urogenital malformations with or without cryptophthalmos. These anomalies were first documented by Fraser in 1962.2 The four major characteristics are cryptophthalmos, syndactyly, genital anomalies and affected siblings and eight minor characteristics are alterations of the nose, ears, larynx, oral clefts, umbilical hernia, renal agenesis (bilateral or unilateral), skeletal anomalies and mental retardation are part of the diagnosis of Fraser syndrome.1 Incidence: 0.043:10,000 liveborn infants and 1.1 : 10,000 stillbirths. Probably autosomal recessive since an unusual proportion of infants is born to consanguineous parents.2 Till now only 95 cases have been documented worldwide. Except genetic counselling there is no known method of prevention. Prognosis of such babies are poor and if they survive no clear prognosis regarding degree of mental retardation can be given = Fraser syndrome can be caused by mutation in the **FRAS1 gene** (607830) or in the **FREM2 gene** (608945). By autozygosity mapping, located the **Fraser syndrome locus to chromosome 4q21**. In each of 2 sibships, Fraser (1962) observed 2 sisters affected at birth by various combinations: cryptophthalmos; absent or malformed lacrimal ducts; middle and outer ear malformations; high palate; cleavage along the midplane of nares and tongue; hypertelorism; laryngeal stenosis; syndactyly; wide separation of symphysis pubis; displacement of umbilicus and nipples; primitive mesentery of small bowel; maldeveloped kidneys; fusion of labia and enlargement of clitoris; and bicornuate uterus and malformed fallopian tubes. In each sibship, 1 sister was stillborn and the other viable. Sex chromatin was positive in both surviving infants. Neither set of parents was consanguineous. See Bowen syndrome (211200) for a comparable but probably distinct syndrome of multiple congenital malformations. 4. Wolfram syndrome (DIDMOD) = a syndrome consisting of Diabetes Insipidus, Diabetes Mellitus, Optic atrophy, and Deafness; the genetic abnormality is located on **chromosome 4p; autosomal recessive** inheritance. 5. Aspartylglycosaminuria= A lysosomal disorder due to deficiency of aspartoglucosaminidase, resulting in accumulation of aspartlyglycosamine in the urine and spinal fluid; characterized by symptoms usually in the first few months of life, with recurrent infections and diarrhea; mental

	retardation, seizures, coarse facial features, and skeletal abnormalities are evident by adolescence. Autosomal recessive inheritance, caused by mutation in the aspartoglucosaminidase gene (AGA) on 4q. 6. Longevity and genes =It is now recognized that there is a single gene controlling how long a person may live1. This gene lies in **chromosome 4** . Studies of siblings who were 90 years or older revealed that they shared the same genetic D.N.A. which gave them their great age. Cloning the D.N.A. could extend peoples lives. Women may live longer than men because they have stronger immune systems i.e. more white or "T" blood cells, males have a higher mortality rate than females before the age of five. It is the thymus gland which manufactures the white blood cells and this production decreases in both sexes with age2 7. Ellis-van Creveld syndrome, also known as "chondroectodermal dysplasia," is a rare genetic disorder characterized by short-limb dwarfism, polydactyly (additional fingers or toes), malformation of the bones of the wrist, dystrophy of the fingernails, partial hare-lip, cardiac malformation, and often prenatal eruption of the teeth. The gene causing Ellis-van Creveld syndrome, EVC, has been mapped to the short arm of **chromosome 4**. As yet, the function of a healthy EVC gene is not known; this is one of the most important questions that must be answered about the disease, since it would give an indication as to the molecular mechanism of the disease. Ellis-van Creveld syndrome is often seen among the Old Order Amish community in Lancaster County, Pennsylvania. Because this group of people is small and isolated, it affords a rare opportunity to observe the passage of this particular disorder from generation to generation. A pattern of inheritance can be observed that has indicated the disease is **autosomal-recessive**. 8. Hypochondroplasia= A skeletal dysplasia characterized by dwarfism with features similar to but much milder than achondroplasia; the skull and facies are normal; features not clinically evident until mid-childhood. Autosomal dominant inheritance, caused in some cases by mutation in the fibroblast growth factor receptor 3 (FGFR3) gene on chromosome 4p. 9. Ellis-van Creveld syndrome = Chondroectodermal dysplasia= triad of chondrodysplasia, ectodermal dysplasia, and polydactyly, with congenital heart defects in over half of patients;

	autosomal recessive inheritance. Maps to human **chromosome 4p16**. Syn: Ellis-van Creveld syndrome. 10. Huntington disease (HD) gene on (4p 16.3)→ Huntingtin Protein (pg 306), (Triplet repeat expansion), Expanded trinucleotide repeat = CAG repeat in 5' coding region (genetics pg 305) . **Less than 29 repeat is normal. (<29 CAG triple repeat is normal). The number of repeats expands in subsequent generations → earlier expression and more sever disease (= anticipation)** (1st aid CK, p 230) = Huntington chorea = a neurodegenerative disorder, with onset usually in the third or fourth decade, characterized by chorea and dementia; pathologically, there is bilateral marked **atrophy of the putamen and the head of the caudate nucleus**. **Autosomal dominant** inheritance with complete penetrance, caused by mutation associated with trinucleotide repeat expansion in the Huntington gene (HD) on **chromosome 4p.** Syn: chronic progressive chorea, degenerative chorea, hereditary chorea, Huntington disease. With Huntington disease get "Darting Tongue", "Milkmaid Grip". With "Westphal Variant of Huntington's Disease" get (stiffness + dyskinesia + ADHD). Westphal Variant of Huntington's Disease = A progressive neurodegenerative disorder characterized initially by bradykinesia and rigidity then choreiform movements. The Westphal variant of Huntington's disease (HD) is a distinct clinical entity of HD characterized by a rigid-hypokinetic syndrome and is often associated with a juvenile onset of disease. 11. Polycystic Kidney Disease (PKD) = Polycystic Disease of Kidneys = **Adult PKD2 (= APKD) (Poly kidney disease), chromosome 4q** (pg144) = a progressive disease characterized by formation of multiple cysts of varying size scattered diffusely throughout both kidneys, resulting in compression and destruction of renal parenchyma, usually with hypertension, gross hematuria, and uremia leading to progressive renal failure. There are two major types: 1) with onset in **infancy or early childhood**, usually of **autosomal recessive** inheritance ; 2) with onset in adulthood, of **autosomal dominant** inheritance with genetic heterogeneity ; may be caused by **mutation in either polycystin-1 gene on chromosome 16p, polycystin-2 gene on 4q**, or gene(s) not identified yet. Approximately 50% of patients with ADPKD have **end-stage renal disease (ESRD)** by the age of 60, but those with ADPKD-2 tend to have later onset and slower progression. Hypertension is common and often precedes renal dysfunction. Hematuria may result from

cyst rupture into the collecting system or from uric acid or **calcium oxalate kidney stones. Nephrolithiasis** occurs in about 20% of patients. Urinary tract infection occurs with increased frequency in ADPKD. Infection in a kidney or **liver cyst** is a particularly serious complication. It is most often due to Gram-negative bacteria and presents with pain, fever, and chills. Numerous extrarenal manifestations of ADPKD highlight the systemic nature of the disease and likely reflect a generalized abnormality in collagen and extracellular matrix. Patients with ADPKD have a risk of **cerebral hemorrhage from a ruptured intracranial aneurysm** as compared to the general population. **Saccular aneurysms** (berry aneurysm??) of the anterior cerebral circulation may be detected in up to 10% of asymptomatic patients on MRA screening. Other vascular abnormalities include **aortic root and annulus dilatation**. Cardiac valvular abnormalities occur in 25% of patients, most commonly **mitral valve prolapse** and **aortic regurgitation**. Although most valvular lesions are asymptomatic, some may progress over time and warrant valve replacement. **Abdominal hernia and inguinal hernia** also occur with a higher frequency than in the general population.

12. t (4, 11) → acute lymphoblastic leukemia (AML) (pg 326)
13. t (4,11) translocation is associated with acute lymphocytic leukemia (ALL) and undifferentiated leukemia.????
14.  = Wolf-Hirschhorn = Deletion, tip of 4p = Wolf-Hirschhorn syndrome, also known as deletion 4p and 4p- syndrome =It is a characteristic phenotype resulting from a partial deletion of chromosomal material of the short arm of chromosome 4.The most common abnormalities seen include severe to profound mental retardation, microcephaly, seizures, hypotonia, and cleft lip and/or palate [Cleft lip **(= cheiloschisis)** and **cleft palate** (= **palatoschisis**)]. Wolf-Hirschhorn syndrome gives a **"Greek helmet facies"**. Characteristic facial features, include strabismus, hypertelorism, down-turned "fishlike" mouth, short upper lip and philtrum, small chin, ear tags or pits, and cranial asymmetry, **dolichocephaly (=Scaphocephaly = pharaoh head)**, microcephaly. Occasional abnormalities include heart defects, hypospadias, scoliosis, ptosis, fused teeth, hearing loss, delayed bone age, low hairline with webbed neck, and renal anomalies. Wolf-Hirschhorn syndrome is caused by a partial deletion of the short arm of chromosome 4, particularly in the region of WHSC1 and

	WHSC2. About 87% of cases represent a de novo deletion, while about 13% are inherited from a parent with a chromosome translocation. In the cases of familial translocation, there is a 2 to 1 excess of maternal transmission. Of the de novo cases, 80% are paternally derived. The symptoms and phenotype do not differ based on the size of the deletion. The critical region for determining the phenotype is at 4p16.3 and can often be detected through genetic testing and fluorescent in situ hybridization (FISH). Genetic testing and genetic counseling is offered to affected families. 15. Scheie syndrome= allelic to Hurler syndrome but with a much milder phenotype; characterized by α-L-iduronidase deficiency, corneal clouding, deformity of the hands, aortic valve involvement, and normal intelligence; autosomal recessive inheritance, caused by mutation in the alpha-L-iduronidase gene (IUDA) on chromosome 4p. Syn: type IS mucopolysaccharidosis. 16. Mutation in the dihydropteridine reductase gene (DHPR) on 4p → Phenylketonuria (PKU). PKU = **infants tend to have fair-haired fair-skinned, and have blue eyes**. An **eczematous rash and a musty odor** have been described. (Kaplan peds, p5) = phenylketonuria = (PKU) = Autosomal recessively inherited inborn error of metabolism of phenylalanine characterized by deficiency of 1) phenylalanine hydroxylase caused by mutation in the phenylalanine hydroxylase gene (PAH) on 12q; 2) occasionally, dihydropteridine reductase, caused by mutation in the dihydropteridine reductase gene (DHPR) on 4p; 3) rarely, dihydrobiopterin synthetase, caused by mutation in the pyruvoyl tetrahydropterin synthase gene (PTS) on 11q; or 4) even more rarely, guanidine triphosphate cyclohydrolase 1. The disorder is characterized by inadequate formation of L-tyrosine, elevation of serum L-phenylalanine, urinary excretion of phenylpyruvic acid and other derivatives, and accumulation of phenylalanine and its metabolites, which can produce brain damage resulting in severe mental retardation, often with seizures, other neurologic abnormalities such as retarded myelination and deficient melanin formation leading to hypopigmentation of the skin and eczema. *Cf.* hyperphenylalaninemia. Syn: Folling disease, phenylpyruvate oligophrenia. 17. Hurler syndrome = Autosomal recessive inheritance, caused by mutation in the alpha-L-iduronidase gene (IDUA) on 4p. (Hunter syndrome is one of the disease of

	mucopolysaccharidosis which is X-linked recessive, other examples are hurler and Sanfilippo that are autosomal recessive) (Kaplan peds, p225). 18. Abetalipoproteinemia= Bassen-Kornzweig syndrome = Autosomal recessive inheritance, caused by mutation in the gene encoding microsomal triglyceride transfer protein (MTP) on chromosome 4q. A disorder characterized by an absence of low-density beta-lipoprotein, presence of acanthocytes in blood, retinal pigmentary degeneration (**Retinitis Pigmentosa**), malabsorption, engorgement of upper intestinal absorptive cells with dietary triglycerides, and neuromuscular abnormalities; autosomal recessive inheritance, caused by mutation in the gene encoding microsomal triglyceride transfer protein (MTP) on chromosome 4q. Syn: Bassen-Kornzweig syndrome.
5	1. Cri-du-chat syndrome, cri du chat syndrome, cat-cry syndrome = a disorder due to deletion of the short arm of chromosome 5, characterized by microcephaly, hypertelorism, antimongoloid palpebral fissures, epicanthal folds, micrognathia, strabismus, mental and physical retardation, and a characteristic high-pitched catlike whine. Syn: cat's cry syndrome, Lejeune syndrome. Cri-du-chat Deletion, tip of 5p (deletion of 5p), cat like cry (pg48) 2. Chylomicron Retention Disease (= CMRD)= ANDERSON DISEASE= ANDD = LIPID TRANSPORT DEFECT OF INTESTINE = HYPOBETALIPOPROTEINEMIA WITH ACCUMULATION OF APOLIPOPROTEIN B-LIKE PROTEIN IN INTESTINAL CELLS = an inherited disorder in which apolipoprotein B-48 is retained in intestine and absent in plasma; results in fat malabsorption. **Autosomal recessive inheritance can be caused by mutation in the SAR1B gene on chromosome "5q31.1"** . 3. Some patient with CMRD also have Marinesco Sjögren syndrome = Chylomicron retention disease (CMRD) with Marinesco Sjögren syndrome 4. Congenital Contractural Arachnodactyly (CCA) = Beals syndrome = Congenital contractural arachnodactyly can be caused by mutation in the gene encoding **fibrillin-2 (FBN2) on chromosome 5q23-q21**. Congenital contractural arachnodactyly is a rare, autosomal dominant connective tissue disorder characterized by contractures, arachnodactyly, scoliosis, and crumpled ears due to mutation in the gen fibrillin-2 (FBN2) on chromosome 5q23-q21. Congenital contractural arachnodactyly shares

	overlapping features with Marfan syndrome, which Marfan syndrome is caused by mutation in the gene encoding fibrillin-1 (FBN1). Congenital contractural arachnodactyly is an a**utosomal dominant** disorder, patient present with tall stature, arachnodactyly, and multiple contractures in large joint. (Remember also get arachnodactyly with Marfan syndrome). 5. Asthma = Linkage to **asthma** on chromosome **2q**. (near the IL-1 family cluster), **6p, 9, and 12q**. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. The search for genes in asthma has now led to several locations on the genome, including genes on **chromosome 5, 11 and 12**. Like the Fc epsilon receptor for IgE on chromosome 11 and the cluster of cytokines on chromosome 5q. 6. Marshall-Smith-Weaver syndrome = Weaver-Smith syndrome (WSS) = Marshall-Smith syndrome = Weaver syndrome = Weaver syndrome: An overgrowth syndrome characterized by accelerated growth and advanced bone age (evident at birth), unusual craniofacial appearance, hoarse low-pitched cry, and hypertonia (increased muscle tone) with camptodactyly (inability to fully extend the fingers). Caused by mutations in a gene called **NSD1 Gene on chromosome 5q35**. The same gene is mutated in more than three-fourths of patients with another overgrowth disorder called Sotos syndrome. Weaver-Smith syndrome is associated with tall stature (Kaplan peds, p 30). 7. Type IB achondrogenesis= achondrogenesis with severely disorganized intracartilaginous ossification; autosomal recessive inheritance, caused by mutation in the diastrophic dysplasia sulfate transporter gene (DTDST) on chromosome 5q. Syn: Parenti-Fraccaro syndrome. 8. (5q,21) = APC = adenomatous polyposis coli gene+ colon cancer (colorectal cancer) (pg 83, 169) = familial adenomatous polyposis (FAP) = polyposis that usually begins in childhood; polyps increase in number, causing symptoms of chronic colitis; pigmented retinal lesions are frequently found; carcinoma of the colon almost invariably develops in untreated cases; **autosomal dominant** inheritance, caused by mutation in the adenomatous polyposis coli gene (APC) on 5q. In Gardner syndrome, which is allelic to FAP, there are extracolonic changes (desmoid tumors, osteomas, jaw cysts). Syn: adenomatous polyposis

coli, familial polyposis coli, multiple intestinal polyposis.

9. Sandhoff Disease = an infantile form of G_{M2} gangliosidosis (lysosomal storage disease) characterized by a defect in the production of hexosaminidases A and B; it resembles Tay-Sachs disease, but occurs predominantly (if not entirely) in non-Jewish children; accumulation of glucoside and ganglioside Gm2, caused by mutation in hexosaminidase B gene (HEX B) on chromosome 5q.
10. Maroteaux-Lamy syndrome= an error of mucopolysaccharide metabolism characterized by excretion of dermatan sulfate in the urine, growth retardation, lumbar kyphosis, sternal protrusion, genu valgum, usually hepatosplenomegaly, and no mental retardation; onset occurs after 2 years of age; autosomal recessive inheritance, caused by mutation in the arylsulfatase B gene (ARSB) on chromosome 5q. Syn: arylsulfatase B deficiency, type VI mucopolysaccharidosis.
11. Cornelia de Lange Syndrome aka CdLS is a little known genetic disorder that can lead to severe developmental anomalies. It affects both the physical and intellectual development of a child. genes responsible for **CdLS** are: **NIPBL on Chromosome 5**, a second gene—**SMC1A on the X chromosome**— and **gene SMC3 is on chromosome 10**. The latter two genes(on chromosome X and chromosome 10) seem to correlate with a milder form of the syndrome. The vast majority of cases are due to spontaneous mutations, although the defected gene can be inherited from either parent, making it **autosomal dominant**. Following are the features and characteristics which help in spotting this disorder: Low birth weight (usually under 5 pounds / 2.5 kilograms), Delayed growth and small stature , Developmental delay, Limb differences (missing limbs or portions of limbs), Small head size (microcephaly), Thick eyebrows, which typically meet at midline (synophrys),Long eyelashes ,Short upturned nose and thin down turned lips , Long philtrum , Excessive body hair , Small hands and feet, Small widely spaced teeth, Low-set ears, Hearing impairments , Vision abnormalities (e.g., ptosis, nystagmus, high myopia, hypertropia) ,Partial joining of the second and third toes , Incurved 5th fingers , Gastroesophageal reflux ,Seizures ,Heart defects, Cleft palate , Feeding problems . Children with this syndrome are often found to have long eyelashes, bushy eyebrows and synophrys (joined eyebrows). Body hair can be excessive and affected individuals are often

	shorter than their immediate family members. CdLS can give rise to its own array of complexities. Children with CdLS often suffer from gastrointestinal tract difficulties, particularly gastroesophageal reflux. Vomiting, intermittent poor appetite, constipation, diarrhea or gaseous distention are known to be a regularity in cases where the GE tract problems are acute. However, symptoms may range from mild to severe. CdLS may also include a number of behavior problems, including self-stimulation, aggression, self-injury or strong preference to a structured routine. Many children with CdLS exhibit autistic-like behaviors and are on the autism spectrum. Behavior problems in CdLS are not inevitable. Many behavior issues associated with CdLS are reactive (i.e., something happens within the person's body or environment to bring on the behavior), and cyclical (comes and goes). Often, an underlying medical issue causes a change in behavior. Once the medical issue is treated, the behavior diminishes. 12. Groenouw corneal dystrophy= **1.** a granular type of corneal dystrophy, with autosomal dominant inheritance, caused by mutation in the transforming growth factor, beta-induced, gene (TGFB1) encoding keratoepithelin on chromosome 5q; **2.** a progressive macular type of corneal dystrophy, characterized by punctate opacities and episodes of photophobia, corneal erosion, and foreign body sensation; autosomal recessive inheritance. 13. Familial adenomatous polyposis syndromes (FAP): autosomal dominant, are characterized by multiple colonic polyps occurring by age 30. phenotypic subtypes include familial polyposis coli(autosomal dominant), Gardner's syndome (**autosomal dominant, epidermal inclusion cysts, colonic polyps and osteomas**) and Turcot syndrome (**autosomal recessive, colonic polyps and brain tumor, especially glioma**) is located in (5q,21) = APC = adenomatous polyposis coli gene. (Surgery BRS, p 322) (Kaplan IM, p 21). 14. Turcot syndrome = medulloblastoma (more common), glioma or other CNS tumors occurring in association with familial adenomatous polyposis (FAP) and adenocarcinoma of the colon is consistent with Turcot syndrome, another form of FAP resulting from mutations in the APC gene. (**Autosomal recessive, colonic polyps and brain tumor, especially glioma**) is located in (5q,21) = APC = adenomatous polyposis coli gene. (Surgery BRS, p 322)

(Kaplan IM, p 21).

15. Gardner syndrome = **autosomal dominant**, multiple polyposis predisposing to carcinoma of the colon; also multiple tumors, osteomas of the skull, epidermoid cysts, and fibromas; supernumerary teeth, autosomal dominant inheritance, caused by mutation in the adenomatous polyposis coli gene (APC) on chromosome 5q. This disorder is allelic to familial adenomatous polyposis (FAP). Patient with Gardner Syndrome typically have multiple epidermal inclusion ("sebaceous") cysts, osteomas, supernumerary teeth, and congenital hypertrophy of the retinal pigment epithelium (CHRPE) in addition to multiple adenomatous polys of the colon. These colonic polyps are likely to undergo malignant transformation typically in the distal colon by the fourth to fifth decade of life, a total colectomy before development of a malignancy typically allow for a normal life span. Gardner syndrome is one subset of the familial adenomatous polyposis (FAP) group of disease, all of which result from mutation in APC. (Kaplan IM, p 21).
16. Treacher Collins syndrome (5q32-33.1), mandibular dyostosis with variable expression in mother and son. Mandibulofacial dysostosis, when limited to the orbit and malar region. **Treacher Collins syndrome is characterized by malformation of the external ear, deafness, micrognathia, antimongoloid eye slanting and coloboma of the lower eyelids** (Q book, p 434). **[Antimongoloid= The condition in which the lateral portion of the palpebral fissure is lower than the medial portion.]**
17. Hereditary lymphedema = Permanent pitting edema usually confined to the legs; two types, 1) congenital (Milroy disease), caused by mutation in the FMS-like tyrosine kinase 4 gene (FLT4) on 5q, or 2) with onset at about the age of puberty (Meige disease); autosomal dominant inheritance. 1) Milroy disease = the congenital type of autosomal dominant lymphedema. 2) Meige disease= autosomal dominant lymphedema with onset at about the age of puberty.
18. Hyperekplexia = A hereditary disorder in which there are pathologic startle responses, i.e., protective reactions to unanticipated, potentially threatening, stimuli of any type, particularly auditory; the stimuli induce often widespread and violent sudden contractions of the head, neck, spinal, and sometimes limb musculature, resulting in involuntary shouting, jerking, jumping, and falling; **autosomal dominant**

	and recessive inheritance forms, with the responsible gene localized to chromosome **5q**; probably the result of lack of inhibitory neurotransmitters, glycine, or GABA. Syn: **kok disease, startle disease** 19. Spinal muscular atrophy (SMA), type III =**juvenile muscular atrophy= chronic juvenile spinal muscular atrophy= Kugelberg-Welander disease= Wohlfart-Kugelberg-Welander disease.** Autosomal recessive inheritance, caused by mutation in the **survival motor neuron gene (SMN1) gene on 5q.** (peds p 236) 20. Spinal muscular atrophy (SMA), type II = autosomal recessive inheritance, caused by mutation in the **survival motor neuron gene (SMN1) gene on 5q** . 21. Diastrophic dysplasia= a skeletal dysplasia characterized by scoliosis, hitchhiker thumb due to shortening of the first metacarpal bone, cleft palate, malformed ear with calcification, chondritis, shortening of the Achilles tendon, clubbed foot, and characteristic radiologic findings; autosomal recessive inheritance, caused by mutation in the diastrophic dysplasia sulfate transporter gene (DTDST) on chromosome 5q. Syn: diastrophic dwarfism. 22. Ringlike corneal dystrophy=threadlike opacities of the anterior corneal stroma, with acute, painful onset followed by decreased vision; autosomal dominant inheritance, caused by mutation in the transforming growth factor, beta-induced, gene (TGFB1) encoding keratoepithelium on chromosome 5q. 23. Cockayne Syndrome is a rare inherited disorder in which people are sensitive to sunlight, have short stature, and have the appearance of premature aging. In the classical form of Cockayne syndrome (Type I), the symptoms are progressive and typically become apparent after the age of 1 year. An early onset or congenital form of Cockayne syndrome (Type II) is apparent at birth. Interestingly, unlike other DNA repair diseases, Cockayne syndrome is not linked to cancer. After exposure to UV radiation (found in sunlight), people with Cockayne syndrome can no longer perform a certain type of DNA repair, known as "transcription-coupled repair." This type of DNA repair occurs "on the fly" right as the DNA that codes for proteins is being replicated. Two genes defective in Cockayne syndrome, CSA and CSB, have been identified so far. The CSA gene is found on **chromosome 5**. Both genes code for proteins that interacts with components of the transcriptional machinery and with DNA repair proteins. Escherichia coli, a bacterium, also

	undergoes transcription-coupled repair, and a yeast counterpart of the CSB gene has also recently been discovered. These similar mechanisms to the one found in humans are invaluable for studying the molecular processes involved in transcription-coupled repair because powerful molecular genetics techniques can be used. A better understanding of the mechanisms involved will help unravel the pathogenesis of disease and may identify potential drug targets. Mutations in the ERCC6 and ERCC8 genes cause Cockayne syndrome. The ERCC6 and ERCC8 genes provide instructions for making proteins that are involved in repairing damaged DNA. If either gene is altered, DNA damage is not rapidly repaired. As a result, damaged DNA accumulates, which probably leads to impaired cell functions and eventually, cell death. Increased cell death likely contributes to features of Cockayne syndrome such as growth failure and premature aging. 24. Lattice corneal dystrophy= a corneal dystrophy due to localized accumulation of amyloid in a reticular pattern; manifest at puberty and progressing slowly until eventually useful vision is lost; autosomal dominant inheritance, caused by mutation in the transforming growth factor, beta-induced, gene (TGFB1) encoding keratoepithelin on 5q. 25. Spinal muscular atrophy (SMA), type I= **degeneration of anterior horn cells** in the spinal cord and of motor nuclei in the brain stem with secondary atrophy of motor never roots and of muscle, patient presents with signs and symptoms of Lower motor neuron lesion=LMN, such as tongue fasciculation, absent Deep tendon reflexes (DTRs)). (Peds, p 227), **brighter kid** (peds p 236) = the early infantile form, characterized by profound muscle weakness and wasting with onset at or shortly after birth; death occurs usually before 2 years of age. **Autosomal recessive inheritance**, caused by mutation in the **survival motor neuron gene (SMN1) on 5q**. (Test will show presence of SMN gene in blood) (Kaplan Peds, p 227). About one-half of patients are also missing both homologs of a neighboring gene that encodes **neuronal apoptosis inhibitory protein (NAIP)**, the loss of which is thought to influence the severity of the disease. Syn: familial spinal muscular atrophy= Hoffmann muscular atrophy= severe infantile muscular atrophy= infantile muscular atrophy = infantile progressive spinal muscular atrophy= progressive infantile spinal muscular

	atrophy, Werdnig-Hoffmann muscular atrophy, Werdnig-Hoffmann disease. (1st aid, p 349), (Kaplan peds, p 227).
6	1. Primary Hemochromatosis=. a specific inherited metabolic defect with increased absorption and accumulation of iron on a normal diet; autosomal recessive inheritance caused by a mutation in the hemochromatosis gene (HFE) on 6p, less florid in females; juvenile hemochromatosis may represent a homozygous state of the same gene. HFE gene with HLA- A (HLA- A3) on (6p) = hemochromatosis (pg 194), (genetics pg 373). Hemochromatosis mutation C282Y screen.(first aid CK, p 144). Hereditary hemochromatosis is an autosomal recessive disorder of iron metabolism that varies in clinical severity. Three mutations (C282Y, H63D, and S65C) have been described in the majority of patients with hemochromatosis. Homozygosity for the C282Y mutation is responsible for up to 90% of hemochromatosis patients. Penetrance of C282Y is under debate. Current studies estimate penetrance as 80% for men and 35% for women over 40. Additional studies estimate much lower penetrance for liver disease (~1%). The second mutation (H63D) has been described in some patients when inherited with the C282Y mutation as a compound heterozygote (C282Y/H63D). This genotype, however, has a reduced penetrance of less than 2%. C282Y/ S65C compound heterozygotes have also been reported, but the penetrance of this genotype is not known. It may contribute to a mild form of hemochromatosis. Heterozygotes for C282Y (C282Y/WT), H63D (H63D/WT), or S65C (S65C/WT) are not significantly associated with hemochromatosis, although other undetected mutations in combination with these mutations may contribute to symptoms of hemochromatosis. Homozygous H63D genotypes (H63D/H63D) rarely show symptoms of hemochromatosis, but several cases have been reported. Mutations in unidentified genes or other mutations in the HFE gene which may cause hemochromatosis are not ruled out by this analysis. Hemochromatosis is associated with increased risk of hepatocellular carcinoma (HCC) in up to 20% of affected individuals (1st Aid CK, p143). Hemochromatosis causes both **restrictive and dilated cardiomyopathy** due to accumulation of **hemosiderin** infiltrate in heart. Hemochromatosis is the only reversible cause of restrictive cardiomyopathy that is reversible with phlebotomy and iron removal (IM, p 150, 153). A disorder of iron metabolism characterized by excessive absorption of ingested iron, saturation of iron-binding protein, and

	deposition of hemosiderin in tissue (= **hemosiderosis**), particularly in the liver, pancreas, and skin; cirrhosis of the liver, diabetes (bronze diabetes), bronze pigmentation of the skin, and, eventually heart failure may occur; also can result from administration of large amounts of iron orally, by injection, or in forms of blood transfusion therapy. 2. Asthma = Linkage to **asthma** on chromosome **2q**. (near the IL-1 family cluster), **6p, 9, and 12q**. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. The search for genes in asthma has now led to several locations on the genome, including genes on **chromosome 5, 11 and 12**. Like the Fc epsilon receptor for IgE on chromosome 11 and the cluster of cytokines on chromosome 5q. 3. Major Histocompatibility Complex (MHC) is located on chromosome 6. MHC encodes the gene for human leukocyte antigens (HLA). HLA proteins are alloantigens (i.e. they differ among members of the same species). Each person has 2 haplotypes, or 2 sets of these genes, maternal and paternal. The protein encoded by both the maternal and paternal chromosomes are expressed (codominance). Class I and II antigen are detected in lab by serologic, polymerase chain reaction (PCR) . the haplotype of class I and II antigens are usually determined for both the donor and recipient before kidney transplantation. The major loci are HLA-A, HLA-B, HLA-DR. a heterozygous individual will have 6 antigen n(2 of each). Minor histocompatibility proteins (antigens) are coded for by genes other than the MHC. (surgery BRS, p 113). [[[These are the HLA association, but I didn't check to see if they are all belong to chromosome 6. HLA-B51→Behçet disease, HLA-DR2 → Goodpasture's syndrome and multiple sclerosis, HLA DR3→ type 1 Diabetes mellitus, HLA-D11→Hashimoto thyroiditis]]]. 4. Major Histocompatibility complex (MHC) antigens on (6p), Both class I and class II MHC genes (micro, pg 24,p155). Both class I and class II , MHC molecules are expressed at high density on the surface of cells of the thymic stoma (mirco p24), autoimmune disease are due to genetic factors (class 2 MHC) as well as HLA (human leukocyte antigen) predisposition. HLA are proteins (= gene product of class 1 and class 2 MHC) → MHC gene produces HLA protein/antigen. Having specific type of HLA in an individual can predispose the individual to autoimmune disease. Both MHC class 1 and 2, as well as HLA are located on short arm of chromosome 6 (= chromosome 6p) → **if**

someone have an autoimmune disease, look for specific HLA on chromosome 6p (micro, pg24).

5. Type 1 diabetes mellitus = type 1 IDDM (insulin dependent diabetes mellitus or juvenile onset) = is associated with **HLA- B8, HLA-B15, HLA-DR3, and HLA- DR4.** (1st aid CK, p 92) (Kaplan IM, p45). [HLA-DR and HLA-DR4 on chromosome 6, (genetics pg 373)]. Human leukocyte antigen (HLA) region located on **chromosome 6.** In diabetes mellitus type 1 there is an increased prevalence of autoantibodies to islet cells and other tissues. (Kaplan IM, p45). For type 1 or IDDM most of the beta cells in the pancreas have been destroyed, the destructive process is most likely **autoimmune** in nature. (Kaplan IM, p46). Pt present with polyuria, polyphagia, polydipsia and weight loss. The most common cause of type 1 diabetes is autoantibody production against pancreatic antigens such as glutamic acid decarboxylase (= **anti-glutamic acid decarboxylase antibodies**). These antibodies are present in over 70% of type 1 diabetes at the time of presentation.
   Anti-GAD =GAD65 = GADAb= Glutamic Acid Decarboxylase (GAD) Autoantibody= Detect the presence of antibodies to glutamic acid decarboxylase, which provides early evidence of autoimmune disease activity; its measurement has been shown to be useful in assisting the physician in the prediction, diagnosis, and management of patients with diabetes. **Glutamic acid decarboxylase (GAD65) is an enzyme that is produced primarily by pancreatic islet cells**. A number of recent studies indicate that patients with insulin-dependent diabetes mellitus (IDDM) often have antibodies to GAD65 and several other islet cell antigens. Insulin-dependent diabetes mellitus (IDDM) characterized by circulating autoantibodies against a variety of islet cell antigens, including **glutamic acid decarboxylase (GAD), tyrosine phosphatase (IA2 = IA2 Autoantibodies), and insulin (=Insulin Autoantibodies (IAA))**. This is consistent with the hypothesis that IDDM is an autoimmune disease and that autoantibody production is an early step in the development of IDDM. Autoantibodies can be detected in many cases prior to the onset of glucose intolerance. The presence of GAD65 autoantibodies has been shown to be a strong predictive marker for the eventual onset of IDDM. Measurement of GAD65 antibody can also be of use in distinguishing insulin-dependent from Non-insulin-dependent diabetics when the clinical history is ambiguous. GAD65 autoantibodies are often markedly elevated in patients with

	the stiff-person syndrome (also referred to as stiff-man syndrome), a condition that is associated with fluctuating stiffness and paroxysmal spasms of the trunk and legs. GAD65 autoantibodies (GAD65Ab) are important markers for type 1 (insulin-dependent) diabetes mellitus. **Anti-pancreatic Islet Cells** = Differential diagnosis of insulin-dependent diabetes from Non-insulin-dependent diabetes 6. HLA-DR and HLA-DR4 on chromosome 6, (genetics pg 373) 7. Polyglandular Autoimmune syndrome type 2 = (PAS II) = Polyglandular Autoimmune (PGA) Syndromes Type 2 = PGAS= Polyglandular Failure Syndromes, Type 2 = Autoimmune Polyendocrine Syndrome, Type II (= APS-II) = Autoimmune Polyglandular syndromes, Type 2 = Polyglandular autoimmune diseases, Type 2 = Schmidt syndrome = Autoimmune polyendocrine syndrome type II (also called Schmidt's syndrome with Addison's disease plus hypothyroidism) = PAS II is more common and occurs in adulthood, mainly in the third or fourth decade. It is characterized by primary adrenal failure (Addison's disease) with autoimmune thyroid disease (Schmidt's syndrome) and/or type 1 diabetes (Carpenter's syndrome). PAS II is a Polygenic dominant inheritance due to mutation of Genes on chromosome 6. **8.** PAS II, PAS III, PAS IV = autoimmune polyendocrine syndrome type II (PAS 2) refers to Addison's disease plus thyroid autoimmunity or type 1A diabetes; autoimmune polyendocrine syndrome type III (PAS 3) refers to thyroid autoimmunity plus another autoimmunity (but not Addison's disease or type 1A diabetes); and autoimmune polyendocrine syndrome type IV (PAS 4) refers to two or more other organ-specific autoimmune diseases. **Tests for all the PAS : [[1) for Addison disease test for 21-hydroxylase autoantibody, corticotrophin level and cortisol level before and after cosyntropin stimulation. 2) for type 1 diabetes mellitus : check GAD 65, pancreatic islet cells autoantibody, C-peptide level, loss of C-peptide is a sign of Beta-cell destruction 3) for Celiac disease : check tissue transglutaminase autoantibody (TTG), if TTG level is high, do small bowel biopsy 4) for immune thyroiditis (ex: Hashimoto's Thyroiditis and Grave's Disease) check thyroid peroxidase antibody (TPO) and thyrotropin level. If have increase thyrotropin level, there is a high risk of future hypothyroidism 5) for pernicious anemia, check for**

	anti-intrinsic factor antibody and Anti- Parietal Cell autoantibody.]] 9. Ankylosing Spondylitis = AS = arthritis of the spine, resembling rheumatoid arthritis, that may progress to bony ankylosis with lipping of vertebral margins; the disease is more common in the male, often with the rheumatoid factor absent and the HLA antigen present. Human leukocyte antigen (**HLA**) region located on **chromosome 6.** There is a striking association with the B27 (**HLA- B27**) , tissue type and the strong familial aggregation suggest an important genetic factor, perhaps inherited as an **autosomal dominant**; the mechanism, however, remains obscure. 90% of patients are positive for HLA-B27 but only 5% of pts with HLA- B27 have ankylosing spondylitis. Therefore HLH-B27 is not specific for ankylosing spondylitis and testing for it is not diagnostic, need to do X-ray of sacroiliac joint and back. (Kaplan IM, p 68-69). Syn: Marie-Strümpell disease, Strümpell-Marie disease, rheumatoid spondylitis. 10. t (6,9) translocation is found in subtypes of Acute Myelogenous Leukemia/Lymphoma AML with basophilia (M1, M2, M4) 11. Zellweger Syndrome = Cerebrohepatorenal Syndrome = a metabolic disorder with neonatal onset, characterized by distinctive facies, muscular hypotonia, hepatomegaly with jaundice, renal cysts, epiphyseal stippling of the patellae, cerebral dysmyelination, and neuronal migration defects and psychomotor retardation; there is a **perturbation in peroxisomal biogenesis (= absence of peroxisomes)**; autosomal recessive inheritance, caused by mutation in any one of several peroxin (PEX) genes on chromosome 6, 7, 8, or 12. 12. Methylmalonic aciduria = Autosomal recessive inheritance, caused by mutations in the methylmalonyl-CoA mutase gene (MCM) on chromosome 6p (biochem p255). Excretion of excessive amounts of methylmalonic acid in urine owing to deficient activity of methylmalonyl-CoA mutase or deficient cobalamin reductase. Two types occur: 1) an inborn error of metabolism resulting in severe ketoacidosis shortly after birth, with long-chain urinary ketones; autosomal recessive inheritance, caused by mutations in the methylmalonyl-CoA mutase gene (MCM) on chromosome 6p ; 2) acquired, a type due to vitamin B_{12} deficiency due to defective synthesis of adenosylcobalamin 13. Mucolipidosis I = lipomucopolysaccharidosis = autosomal recessive inheritance caused by mutation in the

	neuraminidase gene (NEU) on 6p 14. Ocular albinism 3 = caused by mutation in the pinkeye gene (P) on 6q; autosomal recessive inheritance 15. Hereditary progressive arthroophthalmopathy= Stickler syndrome= A skeletal dysplasia associated with multiple dysplasia of the epiphyses, overtubulation of long bones with metaphyseal widening, flattened vertebral bodies, pelvic bone abnormalities, hypermobility of joints, cleft palate, progressive myopia, retinal detachment, and deafness. **Autosomal dominant** inheritance caused by mutation in either the COL2A1 gene on 12q, COL11A1 gene on 1p or COL11A2 gene on 6p. 16. Chondrodystrophy with sensorineural deafness= a skeletal dysplasia characterized by dwarfism, flat nasal bridge, cleft palate, sensorineural deafness, large epiphyses, and flattening of the vertebral bodies; autosomal recessive inheritance, caused by mutation in the type XI collagen gene (COL11A2) on **chromosome 6p; dominant** forms exist. Syn: Nance-Sweeney chondrodysplasia, otospondylomegaepiphyseal dysplasia, OSMED, Nance-Insley syndrome. 17. Cleidocranial dysostosis, cleidocranial dysostosis= a developmental disorder characterized by absence or hypoplasia of clavicles, box-shaped skull with open sutures, frontal bossing, wormian bones, ability to oppose shoulders, and missing teeth; autosomal dominant inheritance, caused by mutation in the transcription factor gene (CBFA1) encoding core-binding factor, runt domain, alpha-subunit 1 on 6p. There is an autosomal recessive form. Syn: craniocleidodysostosis, cleidocranial dysplasia 18. Juvenile myoclonic epilepsy=an epilepsy syndrome typically beginning in early adolescence, and characterized by early morning myoclonic jerks that may progress into a generalized tonic-clonic seizure. A genetic disorder: some families have had gene linkage to chromosome-6. The EEG is characterized by generalized polyspike and wave discharges at 4–6 Hz. 19. Lafora body disease= a form of progressive myoclonus epilepsy beginning from age 6–19; characterized by generalized tonic-clonic seizures, resting and action myoclonus, ataxia, dementia, and classic EEG findings, including polyspike and wave discharges; basophilic cytoplasmic inclusion bodies present in portions of the brain, the liver, and skin, as well as the duct cells of the sweat

	glands. Death usually occurs within 10 years of onset; autosomal recessive inheritance, caused by mutation in the progressive myoclonic epilepsy 2 gene (EPM2A) on chromosome 6q. Syn: Lafora disease. 20. Retinopathy punctata albescens= a disease in which both fundi show numerous white dots or flecks through the retinae, causing night blindness; autosomal dominant inheritance, caused by mutation in the "retinal degeneration, slow" gene (RDS) encoding peripherin on chromosome 6p. There is also a recessive form 21. Rh null syndrome= a condition characterized by lack of all Rh antigens, compensated hemolytic anemia, and stomatocytosis; autosomal recessive inheritance, caused by mutation in the Rhesus-associated polypeptide 50-kD gene (RH50A) on chromosome 6p. 22. Rhizomelic chondrodysplasia punctata= autosomal recessively inherited lethal chondrodysplasia caused by mutation in the PEX 7 gene encoding the peroxisomal type 2 targeting signal (PTS2) receptor on chromosomal 6q. 23. Selective gamma-A-globulin deficiency (Ig A deficiency) , with **dominant autosomal inheritance** (= autosomal dominant inheritance) (Kaplan peds, p 119) .Immunoglobulin A (IgA) deficiency (IgAD) is characterized by a defect of terminal lymphocyte differentiation, leading to a lack of IgA in serum and mucosal secretions. Familial clustering, variable population prevalence in different ethnic groups, and a predominant inheritance pattern suggest a strong genetic predisposition to IgAD. The genetic susceptibility to IgAD is shared with a less prevalent, but more profound, defect called "common variable immunodeficiency" (CVID). Here we show an **increased allele sharing at chromosome 6p21 in affected** members of 83 multiplex IgAD/CVID pedigrees and demonstrate, using transmission/disequilibrium tests, family-based associations indicating the presence of a predisposing locus, designated "IGAD1," in the proximal part of the major histocompatibility complex (MHC). The recurrence risk of IgAD was found to depend on the sex of parents transmitting the defect: affected mothers were more likely to produce offspring with IgAD than were affected fathers. Carrier mothers but not carrier fathers transmitted IGAD1 alleles more frequently to the affected offspring than would be expected under random segregation. The differential parent-of-origin penetrance is proposed to reflect a maternal effect mediated by the production of anti-IgA antibodies tentatively linked to

IGAD1. This is supported by higher frequency of anti-IgA-positive females transmitting the disorder to children, in comparison with female IgAD nontransmitters, and by linkage data in the former group. Such pathogenic mechanisms may be shared by other MHC-linked complex traits associated with the production of specific autoantibodies, parental effects, and a particular MHC haplotype.

24. Congenital Adrenal Hyperplasia = CAH = **autosomal recessive**, 21-hydroxylase deficiency, caused by mutation in the cytochrome P450 21-hydroxylase gene (CYP21) on **chromosome 6p.** A group of autosomal recessively inherited disorders associated with a deficiency of one of the enzymes involved in cortisol biosynthesis, resulting in **elevation of ACTH levels, adrenal insufficiency** (also **increase in Melanocyte stimulating hormone =MSH → hyperpigmentation of skin**) and overproduction and accumulation of cortisol precursors proximal to the block; androgens are produced in excess, causing virilization. The most common disorder is the **21-hydroxylase deficiency**, caused by mutation in the cytochrome P450 21-hydroxylase gene (CYP21) on chromosome 6p. There are four major types with some clinical similarities but distinctive genetic and biochemical differences: 1) the salt-losing form = salt wasting , 2) the hypertensive form, 3) the simple virilizing form, and 4) the pseudohermaphrodite form. Congenital virilizing adrenal hyperplasia= Congenital Adrenal Hyperplasia (CAH) = **Autosomal recessive** (Kaplan OB, pg 5) (Kaplan peds, p 195) (CK p 102) (IM p 54) any inborn error of metabolism causing **hyperplasia of the adrenal cortex and overproduction of virilizing hormones**. Most forms are due to partial or complete **21-hydroxylase deficiencies**, leading to increased **ACTH production by the pituitary, stimulating adrenal growth and function**. Clinical features include **ambiguous external genitalia (= female pseudohermaphrodism = it means ovaries are present), enlarged clitoris (= clitoromegaly), virilization**, partial or complete fusion of the labia, and salt wasting. Patients may be male at birth with macrogenitosomia (= big genital and big body size) ; postnatally this is associated with **precocious puberty** (Kaplan IM, p 54). Congenital Adrenal hyperplasia is most commonly **due to 21-beta-hydroxylase deficiency**, leading to virilization of female from excessive buildup of androgens. Administration of **dexamethasone** to pregnant mother should be started no later than the 6th week

	of embryonal development. Chorionic Villous Sampling (CVS) at 10 weeks will determine fetal gender and if female, dexamethasone should be continued until birth. If the fetus is a male, dexamethasone can be stopped. The majority of cases of congenital adrenal hyperplasia are due to 21-hydroxylase deficiency, and most of these are the classic, salt-losing form. Due to a deficiency of the enzyme**, there is a block in the biosynthesis of cortisol and aldosterone**. Because of this, prior to the block there is buildup of the major substance, which is 17-hydroxyprogesterone and shunting of the pathways to androstenedione, which is then **converted to testosterone (→ get increase level of testosterone)**. The major effect of this is virilization in female fetuses. One generally finds clitoral enlargement, partial or complete labial fusion, and a urogenital sinus (vagina and urethra with common opening). If undiagnosed at birth (which would happen in a male), the baby develops progressive weight loss, weakness, vomiting, dehydration, hypoglycemia , hyperkalemia and hyponatremia, resulting in cardiac arrhythmias, shock and death. If untreated, affected patients develop further virilization after birth due to postnatal androgen excess-accelerated growth and skeletal maturation resulting in early epiphyseal closure and premature pubertal changes. Diagnosis is established by measuring 17-hydroxyprogesterone in the blood before and after stimulation with a cortisol derivative. The main goal of management in subsequent pregnancies is to prevent masculinization of affected female. Treatment of any at-risk pregnancy (= which there is a chance that baby might have 21-beta-hydroxylase deficiency) is to administer dexamethasone to the mother beginning no later than 6 weeks of gestation. Dexamethasone crosses the placenta and will suppress fetal adrenal steroid secretion and prevent masculinization. Chorionic Villous Sampling (CVS) is then performed to determine the genotype and therapy is continued (= keep giving Dexamethasone) if the fetus is female. Therapy is then continued until genetic analysis confirms the absence of abnormal genes. The mother must be followed carefully for steroid side effects. There is no deleterious effect on the unaffected fetus. Note: **female pseudohermaphrodism = it means ovaries are present) is due to Congenital adrenal hyperplasia and Male pseudohermaphrodism = it means testis are present) is due to 5-alpha reductase deficiency as one of its etiologies.** 25. Multiple sclerosis (MS) = common demyelinating disorder of the central nervous system, causing patches of sclerosis (plaques) in the brain and spinal cord; occurs

	primarily in young adults, and has protean clinical manifestations, depending upon the location and size of the plaque; typical symptoms include visual loss, diplopia, nystagmus, dysarthria, weakness, paresthesias, bladder abnormalities, and mood alterations; characteristically, the plaques are “separated in time and space” and clinically the symptoms show exacerbations and remissions. MRI of the brain will show areas of ventricular **plaques**. Syn: disseminated sclerosis, insular sclerosis. Genetic factors probably play some role in making a person susceptible to the disease process leading to multiple sclerosis. In particular, abnormalities in the **human leukocyte antigen (HLA) region located on chromosome 6** appear to be more prevalent among people with MS. Researchers theorize, however, that a combination of genes (not a single gene) is implicated in the development of MS, and the risk for someone inheriting all of these genetic factors is less than 5%. Advanced techniques called microarray technologies are now making it possible to scan hundreds of genes and identify those most likely to be contributors to MS. Genetic research may also pave the way for the development of new drugs to treat this disease. For example, researchers have recently identified the Olig1 gene as a key regulator in repairing damaged myelin-producing cells. In addition, increasing scientific evidence suggests that genetics may play a role in determining a person's susceptibility to multiple sclerosis. Some populations, such as Gypsies, Eskimos, and Bantus, never get multiple sclerosis. Native Indians of North and South America, the Japanese, and other Asian peoples have very low incidence rates. It is unclear whether this is due mostly to genetic or environmental factors. In Caucasian populations of Northern European descent, the **DR15 haplotype (DRB1*1501-DQA1*0102-DQB1*0602)** has been hypothesized to be the primary HLA genetic susceptibility factor for MS. Background **Female gender, human leukocyte antigen (HLA) DR2, tobacco smoking and Epstein-Barr virus (EBV)** are established risk factors for multiple sclerosis (MS). Results Anti-Epstein-Barr VCA immune globulin G levels were positively correlated with **female gender and HLA DR2**. Furthermore, current smoking and cumulative tobacco consumption were positively associated with EBV antibody levels. Conclusion The association between Epstein-Barr VCA antibody levels and non-viral MS risk factors support the view that EBV is critically involved in the etiology of MS. Please Note that the differential diagnosis for Multiple sclerosis is acute

	disseminated encephalomyelitis which is not a genetic disease. Acute disseminated encephalomyelitis (= A-Dem)= can be congenital or acquired. Often viral infection → inflammation of brain and spinal cord that damage myelin caused by viral infection or less often vaccination for measles, mumps or rubella. Acute disseminated encephalomyelitis is an acute demyelinating disorder of the central nervous system, in which focal demyelination is present throughout the brain and spinal cord. This process is common to postinfectious, postexanthem, and postvaccinal encephalomyelitis.
7	1. Cystic fibrosis = **autosomal recessive inheritance**, chromosome 7q , CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene (for chloride channel) (pg51) = a congenital metabolic disorder in which secretions of exocrine glands are abnormal; excessively viscid mucus causes obstruction of passageways (including pancreatic and bile ducts, intestines, and bronchi), and the sodium and chloride content of sweat are increased (= salty taste of sweat) throughout the patient's life; symptoms usually appear in childhood and include **meconium ileus**, poor growth despite good appetite (= Failure to Thrive = FTT), malabsorption and foul bulky stools (=**Steatorrhea** =Fatty stool) secondary to **pancreatic insufficiency, fat soluble vitamin deficiency (vitamin A,D,E,K)**, **nasal polyps, rectal prolapse** (Kaplan Peds, p 143), chronic bronchitis with cough, recurrent pneumonia, bronchiectasis, emphysema, clubbing of the fingers, and salt depletion in hot weather, patient will get **Hypochloremic alkalosis** if pt with CF get dehydration. Detailed genetic mapping and molecular biology have been accomplished by the methods of reverse genetics; **autosomal recessive inheritance**, caused by mutation in the cystic fibrosis conductance regulator gene (CFTR) on chromosome 7q. Syn: fibrocystic disease of the pancreas, mucoviscidosis, Clarke-Hadfield syndrome, viscidosis. 2. Russell-Silver syndrome = The genetic causes of Russell-Silver syndrome are complex. The disorder often results from the abnormal regulation of certain genes that control growth. Research has focused on genes located in particular regions of **chromosome 7 and chromosome 11**. Most cases of Russell-Silver syndrome are sporadic, which means they occur in people with no history of the disorder in their family. Less commonly, Russell-Silver syndrome can run in families. In some affected families, the condition appears to have an autosomal dominant pattern of inheritance.

	Defect in a **gene called the maternal uniparental disomy (UPD) for chromosome 7**. 3. CHARGE Association= CHARGE Syndrome (Kaplan Peds, p 130) = A constellation of congenital malformations (birth defects). The name of the condition is an acronym of some of the most frequent features: C = Coloboma (cleft) of the eye (80% of cases) and Cranial nerve abnormalities, H = Heart malformation (such as TOF, PDA), A = Choanal Atresia (= Atresia choanae= blockage of the nasal passageways) (58% of cases) (Kaplan Peds, p 130), R = Retardation of growth after birth (87% of cases) and Retardation of development (94% of cases), G = Genital hypoplasia (underdevelopment) in males (75% of cases) and urinary tract malformations, and E = Ear malformations and/or deafness (88% of cases). Most affected individuals with CHARGE syndrome have mutations involving the **chromodomain helicase DNA-binding protein-7 (CHD7; Gene map locus on chromosome 8q12.1)**. The phenotype can also be caused by mutation in the **semaphorin-3E gene (SEMA3E; Gene map locus on chromosome 7q21.11**). Pt has cyanosis (blue=cyanotic) but when cries turn pink. The best initial step to evaluate the Choanal Atresia is to insert a catheter through the nose, if the catheter cannot be passed from nose to oropharynx, the diagnosis of choanal atresia should be suspected but not yet confirmed. The diagnosis is confirmed by CT with intranasal contrast that shows narrowing of the posterior nasal cavity at the level of the pterygoid plate. Intubation via the oropharynx will provide immediate relief for the patient and surgery should then be performed for definitive correction. (Kaplan Peds, p 130). 4. Zellweger Syndrome = Cerebrohepatorenal Syndrome = a metabolic disorder with neonatal onset, characterized by distinctive facies, muscular hypotonia, hepatomegaly with jaundice, renal cysts, epiphyseal stippling of the patellae, cerebral dysmyelination, and neuronal migration defects and psychomotor retardation; there is a **perturbation in peroxisomal biogenesis (= absence of peroxisomes)**; autosomal recessive inheritance, caused by mutation in any one of several peroxin (PEX) genes on chromosome 6, 7, 8, or 12. 5. Saethre-Chotzen syndrome=condition characterized by craniosynostosis, asymmetry of skull (plagiocephaly), ptosis, prominent ear crus, and cutaneous syndactyly of fingers 2–3 and toes 3–4; autosomal dominant inheritance, caused by

mutation in the TWIST transcription factor gene on chromosome 7p. Syn: type III acrocephalosyndactyly, Chotzen syndrome

6. Leptin = A helical protein secreted by adipose tissue and acting on a receptor site in the ventromedial nucleus of the hypothalamus to curb appetite and increase energy expenditure **(increase leptin makes you become thin)** as body fat stores increase. Leptin levels are 40% higher in women, and show a further 50% rise just before menarche, later returning to baseline levels; levels are lowered by fasting and increased by inflammation. Human genes encoding both leptin **(locus 7q31.3)** and the leptin receptor site **(1p31)** have been identified. Laboratory mice having mutations on the ob gene, which encodes leptin, become morbidly obese, diabetic, and infertile; administration of leptin to these mice improves glucose tolerance, increases physical activity, reduces body weight by 30%, and restores fertility. Leptin (Greek leptos meaning thin) is a 16 kDa protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism. It is one of the most important adipose derived hormones. The Ob(Lep) gene (Ob for obese, Lep for leptin) is located on chromosome 7 in humans. [**Ghrelin levels increase before meals and decrease after meals**. **Ghrelin** is **considered the counterpart of the hormone leptin**, produced by adipose tissue, which induces satiation when present at higher levels. In some bariatric procedures, the **level of ghrelin is reduced in patients**, thus causing satiation before it would normally occur]. (Is this correct: increase ghrelin secretion and decrease leptin secretion make you fat. Because the function of ghrelin and leptin is opposite of each other??).
7. Dermatochalasis=A congenital or acquired condition characterized by deficient elastic fibers of the skin, which may hang in folds; vascular anomalies may be present; inheritance is either autosomal dominant or recessive, the latter sometimes in association with pulmonary emphysema and diverticula of the alimentary tract or bladder. The dominant form is caused by mutation in the elastin gene (ELN) on 7q. There is also an X-linked form that is due to mutation in the Menkes gene (MNK), encoding copper-transporting ATPase on Xq. Syn: cutis laxa , generalized elastolysis, loose skin.
8. Osteogenesis imperfecta type 2 (genetic p302) = Osteogenesis imperfecta (OI) = a group of connective tissue disorders of type I collagen, characterized by **bone**

	fragility, fractures on trivial trauma, skeletal deformity, blue sclerae, ligament laxity, and hearing loss. The Sillence system, which is a clinical, radiographic, and genetic classification, shows four types; inherited as autosomal dominant, caused by mutation in either the collagen type I alpha-1 gene (COL1A1) on chromosome 17q or the alpha-2 gene (COL1A2) on 7q. Syn: brittle bones 9. Supravalvar Aortic Stenosis Syndrome= Autosomal dominant inheritance; this is a contiguous gene deletion syndrome and one of the genes mutated is the elastin gene (ELN) on chromosome 7q. (genetics pg 344) 10. Argininosuccinicaciduria = (disorder of urea cycle)= deficiency of argininosuccinate lyase; Autosomal recessive inheritance, caused by mutation in argininosuccinate lyase gene (ASL) on chromosome 7q. (biochem p 252) 11. MODY = Maturity Onset Diabetes of the Young, mutation of glucokinase gene (GCK) , diabetogenic gene MODY on chromosome 7. 12. Greig Cephalopolysyndactyly Syndrome= an autosomal dominant disorder characterized by polysyndactyly of the hands and feet, macrocephaly, frontal bossing, hypertelorism, and flat nasal bridge, caused by mutation in the GLI3 gene on chromosome 7p13. 13. Refsum disease = a rare degenerative disorder due to a deficiency of phytanic acid α-hydroxylase; clinically characterized by **retinitis pigmentosa**, ichthyosis, demyelinating polyneuropathy, deafness, and cerebellar signs; autosomal recessive inheritance caused by mutation in the gene encoding phytanoyl-CoA hydroxylase (PAHX or PAYH) on chromosome 10p. Infantile Refsum disease is an impaired peroxisomal function with accumulation of phytanic acid, pipecolic acid; autosomal recessive inheritance, caused by mutation in the PEX 1 gene on 7q. Syn: heredopathia atactica polyneuritiformis, Refsum syndrome. 14. Pendred syndrome= characterized by congenital sensorineural hearing impairment with goiter (usually small) due to defective organic binding of iodine in the thyroid; afflicted individuals are usually euthyroid; autosomal recessive inheritance, caused by mutation in the Pendred syndrome gene (PDS) encoding pendrin on chromosome 7q. 15. Myotonia congenita = an uncommon muscle disorder, with onset in infancy or early childhood, characterized by muscle hypertrophy, myotonia, and a nonprogressive course; autosomal dominant inheritance; caused by mutations in the skeletal muscle chloride channel gene (CLCN1) on

	chromosome 7q. Syn: Thomsen disease 16. Distal Spinal Muscular Atrophy (SMA) with upper limb predominance = (chromosome 7, glycyl tRNA synthase). Due to mutation on **chromosome 7**, glycyl tRNA synthase gene. 17. Williams Syndrome = Elfin facies syndrome= supravalvar aortic stenosis-infantile hypercalcemia syndrome = Williams-Beuren syndrome (=WBS) = disorder characterized by distinctive facies with shallow supraorbital ridges, medial eyebrow flare, stellate patterning of the irises, small nose with anteverted nares, malar hypoplasia with droopy cheeks, full lips, **supravalvar aortic stenosis. Patient is friendly, talkative personality, hoarse voice, Elfin facies, prominent lips with open mouth, renal artery stenosis with hypertension, blue eyes, stellate patterns of eyebrows, joint limitation, hypercalcemia (increase calcium)** (Kaplan peds, p 250), neonatal hypocalcemia, mild mental retardation, and loquacious personality. **Autosomal dominant** inheritance; this is a contiguous **gene deletion** syndrome and one of the genes mutated is the elastin gene (ELN) on **chromosome 7q**. 18. CAVE complex = cerebroacrovisceral early lethality complex = Hall-Pallister syndrome = hypothalamic hamartoblastoma syndrome = PHS = Pallister-Hall syndrome =is a disorder that affects the development of many parts of the body. Most people with this condition have extra fingers and/or toes (polydactyly), and the skin between some fingers or toes may be fused (cutaneous syndactyly). An abnormal growth in the brain called a hypothalamic hamartoma is characteristic of this disorder. In many cases, these growths do not cause any medical problems; however, some hypothalamic hamartomas lead to seizures or hormone abnormalities that can be life-threatening in infancy. Other features of Pallister-Hall syndrome include a malformation of the airway called a bifid epiglottis, an obstruction of the anal opening (imperforate anus), and kidney abnormalities. Although the signs and symptoms of this disorder vary from mild to severe, only a small percentage of affected people have serious complications. **Mutations in the GLI3 (Greig cephalopolysyndactyly syndrome) gene in chromosome 7**, cause Pallister-Hall syndrome. The GLI3 gene provides instructions for making a protein that controls gene

	expression, which is a process that regulates whether genes are turned on or off in particular cells. By interacting with certain genes at specific times during development, the GLI3 protein plays a role in the normal shaping (patterning) of many organs and tissues before birth. Mutations that cause Pallister-Hall syndrome typically lead to the production of an abnormally short version of the GLI3 protein. Unlike the normal GLI3 protein, which can turn target genes on or off, the short protein can only turn off (repress) target genes. Researchers are working to determine how this change in the protein's function affects early development. It remains uncertain how GLI3 mutations can cause polydactyly, hypothalamic hamartoma, and the other features of Pallister-Hall syndrome. This condition is inherited in **an autosomal dominant** pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder. In some cases, an affected person inherits a mutation in the GLI3 gene from one affected parent. Other cases result from new mutations in the gene and occur in people with no history of the disorder in their family. People with Pallister- Hall syndrome get gelastic seizures. 19. Familial goiter = a group of heritable thyroid disorders in which goiter is commonly apparent first during childhood; often associated with skeletal and/or mental retardation, and with other signs of hypothyroidism that may develop with age. Various types of familial goiter have been identified: 1) iodide transport defect ; of autosomal recessive inheritance caused by mutation in the sodium iodide symporter gene (SLC5A5) on 19p, in which the gland is unable to concentrate iodide; 2) organification defect , in which the iodination of tyrosine is defective; 3) Pendred syndrome ; autosomal recessive inheritance caused by mutation in the Pendred syndrome gene (PDS) on 7q; 4) coupling defect, in which cretinism results from defective coupling of iodotyrosines to form iodothyronine ; 5) iodotyrosine deiodinase defect, in which deiodination of iodotyrosine is defective, considerable glandular loss of these hormonal precursors occurs, and cretinism may be present 6) plasma iodoprotein disorder , in which an abnormal iodinated serum protein that is insoluble in acidic butanol is present; 7) hereditary hyperthyroidism.
8	1. C-myc oncogene → tumor is growing crazy (pg 83) 2. C-myc over expression and C-myc activation→ tumor is growing crazy = Burkitt lymphoma = small non cleaved lymphoma (pg 83,212, 218). 3. Hereditary multiple exostoses (HME) = Hereditary multiple exostoses (HME) is a rare medical condition in

	which multiple bony spurs or lumps (also known as exostoses, or osteochondromas) develop on the bones of a child. HME is synonymous with Multiple hereditary exostoses and Multiple osteochondromatosis. HME can cause pain to people of all ages. To children, this can be especially painful. HME is an **autosomal dominant** hereditary disorder. HME has thus far been linked with mutations in three genes. 1) **EXT1 which maps to chromosome 8q24.1** 2) **EXT2 which maps to 11p13** 3) **EXT3 which maps to the short arm of Chromosome 19** (though its exact location has yet to be precisely determined). 4. Human insulin receptor substrate-1 gene (IRS1): chromosomal localization to **chromosome 2 (2q35-q36.1)** and identification of a simple tandem repeat DNA polymorphism2) The human IRS-1 gene contains the entire 5'-untranslated region and protein coding region in a single exon and was localized on **chromosome 2 q36-37** by in situ hybridization. 3) IRS1 insulin receptor substrate 1 Gene on **Chromosome 13.** 4) The IRS-2 Gene on Murine **Chromosome 8** Encodes a Unique Signaling Adapter for Insulin and Cytokine Action. Insulin receptor substrate-1 = a cytoplasmic protein that is a direct substrate of the activated insulin receptor kinase. Insulin exposure results in its rapid phosphorylation at multiple tyrosine residues. Its phosphorylated sites associate with high affinity to certain cellular proteins. IRS-1 thus acts as an adaptor molecule that links the receptor kinase to various cellular activities regulated by insulin. IRS-1 is also phosphorylated after stimulation by insulinlike growth factor-1 and several interleukins. 5. Trisomy 8 syndrome= the full trisomy 8 is usually associated with early lethality, but most affected individuals are mosaic with craniofacial dysmorphism; short, wide neck; narrow cylindrical trunk; multiple joint and digital abnormalities; and deep creases of the palms and soles. 6. CHARGE association=A constellation of congenital malformations (birth defects). The name of the condition is an acronym of some of the most frequent features: C = Coloboma (cleft) of the eye (80% of cases) and Cranial nerve abnormalities, H = Heart malformation, A = Choanal Atresia (blockage of the nasal passageways) (58% of cases), R = Retardation of growth after birth (87% of cases) and Retardation of development (94% of cases), G = Genital hypoplasia (underdevelopment) in males (75% of cases) and

	urinary tract malformations, and E = Ear malformations and/or deafness (88% of cases). Most affected individuals with CHARGE syndrome have mutations involving the **chromodomain helicase DNA-binding protein-7 (CHD7; Gene map locus on chromosome 8q12.1)**. The phenotype can also be caused by mutation in the **semaphorin-3E gene (SEMA3E; Gene map locus on chromosome 7q21.11).** 7. Familial Benign neonatal convulsions = a familial, self-limited epilepsy, beginning at 2, 3, or 6 days of age and resolving spontaneously by six months of age; **autosomal dominant inheritance**. The familial benign neonatal convulsion is linked to **chromosome 8 and chromosome 20**. 8. Sanfilippo Syndrome= Mucopolysaccharidosis III =MPS-III= an error of the mucopolysaccharide metabolism, with excretion of large amounts of heparan sulfate in the urine; characterized by severe mental retardation with hepatomegaly; skeleton may be normal or may present mild changes similar to those in Hurler syndrome; several different types (A, B, C, and D) have been identified according to the enzyme deficiency; autosomal recessive inheritance. Syn: type III mucopolysaccharidosis. (Hunter syndrome is one of the disease of mucopolysaccharidosis which is X-linked recessive, other examples are hurler and Sanfilippo that are autosomal recessive) (Kaplan peds, p225). Sanfilippo syndrome is a rare **autosomal recessive** lysosomal storage disease caused by a deficiency in one of the enzymes needed to break down the glycosaminoglycan heparan sulfate (which is found in the extra-cellular matrix and on cell surface glycoproteins). Although undegraded heparan sulfate is the primary stored substrate, glycolipids such as gangliosides are also stored despite no genetic defect in the enzymes associated with their breakdown. The four types of MPS-III are due to specific enzyme deficiencies affecting the breakdown of heparan sulfate, which then builds up in various organs. **All four types have autosomal recessive inheritance**. 3) Sanfilippo syndrome type-C = MPS-III type-C: deficiency in enzyme acetyl-CoA:alpha-glucosaminide acetyltransferase , gene location on **chromosome 8p11- q13** 9. Zellweger Syndrome = Cerebrohepatorenal Syndrome = a metabolic disorder with neonatal onset, characterized by distinctive facies, muscular hypotonia, hepatomegaly with jaundice, renal cysts, epiphyseal stippling of the patellae, cerebral dysmyelination, and neuronal

migration defects and psychomotor retardation; there is a **perturbation in peroxisomal biogenesis** (= **absence of peroxisomes**); autosomal recessive inheritance, caused by mutation in any one of several peroxin (PEX) genes on chromosome 6, 7, 8, or 12.

10. Werner syndrome = a prematurely aging disorder consisting of scleroderma-like skin changes, bilateral juvenile cataracts, progeria, hypogonadism, and diabetes mellitus; autosomal recessive inheritance, caused by mutation in the WRN gene, which encodes a helicase protein on chromosome 8p.
11. Burkitt lymphoma = a form of malignant lymphoma reported in African children, frequently involving the jaw and abdominal lymph nodes. Geographic distribution of Burkitt lymphoma suggests that it is found in areas with endemic malaria. It is primarily a B-cell neoplasm and is believed to be caused by Epstein-Barr virus, a member of the family *Herpesviridae*, which can be isolated from tumor cells in culture; occasional cases of lymphoma with similar features have been reported in the United States. t (8,14) Burkitt lymphoma caused by Epstein Barr virus (EBV) (translocation juxtaposes c- myc oncogene near the active immunoglobulin genes in infected cell) (genetics pg 341) (micro pg 402). Burkitt's lymphoma = common variant t (8,14) (q24, q32), involving the oncogene myc on chromosome 8 and the heavy immunoglobulin chain on chromosome 14.
12. The other two variants of Burkitt lymphoma are t (8,22) (q24, q11) involving myc and the lambda light chain immunoglobulin site and t (2,8)(p12, 24) involving the kappa light chain and myc.
13. t (8,21) translocation is seen in M2 leukemia, also known as acute myeloid leukemia (AML) with maturation and some M4 (AML with granulocytic and monocytic maturation).
14. Trisomy 8 is one of the rare causes of live birth. (genetic p 334)
15. Pfeiffer syndrome= disorder characterized by broad, short thumbs and great toes, often with duplication of the great toes, and variable syndactyly of the digits; craniosynostosis is a variable feature. Autosomal dominant inheritance caused by mutation in the fibroblast growth factor receptor 1 gene (FGFR1) on chromosome 8p or FGFR2 gene on 10q. Syn: type V acrocephalosyndactyly, Noack syndrome.
16. Type I familial hyperlipoproteinemia = familial hyperchylomicronemia = familial fat-induced

	hyperlipemia = idiopathic hyperlipemia = familial hypertriglyceridemia(1) = Bürger-Grütz syndrome = **Autosomal recessive inheritance**; caused by mutation in the lipoprotein lipase gene (LPL) on chromosome 8p. hyperlipoproteinemia characterized by the presence of large amounts of chylomicrons and triglycerides in the plasma when the patient has a normal diet, and their disappearance on a fat-free diet; low α- and β-lipoproteins on a normal diet, with increase on a fat-free diet; decreased plasma postheparin lipolytic activity; and low tissue lipoprotein lipase activity. It is accompanied by bouts of abdominal pain, hepatosplenomegaly, pancreatitis, and eruptive xanthomas; autosomal recessive inheritance; caused by mutation in the lipoprotein lipase gene (LPL) on chromosome 8p. See Also: familial lipoprotein lipase inhibitor. 17. Hereditary multiple exostoses = dominant inheritance with genetic heterogeneity of which some cases are due to mutation in the exostosis-1 gene (EXT1) on 8q. 18. Hereditary spherocytosis = Autosomal dominant inheritance, caused by mutation in the ankyrin gene (ANK1) on 8p. However, as with elliptocytosis, there is an autosomal recessive form , caused by mutation in the alpha-spectrin 1 gene (SPTA1) on chromosome 1q.
9	1. Asthma = Linkage to **asthma** on chromosome **2q**. (near the IL-1 family cluster), **6p, 9, and 12q**. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. The search for genes in asthma has now led to several locations on the genome, including genes on **chromosome 5, 11 and 12**. Like the Fc epsilon receptor for IgE on chromosome 11 and the cluster of cytokines on chromosome 5q. 2. Friedreich ataxia = hereditary spinal ataxia = heredoataxia = a neurologic disorder characterized by **ataxia, dysarthria, dysarthric speech, nystagmus**, **scoliosis**, high-arched foot or pes cavus, **hammer toes, kyphoscoliosis** and other skeletal deformities and paralysis of the muscles, especially of the lower extremities, **absent deep tendon reflexes (= absent DTRs)**; onset usually in childhood or youth with **sclerosis** of the **posterior and lateral columns of the spinal cord (get loss of vibration and position sense)**; autosomal recessive inheritance, caused by mutation involving trinucleotide repeat expansion in Friedreich ataxia gene (FRDA) on chromosome 9q (9q13- q21.1). Friedreich

	ataxia is caused by expended "**GAA**" triplet repeats in the **Frataxin gene**. Frataxin is a mitochondrial protein involved in iron hemostasis (Kaplan Peds, p 223). Friedreich ataxia (9q), autosomal recessive, triple nucleotide repeat of " GAA expansion" on Frataxin gene = Friedreich ataxia gene (FRDA) gene on chromosome 9q. Associated with ataxia and severe dysarthria and loss of reflexes, spasticity.(pg308) 3. Dandy-Walker syndrome = developmental anomaly of the fourth ventricle associated with atresia of the foramina of Luschka and Magendie that results in cerebellar hypoplasia, hydrocephalus, and posterior fossa cyst formation. The etiology is heterogenous, and familial occurrence also has been reported. A few cases resulting from autosomal recessive genes. An unusual case of an infant with both Ellis-van Creveld and dandy-walker syndromes and with homozygosity for an unusually long heterochromatic segment of the long arm of chromosome 9 (9qh+) was reported. (www.emedine.com/Radio/topic206.htm) . Dandy Walker malformation refers to a constellation of anomalies that include an abnormally large posterior fossa, absence of cerebellar vermis, and development of a large, ependyma-lined cyst that represents an expend 4th ventricle. 4. Familial Dysautonomia= Riley-Day syndrome = a congenital syndrome with specific disturbances of the nervous system and aberrations in autonomic nervous system function such as indifference to pain, diminished lacrimation, poor vasomotor homeostasis, motor incoordination, labile cardiovascular reactions, hyporeflexia, frequent attacks of bronchial pneumonia, hypersalivation with aspiration and difficulty in swallowing, hyperemesis, emotional instability, and an intolerance for anesthetics; **autosomal recessive inheritance**. Mapped to human chromosome 9q31–q33. Riley- Day syndrome seen in Ashkenazi Jewish ancestry, characterized by gross dysfunction of the autonomic nervous system with severe **orthostatic hypotension**. 5. Oculocutaneous albinism=a disorder characterized by deficiency of pigment in skin, hair, and eyes, photophobia, nystagmus, and decreased visual acuity; there are two groups: tyrosinase-negative in which there is absence of tyrosinase, and tyrosinase-positive in which normal tyrosinase cannot enter pigment cells; the compound heterozygote is normal so the two forms are not allelic. There are several forms of autosomal recessive inheritance: **Oculocutaneous albinism type 1 (= OCA 1)** = type IA is characterized by congenital and lifelong full body depigmentation, absence of tyrosinase

	with life-long complete absence of melanin, marked photophobia, and nystagmus, caused by **mutation in the tyrosinase gene (TYR)** on chromosome 11q. Type II has normal tyrosinase activity and is the most common; hair darkens and nevi and freckles develop; caused by mutation in the oculocutaneous albinism gene (OCA2) on 15q. Type III is characterized by absent tyrosinase but pigmentation of the iris in the first decade; caused by mutation in the tyrosine-related protein-1gene (TYRP1) on 9p. Type IV is found in Africans with normal tyrosinase and type V is associated with red hair. Type VI is synonymous to Hermansky-Pudlak syndrome , with low to absent tyrosinase and hemorrhage due to platelet deficiency, caused by mutation in the Hermansky-Pudlak gene (HPS) on 10q. 6. Nail-Patella Syndrome= a skeletal disorder characterized by absence or hypoplasia of the patella, iliac horns, dysplasia of the fingernails and toenails, and thickening of the glomerular lamina densa; the lower ends of the femur have a shape very similar to **Erlenmeyer flask deformity**; **autosomal dominant inheritance**, caused by mutation in the gene encoding LIM-homeodomain protein (LMX1B) on chromosome 9q. 7. C-abl (oncogene) for Philadelphia chromosome in CML (chronic myelogenous leukemia) (pg226) → t (9, 22) = chronic myelogenous leukemia (genetic pg 341), have Abl-BCR hybrid (bcr-c-abl) 8. p-16 (= p16) tumor suppressor gene = Familial Malignant Melanoma (pg 319) = Familial Melanoma Syndrome = most likely associated with a germline mutation in the cyclin-dependent kinase inhibitor 2A (**CDKN2A**) gene , also know as p16INK4/P14ARF. This diagnosis is supported by the fact that patient is diagnosed with melanoma and have significant family history of melanoma and **presence of pancreatic cancer in sibling** (= cancer of pancreas) which is also the other major malignancy commonly associated with this mutation. Those with the CDKN2A mutation are also more likely to develop melanoma at a much earlier age (20's-30's). The proteins coded for by CDKN2A are **tumor supressor genes** that serve as checkpoint in the cell cycle. Loss of function of these proteins (loss of heterozygosity) lead to unchecked cellular proliferation. Familial Melanoma is associated with germline mutations in tumor suppressor genes such as CDKN2A. A loss of heterozygosity (=LOH) or a "second hit" will lead to tumorigenesis. Germline CDKNA2A mutations are also

	associated with an increased risk of pancreatic cancer. 9. t (6,9) translocation is found in subtypes of AML with basophilia (M1, M2, M4) 10. Citrullinemia (Urea cycle disorder) deficiency of arginosuccinate synthetase (ASS); autosomal recessive inheritance, caused by mutation in the ASS gene on chromosome 9 in some patient. (biochem pg 252) 11. Ehlers-Danlos syndrome (EDS) = autosomal dominant, caused by mutation in one of the following genes: the collagen V alpha-1 gene (COL5A1) on chromosome 9q or the collagen V alpha-2 gene (COL5A2) on 2q or COL3A1 gene on 2q. (Kaplan peds, p 252) 12. Hereditary fructose intolerance = Autosomal recessive inheritance caused by mutation in aldolase B gene (ALDOB) on chromosome 9q. 13. Hereditary Hemorrhagic Telangiectasia (HHT) = Rendu-Osler-Weber Syndrome = hereditary telangiectasia = Osler-Weber- Rendu Syndrome = **Autosomal dominant** inheritance, caused by mutation in the gene (ENG) encoding endoglin on chromosome 9q = a disease with onset usually after puberty, marked by multiple small **telangiectases and dilated venules that develop slowly on the skin and mucous membranes; the face, lips, tongue, nasopharynx, and intestinal mucosa** are frequent sites, and **recurrent bleeding, epistaxis** may occur. Acute gastrointestinal bleeding is usually treated with hemodynamic stabilization of the patient followed by endoscopic ablation therapy. Patients develop **pulmonary AVM** (Arteriovenous malformation) associated with **hemoptysis, right to left shunt**, causing **chronic hypoxia, finger clubbing** and **reactive polycythemia**. Osler-weber-Rendu syndrome also know as hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant fibrovascular dysplasia in which vascular lesions (telangiectasis, arteriovenous malformation (AVM) and aneurysms, patient gets multiple rectal bleed and epistaxis) are found through the body particularly tin the lungs, brain and gastrointestinal tract. 14. Hereditary Inclusion Body Myopathies = Another type of HIBM (Hereditary Inclusion Body Myopathies), inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD), is linked to a slightly different gene on chromosome 9 (located at 9p13-p12). d). Another type of HIBM (Hereditary Inclusion Body Myopathies), inclusion body myopathy-3 (IBM3) is linked to mutations in a gene encoding myosin heavy chain II proteins

on chromosome 17 (located at 17p13.1).

15. Tuberous sclerosis = Bourneville disease= epiloia= TSC1 is the gene responsible for tuberous sclerosis. phacomatosis characterized by the formation of multisystem hamartomas producing seizures, mental retardation, and **angiofibromas (= fibroangioma = adenoma sebaceum)** of the face; the cerebral and retinal lesions are glial nodules; other skin lesions are hypopigmented macules, shagreen patches, and periungual fibromas; autosomal dominant inheritance with variable expression, caused by mutation in either the tuberous sclerosis Complex gene **(T9SC1)** which encodes for protein hamartin on **chromosome 9q (9q34)** or **TSC2** which encodes for protein tuberin on **chromosome 16 (16p13.3)**. (Kaplan peds, p232). TSC2 is contiguous with PKD1 , the gene involved in one from of polycystic kidney disease (PKD). Gross deletions affecting both genes may account for the 2% of individuals with TSC who also develop PKD in childhood. Spontaneous pneumothorax happens in people with tuberous sclerosis.
16. Leigh disease =subacute encephalomyelopathy affecting infants, causing seizures, spasticity, optic atrophy, and dementia; the genetic causation is heterogeneous; may be associated with deficiency of cytochrome c oxidase or NADH-ubiquinone oxidoreductase or other enzymes involved in energy metabolism. Autosomal recessive, X-linked recessive and mitochondrial inheritance have been described; mutations have been identified in the surfeit-1 gene (SURF) on chromosome 9, in a mtDNA-encoded subunit of ATP synthase , in the X-linked E1-alpha subunit of pyruvate dehydrogenase , and in several subunits of mitochondrial complex I . Syn: necrotizing encephalomyelopathy , necrotizing encephalopathy.(path, p50)
17. Basal cell nevus = a hereditary disease noted in infancy or adolescence, characterized by lesions of the eyelids, nose, cheeks, neck, and axillae, appearing as uneroded flesh-colored papules, some becoming pedunculated, and histologically indistinguishable from basal cell epithelioma; also noted are punctate keratotic lesions of the palms and soles; the lesions usually remain benign, but in some cases ulceration and invasion occur and are evidence of malignant change; autosomal dominant inheritance; caused by mutation in the human PTCH, the homolog of the “patched gene” of *Drosophila*. PTCH is found on chromosome 9q22. Basal cell nevus syndome a genetic form of BCC is associated with a

	mutation in the PTCH gene [=Patched (Drosophila) homolog (nevoid basal cell carcinoma syndrome) on chromosome 9q22.3] 18. Basal cell nevus syndrome= Gorlin syndrome = a syndrome of myriad basal cell nevi with development of basal cell carcinomas in adult life, odontogenic keratocyst, erythematous pitting of the palms and soles, calcification of the cerebral falx, and frequently skeletal anomalies, particularly ribs that are bifid or broadened anteriorly; **autosomal dominant inheritance**, caused by mutation in the PTCH gene, the human homolog of the "patched" gene of Drosophila on 9q. The PTCH gene codes for the receptor for the sonic hedgehog signaling protein in basal keratinocytes, it functions as a tumor suppressor gene. Inherited defect in the PTCH gene cause the basal cell nevus syndrome (Gorlin syndome) a disease characterized by multiple basal cell carcinomas, among other features. 19. PTCH gene codes for the receptor for the sonic hedgehog signaling protein in basal keratinocytes, it functions as a tumor supressor gene. Inherited defect in the PTCH gene cause the basal cell nevus syndrome (Gorlin syndome) a disease characterized by multiple basal cell carcinomas, among other features. 20. Galactosemia= An inborn error of galactose metabolism due to congenital deficiency of the enzyme galactosyl-1-phosphate uridylyltransferase (= **galactose 1-phospahte uridyl transferase deficiency**), resulting in tissue accumulation of galactose 1-phosphate; manifested by nutritional failure, hepatosplenomegaly with cirrhosis, cataracts (and **congenital cataract**), mental retardation, galactosuria, aminoaciduria, and albuminuria that regress or disappear if galactose is removed from the diet; autosomal recessive inheritance; caused by mutation in the galactose-1-phosphate uridyltransferase gene (GALT) on 9p. See Also: galactokinase deficiency. (Kaplan Peds, p 6) 21. Nonketotic hyperglycinemia= an inborn error of glycine metabolism, due to a deficiency of glycine dicarboxylase P protein (GCSP), a component of glycine cleavage system; characteristically overwhelming disease in the newborn period, with coma, seizures and death, or, less often, gradual onset with failure to thrive, focal seizures, and mental retardation; there is massive elevation of plasma glycine, with increased levels in cerebrospinal fluid and urine; plasma hyperosmolality, severe dehydration occur without ketoacidosis; autosomal recessive inheritance; caused

	by mutation in the GCSP ***gene*** on chromosome 9p. 22. Cartilage-hair hypoplasia= a skeletal dysplasia prevalent among the Amish, characterized by short-limb dwarfism, sparse, light-colored hair, T-cell immunologic defect rendering them susceptible to infections, and radiographic findings of metaphyseal dysplasia. Autosomal recessive inheritance, the gene maps to 9p. Syn: McKusick metaphyseal dysplasia.
10	1. Multiple endocrine neoplasia 2 = MEN 2= Sipple syndrome = RET oncogene mutation on chromosome (10q, 11.2) , missense mutations on chromosome 1 (pg263),), (1st aid surgery, p 153). Multiple endocrine neoplasia syndrome, type 2A= multiple endocrine neoplasia, type 2A = an **autosomal-dominant** predisposition to tumors of thyroid C cells (medullary carcinoma), adrenal medulla (pheochromocytoma), and nodular hyperplasia of parathyroid glands. Sipple syndrome = pheochromocytoma, medullary carcinoma of the thyroid, and parathyroid adenomas; autosomal dominant inheritance, caused by mutation in the R**ET oncogene on chromosome 10q** . 2. 17-hydroxylase deficiency syndrome= congenital deficiency of adrenocortical, and possibly ovarian, steroid C-17α-hydroxylase; the resulting excessive secretion of corticosterone and deoxycorticosterone produces amenorrhea, ambiguous genitalia, hypertension, and hypokalemic alkalosis; autosomal recessive inheritance caused by mutation in one of the cytochrome P450 genes (CYP17) on chromosome 10q. 3. A 2005 study published in the American Journal of Human Genetics found a link between endometriosis and chromosome 10q26. 4. Cornelia de Lange Syndrome aka CdLS is a little known genetic disorder that can lead to severe developmental anomalies. It affects both the physical and intellectual development of a child. genes responsible for **CdLS** are: **NIPBL on Chromosome 5**, a second gene— **SMC1A on the X chromosome**— and **gene SMC3 is on chromosome 10**. The latter two genes(on chromosome X and chromosome 10) seem to correlate with a milder form of the syndrome. The vast majority of cases are due to spontaneous mutations, although the defected gene can be

	inherited from either parent, making it **autosomal dominant**. 5. Multiple endocrine neoplasia Type 3 = multiple endocrine neoplasia 2B = MEN type 3 (=2b) on (10q, 11.2) , syndrome characterized by tumors found in MEN2, tall, thin habitus, prominent lips, and neuromas of the tongue and eyelids; autosomal dominant inheritance, caused by mutation in the RET oncogene on 10q (pg 263), (1st aid surgery, p 153) 6. Refsum disease = a rare degenerative disorder due to a deficiency of phytanic acid α-hydroxylase; clinically characterized by retinitis pigmentosa, ichthyosis, demyelinating polyneuropathy, deafness, and cerebellar signs; autosomal recessive inheritance caused by mutation in the gene encoding phytanoyl-CoA hydroxylase (PAHX or PAYH) on chromosome 10p. Infantile Refsum disease is an impaired peroxisomal function with accumulation of phytanic acid, pipecolic acid; autosomal recessive inheritance, caused by mutation in the PEX 1 gene on 7q. Syn: heredopathia atactica polyneuritiformis, Refsum syndrome 7. Oculocutaneous albinism=a disorder characterized by deficiency of pigment in skin, hair, and eyes, photophobia, nystagmus, and decreased visual acuity; there are two groups: tyrosinase-negative in which there is absence of tyrosinase, and tyrosinase-positive in which normal tyrosinase cannot enter pigment cells; the compound heterozygote is normal so the two forms are not allelic. There are several forms of autosomal recessive inheritance: type IA is characterized by absence of tyrosinase with life-long complete absence of melanin, marked photophobia, and nystagmus, caused by mutation in the tyrosinase gene (TYR) on chromosome 11q. Type II has normal tyrosinase activity and is the most common; hair darkens and nevi and freckles develop; caused by mutation in the oculocutaneous albinism gene (OCA2) on 15q. Type III is characterized by absent tyrosinase but pigmentation of the iris in the first decade; caused by mutation in the tyrosine-related protein-1gene (TYRP1) on 9p. Type IV is found in Africans with normal tyrosinase and type V is associated with red hair. Type VI is synonymous to Hermansky-Pudlak syndrome , with low to absent tyrosinase and hemorrhage due to platelet deficiency, caused by mutation in the Hermansky-Pudlak gene (HPS) on 10q.

	8. Gyrate atrophy of choroid and retina= a slowly progressive atrophy of the choriocapillaris, pigmentary epithelium, and sensory retina, with irregular confluent atrophic areas and an associated ornithinuria; autosomal recessive inheritance; due to a deficiency of ornithine, -aminotransferase, caused by mutation in the ornithine ,-aminotransferase gene (OAT) on chromosome 10q. 9. Metachromatic leukodystrophy = MLD = a metabolic disorder, with onset usually in the second year of life and death often before 5 years, with loss of myelin and accumulation of metachromatic lipids (galactosyl sulfatidates) in the white matter of the central and peripheral nervous systems leading to motor symptoms, paralysis, convulsions, and progressive cerebral deterioration**. Autosomal recessive** inheritance, caused by mutation in either the **arylsulfatase A gene (ARSA) on 22q** or the **prosaposin gene (PSAP) on 10q**. (Kaplan Peds, p 225) 10. Apert syndrome = type I acrocephalosyndactyly = disorder characterized by craniosynostosis and syndactyly of all the fingers and usually the toes as well; the thumbs are free; mental retardation is a variable feature. **Autosomal dominant** mutation with most cases sporadic, caused by mutation in the **fibroblast growth factor receptor 2 gene (FGFR2) on 10q**. Apert's syndrome include craniosynostosis of the coronal sutures with brachycephaly of the calvarium, **maxillary hypoplasia**, and a depressed nasal bridge , in addition to polydactyly and syndactyly involving both the hands and feet. **(Don't mix Apert syndrome (chromosome 10q) with Alport syndrome (x-liked, chromosome 2q)**. 11. Congenital erythropoietic porphyria = enhanced porphyrin formation by erythroid cells in bone marrow, leading to severe porphyrinuria, often with hemolytic anemia and persistent cutaneous photosensitivity; caused by a deficiency of uroporphyrinogen III cosynthetase; **autosomal recessive** inheritance, caused by mutation in the uroporphyrinogen III synthase **gene (UROS) on chromosome 10q**; there is an overproduction of type I porphyrin isomers. 12. **Dubin-Johnson syndrome= chronic idiopathic jaundice =** an inherited defect in hepatic excretory function characterized by jaundice with levels of serum bilirubin up to about 6 mg/dL, over half of

	which is **conjugated bilirubin (= Direct Bilirubin)**, and excretion of **abnormal proportions of coproporphyrin I** in urine (but Kaplan Q bank says Rotor syndrome produces **coproporphyrin** in the urine and Dubin-Johnson syndrome dose NOT produce **coproporphyrin** in the urine???). There is also retention of a **dark pigment in the hepatocytes** that is derived either from **melanin or catecholamines**, but otherwise liver histology is normal. Oral cholecystogram fails to visualize the gallbladder, and excretion of test substances (e.g., bromosulfothalein) by the liver is abnormal. The basic defect is apparently in canalicular transport. **No therapy is necessary**; **autosomal recessive inheritance** caused by mutation in the canalicular multispecific organic anion transporter gene (CMOAT) on 10q. In Dubin Johnson syndrome get increase in **conjugated bilirubin**. **Jaundice in these patients gets exacerbated by infections, pregnancy, and birth control pills**. Biopsy reveals black pigmentation in hepatocyte (=black liver). Reassurance alone is the appropriate management (CK p 139). Get **conjugated hyperbilirubinemia** with Dubin- Johnson syndrome. **(Conjugated bilirubin is insoluble in water and is bound to albumin and can NOT be filtered by the glomerulus and there for is not excreted in the urine. Unconjugated bilirubin is water soluble and in case of unconjugated hyperbilirubinemia can be excreted from the body in the urine through kidneys)** 13. **Crouzon syndrome = Crouzon disease = craniofacial dysostosis** = craniosynostosis with broad forehead, ocular hypertelorism, exophthalmos, beaked nose, and hypoplasia of the maxilla; autosomal dominant inheritance, caused by mutation in the fibroblast growth factor receptor 2 gene (FGFR2) on chromosome 10q. Crouzon syndrome with acanthosis nigricans is due to mutation in the fibroblast growth factor receptor 3 gene (FGFR3) on 4p. 14. **Pfeiffer syndrome=** disorder characterized by broad, short thumbs and great toes, often with duplication of the great toes, and variable syndactyly of the digits; craniosynostosis is a variable feature. Autosomal dominant inheritance caused by mutation in the fibroblast growth factor receptor 1 gene (FGFR1) on chromosome 8p or FGFR2 gene on 10q. Syn: type V acrocephalosyndactyly, Noack syndrome. 15. Cowden disease= multiple hamartoma

	syndrome = genetic disease, **autosomal dominant due to mutation in the PTEN gene on chromosome 10** (Kaplan IM, p 21)**,** associated with breast cancer (1st aid surgery, p 143) = hypertrichosis and gingival fibromatosis from infancy, accompanied by postpubertal fibroadenomatous breast enlargement; papules of the face are characteristic of multiple trichilemmomas. = is another polyposis syndrome with hamartomas that gives only a very slightly increased risk of colon cancer compared with general population. These polyposis syndrome can present with rectal bleeding in a child (Kaplan IM, p 21). Cowden syndrome is associated with breast cancer, thyroid cancer, and nodular gingival hyperplasias (from USMLE world Q bank)**.** Oral Papillomas and palmar pits occur together with hamartomatous polyps of the GI tract with little risk for malignant transformation in Cowden Syndrome, an **autosomal dominant** condition resulting form **mutation in the PTEN gene on chromosome 10**. **PTEN [=PTEN (phosphatase and tensin homolog deleted on chromosome 10)]** is a tumor suppressor gene located on chromosome 10q23.Mutation of this gene results in the multiple hamartoma syndrome (Cowden disease), characterized by the development of trichilemmomas, oral mucous papillomas, acral keratoses, breast cancer in women, and medullary carcinoma of the thyroid in both men and women. 16. Cholesterol ester storage disease= a lipidosis caused by a deficiency of lysosomal acid lipase activity resulting in widespread accumulation of cholesterol esters and triglycerides in viscera with xanthomatosis, adrenal calcification, hepatosplenomegaly, foam cells in bone marrow and other tissues, and vacuolated lymphocytes in peripheral blood; autosomal recessive inheritance, caused by mutation in the lysosomal acid lipase gene (LIPA) on chromosome 10q. Syn: cholesteryl ester storage disease, Wolman disease, Wolman xanthomatosis.
11	1. Tyrosinase negative oculocutaneous albinism (p153) 2. Hereditary multiple exostoses (HME) = Hereditary multiple exostoses (HME) is a rare medical condition in which multiple bony spurs or lumps (also known as exostoses, or osteochondromas) develop on the bones of a child. HME is synonymous with Multiple hereditary

	exostoses and Multiple osteochondromatosis. HME can cause pain to people of all ages. To children, this can be especially painful. HME is an **autosomal dominant** hereditary disorder. HME has thus far been linked with mutations in three genes. 1) **EXT1 which maps to chromosome 8q24.1** 2) **EXT2 which maps to 11p13** 3) **EXT3 which maps to the short arm of Chromosome 19** (though its exact location has yet to be precisely determined). 3. Laurence-Moon-Bardet-Biedl Syndrome (LMBBS) = is an **autosomal recessive** genetic disorder characterized by obesity, retinal degeneration, extra digits on the hands and feet, and intellectual impairment. The gene responsible for LMBBS was located on chromosome **16q21** (type 2). Shortly thereafter, another gene on chromosome **11q13** (type 1) was identified. Since then, two others were found on chromosomes **3p12** (type 3) and **15q22** (type 4). The most common form of LMBBS is type 1 and the most rare form is type 3. It is expected, however, that another gene that causes the syndrome also exists because there are identified cases that have none of these four defects. Recently, however, the Laurence-Moon-Bardet-Biedl syndrome (LMBBS) was split into Laurence-Moon (LMS) and Bardet-Biedl (BBS), where LMS is characterized as the cases involving mental retardation and spastic paresis and BBS involved obesity, polydactyly, and learning disabilities. It has been shown that BBS represents the majority of published cases. Characteristics that have been seen in children with LMBBS are as follows, Not all children will exhibit all of these features: Rod-cone dystrophy (retinitis pigmentosa) , Strabismus , Nystagmus ,Myopia, Optic atrophy, Macular dystrophy, Glaucoma ,Cataracts , Polydactyly (extra fingers and toes), Brachydactyly (short, stubby fingers and toes), Syndactyly (webbing of the toes) , **Obesity** (excess weight gain begins around ages 1 to 2 years) (Kaplan peds, p 32) , Learning disabilities, Developmental delay (delay in sitting, standing, and walking) , Speech delay, Behavioral difficulties, Kidney abnormalities, Hepatic fibrosis, Hypertension (likely a consequence of obesity), Diabetes mellitus, Hypothyroidism, Hypogonadism, Small penis (hypogonadism), Undescended testes (cryptorchidism), Infertile males ,Unusually short tooth roots, Short stature, Ataxic gaits, Deep-set eyes, Premature frontal balding in adult males. 4. WAGR Microdeletion of 11p =WAGR complex on (11p 13) (pg48) , WAGR syndrome = WAGR = ***W***ilms tumor

	(which is on **gene WT1** on chromosome 11), ***a***niridia (which is on **gene PAX6** in chromosome 11) , ***g***enitourinary malformations (such as undescended testes/cryptorchidism), and mental ***r***etardation. (CK, p 320) 5. Russell-Silver syndrome = The genetic causes of Russell-Silver syndrome are complex. The disorder often results from the abnormal regulation of certain genes that control growth. Research has focused on genes located in particular regions of **chromosome 7 and chromosome 11**. Most cases of Russell-Silver syndrome are sporadic, which means they occur in people with no history of the disorder in their family. Less commonly, Russell-Silver syndrome can run in families. In some affected families, the condition appears to have an autosomal dominant pattern of inheritance. Defect in a **gene called the maternal uniparental disomy (UPD) for chromosome 7**. 6. Asthma = Linkage to **asthma** on chromosome **2q**. (near the IL-1 family cluster), **6p, 9, and 12q**. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. The search for genes in asthma has now led to several locations on the genome, including genes on **chromosome 5, 11 and 12**. Like the Fc epsilon receptor for IgE on chromosome 11 and the cluster of cytokines on chromosome 5q. 7. Romano-Ward syndrome = a prolonged Q-T interval (QT interval) in the electrocardiogram in children subject to attacks of unconsciousness that result from ventricular arrhythmias including ventricular fibrillation; autosomal dominant inheritance, with one form caused by mutation in the potassium channel gene (KVLQT1) on chromosome 11p. *Cf.* Jervell and Lange-Nielsen syndrome. Syn: Ward-Romano syndrome. **8.** Jervell and Lange-Nielsen syndrome= Jervell - Lange-Nielsen syndrome = surdocardiac syndrome = is a form of congenital long QT syndrome = is a genetic/inherited potassium channelopathy = a prolonged Q-T interval (QT interval) recorded in the electrocardiogram of certain congenitally deaf children subject to attacks of unconsciousness resulting from Adams-Stokes seizures and ventricular fibrillation; patient with this syndrome are predisposed to a particular type of ventricular tachycardia called torsades De pointes. Torsades De pointes causes syncopal episodes and sudden death. Jervell and Lange-Nielsen syndrome is **autosomal recessiv**e inheritance, caused by homozygosity for a mutation in the **potassium**

	channel gene (KVLQT1) on chromosome 11 or minimal potassium ion channel gene (KCNE1) on 21, (potassium channelopathy) (Kaplan IM, p 87). **Channelopathies** are diseases caused by disturbed function of ion channel subunits or the proteins that regulate them. These diseases may be either congenital (often resulting from a mutation or mutations in the encoding genes) or acquired (often resulting from autoimmune attack on an ion channel). **Tx of Jervell - Lange-Nielsen syndrome: beta-blocker such as propranolol (to control heart rate) and a DDD pacemaker (=to pace the heart in life threatening event).** 9. Wilms tumor, (WT 1 = 11p13), (WT 2= 11p15) (pg 83), (Kaplan peds, p 215) = a malignant renal tumor of young children, composed of small spindle cells and various other types of tissue, including tubules and, in some cases, structures resembling fetal glomeruli, and striated muscle and cartilage. Often inherited as an **autosomal dominant** trait. Syn: nephroblastoma. 10. Beta thalassemia gene is on **chromosome 11**(pg 203): patient with beta thalassemia major are homozygous for mutations of both genes coding for the beta hemoglobin gene (Kaplan IM, p 175) 11. Sickle cell anemia = an autosomal recessive anemia, substitution valine for glutamic acid in the sixth position of the β-chain of hemoglobin the gene of which is on chromosome 11 12. Intermittent acute porphyria (IAP) = autosomal dominant inheritance, exhibit variable expression, caused by mutation in the human porphobilinogen deaminase gene on 11q24 13. Bcl-1 overexpression = Mantle cell NHL (Non Hodgkin lymphoma) (pg 212, 217) = cyclin D. 14. t (11, 14) mantle cell lymphoma (cyclin D) , translocation of Bcl-1 and heavy chain. BCL1 is on chromosome 11 , and heavy chain is on chromosome 14 (genetics pg 341) 15. t (4, 11) → acute lymphoblastic/ lymphocytic leukemia (ALL), (pg 326), associated with unfavorable prognosis. Translocation of t (4,11) translocation is associated with acute lymphocytic leukemia (ALL) and undifferentiated leukemia. ??? 16. Multiple endocrine neoplasia Type 1 = MEN 1 gene on (11q 12-13 deletion) = Wermer Syndrome (pg 263) = an autosomal-dominant predisposition to tumors of parathyroid glands, anterior pituitary, endocrine pancreas, and less commonly, other organs **Please Note: [**Zollinger-

	Ellison syndrome = peptic ulceration with gastric hypersecretion and **gastrinoma** of the pancreas or duodenum, sometimes associated with familial multiple endocrine adenomatosis type 1.] 17. Familial hypoparathyroidism=inherited isolated hypoparathyroidism characterized by hypocalcemia, hyperphosphatemia, cataracts, intracerebral calcifications, and tetany; all three mendelian forms (sex-linked, autosomal dominant and recessive) of inheritance are known. The autosomal dominant form is caused by mutation in either the parathyroid hormone gene (PTH) on chromosome 11p or the calcium sensing receptor gene (CASR) on 3q. 18. **Mutations in the sulfonylurea receptor gene** in familial persistent hyperinsulinemic hypoglycemia of infancy = Familial persistent hyperinsulinemic hypoglycemia of infancy (PHHI), an **autosomal recessive** disorder characterized by unregulated insulin secretion, is linked to **chromosome 11p14-15.1**. The newly cloned high-affinity sulfonylurea receptor (SUR) gene, a regulator of insulin secretion, was mapped to 11p15.1 by means of fluorescence in situ hybridization. Two separate SUR gene splice site mutations, which segregated with disease phenotype, were identified in affected individuals from nine different families. Both mutations resulted in aberrant processing of the RNA sequence and disruption of the putative second nucleotide binding domain of the SUR protein. Abnormal insulin secretion in PHHI appears to be caused by mutations in the SUR gene. 19. Hyperinsulinemic hypoglycemia, familial, Type 2= HHF2 = A disorder where too much insulin causes low blood sugar in infants. Prompt treatment is needed to avoid the brain being damaged by repeated periods of low blood sugar. The various types of familial hyperinsulinemic hypoglycemia are distinguished by their genetic origin. HHF2 is due to a **mutation in the gene for Kir6.2 on chromosome 11p15.1**. High insulin level in infants. Symptoms of Hyperinsulinemic hypoglycemia, familial, Type 2 : Nesidioblastosis, Low blood sugar(= Hypoglycemia), Vomiting , Diarrhea. 20. Acatalasia= Absence or deficiency of catalase from blood and tissues, often manifested by recurrent infection or ulceration of the gums and related oral structures and caused by mutations in the catalase gene (CAT) on 11p. Homozygotes may have complete absence (Japanese variety)

	or very low levels (Swiss variety) of catalase; heterozygotes have reduced catalase levels (hypocatalasia), which overlap with the normal range. Syn: acatalasemia, Takahara disease 21. (rarely) Mutation in the pyruvoyl tetrahydropterin synthase gene (PTS) on 11q → Phenylketonuria (PKU) 22. Niemann-Pick Disease = lipidosis with **accumulation of sphingomyelin (= ceramide phosphorylcholine)** in histiocytes and endothelial cells in the liver, spleen, lymph nodes, bone marrow and brain due to a **deficiency of sphingomyelinase**; associated with **hepatosplenomegaly**, hypotonia, cervical lymphadenopathy, protruding abdomen , physical, and **mental retardation** and neurologic manifestations; macular cherry-red spots on retinal examination may occur at a later stage (CK p 305); occurs most commonly in Ashkenazi Jewish infants and leads to early death (patient dies by age 3) ; a more benign form may occur in adults. **Niemann-Pick Disease gives "sea-blue" histiocytes on bone marrow biopsy.** There are several variants of Niemann-Pick disease: Type A, the classic infantile form; Type B, the visceral form; Type C, the juvenile form; Type D, the Nova Scotia variant; and Type E, the adult form; all are of autosomal recessive inheritance with **Types A (classic infantile form) and Type B (the visceral form) caused by mutation in the acid sphingomyelinase gene (SMPD) on chromosome 11p**. Syn: Niemann disease, sphingomyelin lipidosis. (CK p 305) 23. Louis-Bar Syndrome = Ataxia Telangiectasia = Louis-Bar's syndrome = Boder-Sedgwick Syndrome = Louis-Bar syndrome = Ataxia-Telangiectasia =Ataxia Telangiectasia Syndrome, autosomal recessive trait, caused by several mutations in PI3ckinase gene, chromosome 11, increased numbers of translocations, especially involving the T-cell receptor loci, see prominent telangiectasis around the eye. ATM gene is a member of PI-3 kinase family involved in mitogenic signal transduction, detection of DNA damage and cell cycle control. Ataxia telangiectasia mutation (ATM) **occur at 11q 22-23** which code for DNA dependent protein kinase. Ataxia telangiectasia syndrome is associated with breast cancer. (1st aid, surgery, p 143). Ataxia Telangiectasia (AT) is an autosomal recessive cerebellar ataxia characterized by the onset of truncal ataxia at the time of walking. Laboratory analysis shows low levels of IgA and IgG/ Ig E immunoglobulins.(Kaplan Peds, p 252). In ataxia telangiectasia get both Cellular immunodeficiency (T-

	lymphocyte → T-helper cells have defect → have low CD 3 and Low CD 4 T-cells with increase number of CD 8 (TH2)) as well as Humoral immunodeficiency (B-lymphocyte → intrinsic B cells have defect →defect in production of immunoglobulins → **get decrease level of Ig A, Ig M, Ig E immunoglobulin**) (peds p 122). = Ataxia telangiectasia is a degenerative brain disease characterized by progressive cerebellar ataxia, athetoid movements, nystagmus, slow dysarthric speech, telangiectasis of the bulbar conjunctiva, recurrent respiratory infections, mental retardation (50%) and an increased incidence of lymphoreticular malignancies. It affects both sexes equally, with onset at the age of about four years. Death usually occurs in adolescence or early adulthood of a pulmonary infection or a lymphoreticular malignant tumor. It is transmitted as an autosomal recessive trait. = Ataxia telangiectasia is a slowly progressive multisystem disorder with the following manifestations: ataxia appearing with the onset of walking; telangiectases of the conjunctiva and skin of the face, neck, and ears; athetosis and nystagmus; and recurrent infections of the respiratory system caused by immunoglobulin deficiencies. Due to an autosomal recessive trait, with major pathologic changes involving the cerebellar cortex, posterior columns, spinocerebellar tracks, anterior horn cells, dorsal roots, and peripheral nerves. A high percentage of the patients have an IgA deficiency concomitant with decreased T-helper cell function. There are numerous chromosome breaks and α-fetoprotein levels in the sera are usually elevated; caused by several mutations in PI3′kinase gene. Syn: ataxia telangiectasia syndrome, Louis-Bar syndrome. (Compare with Nezelof syndrome). 24. Omenn syndrome = a rapidly fatal immunodeficiency disease characterized by erythroderma, diarrhea, repeated infections, hepatosplenomegaly, and leukocytosis with eosinophilia; **autosomal recessive** inheritance, caused by mutation in either the recombination activating gene 1 (RAG1) or the adjacent RAG2 gene on chromosome 11p. 25. Hereditary angioneurotic edema (HANE)= a relatively rare form of edema characterized by onset, usually in adolescence, of erythema followed by edema, involving the upper respiratory or gastrointestinal tracts, associated with either a deficiency of C1 esterase inhibitor or a functionally inactive form of the inhibitor. There are two clinically indistinguishable forms: type I, in which the serum level of C1 esterase inhibitor is low (up to 30% of normal) and type

	II, in which the level is normal or elevated. There is uncontrolled activation of early complement components and production of a kinin-like factor that induces the angioedema; death may occur from upper respiratory tract e. and asphyxia. Inheritance is autosomal dominant, caused by mutation in the C1-esterase inhibitor gene (C1NH) on chromosome 11q. 26. Beckwith-Wiedemann syndrome = EMG syndrome = Exomphalos-Macroglossia-Gigantism Syndrome = an overgrowth syndrome characterized by **exomphalos, macroglossia, and gigantism**, often with neonatal hypoglycemia; there is an association with hemihypertrophy and Wilms tumor. **Autosomal dominant** inheritance, with most cases sporadic; influenced by genomic imprinting and uniparental disomy; caused by mutation in the P57 (KIP2) **gene on chromosome 11p**. A syndrome of multiple defects characterized primarily by umbilical hernia , MACROGLOSSIA, and GIGANTISM and secondarily by visceromegaly, HYPOGLYCEMIA, and ear abnormalities. Chromosome 11p encodes for **gene IGF-2** which cause **macrosomia**. Beckwith-Wiedemann syndrome occurs in about 1/14000 birth. It is characterized by **macrosomia** and accelerated osseous maturation. Mild to moderate mental deficiency may be present, patients may have normal intelligence. Physical examination is remarkable for **macroglossia**, a large fontanel, a linear fissure in the external ear, and indentations along the posterior rim of the helix. Organomegaly of the pancreas and kidney also occurs, as well as **omphalocele** (Kaplan Peds, p 253). **Hypoglycemia** occurs in one third to one half of patients, presenting in early infancy. In the neonate, apnea cyanosis and feeding problems may be related to the macroglossia. Neonates also have seizures and hypoglycemia. Patients are at higher risk for neonatal polycythemia and Wilms tumor (Kaplan peds, p 217) and other tumors (gonads, hepatoblastoma). Routine ultrasound and alpha-fetoprotein should be performed every 6 months until 6 years of age. Survivors of infancy tend to do well, and the excessive growth rate slows down. (Kaplan peds, p 30, p 217, p 253), (CK, p 320). Beckwith-Wiedemann syndrome is characterized by perinatal growth acceleration, macroglossia, linear ear creases, abdominal wall defects, exophthalmos and transient neonatal hypoglycemia. These children are at increased risk for developing Wilms' tumor, neuroblastoma, hepatoblastoma, and gonadoblastoma. It is recommended that screening with abdominal ultrasound and serum AFP be performed every 6 month until the age of 6 years.

	27. Spinal Muscular Atrophy (SMA) with Respiratory Distress (SMARD 1) (chromosome 11, IGHMBP2 gene). The term spinal muscular atrophy thus refers to atrophy of muscles due to loss of motor neurons within the spinal cord. Spinal muscular atrophy (SMA)= a heterogeneous group of degenerative diseases of the anterior horn cells in the spinal cord and motor nuclei of the brainstem; all are characterized by weakness. Upper motor neurons remain normal. These diseases include Werdnig-Hoffmann disease (SMA type 1), SMA type 2, and Kugelberg-Welander disease (SMA type 3) 28. Bartter syndrome=**Autosomal recessive,** a disorder due to a defect in active chloride reabsorption in the loop of Henle; characterized by primary juxtaglomerular cell hyperplasia with secondary hyperaldosteronism, hypochloremia, high rennin and high aldosterone level, **hypokalemic alkalosis** (1st aid CK, p 360) , hypercalciuria, elevated renin or angiotensin levels, normal or low blood pressure, and growth retardation; edema is absent. **Autosomal recessive inheritance**, caused by mutation in either the **Na-K-2Cl cotransporter gene (SLC12A1) on chromosome 15q or the K (+) channel gene (KCNJ1) on 11q**.
12	1. t(12,22) = clear cell sarcoma = malignant melanoma of soft part ??? 2. Zellweger Syndrome = Cerebrohepatorenal Syndrome = a metabolic disorder with neonatal onset, characterized by distinctive facies, muscular hypotonia, hepatomegaly with jaundice, renal cysts, epiphyseal stippling of the patellae, cerebral dysmyelination, and neuronal migration defects and psychomotor retardation; there is a **perturbation in peroxisomal biogenesis (= absence of peroxisomes)**; autosomal recessive inheritance, caused by mutation in any one of several peroxin (PEX) genes on chromosome 6, 7, 8, or 12. 3. Noonan Syndrome = Turner like syndrome affects both male and females (= boys and girls with turner phenotype) = a syndrome found in both males and females, with a phenotype reminiscent of Turner syndrome; characterized by hypertelorism, downslanting of palpebral fissures, webbing of the neck, short stature, and congenital heart disease, especially pulmonary stenosis; **normal chromosomal karyotype; autosomal dominant inheritance**. (Kaplan peds, p 154). Most common Noonan syndrome **mutation is the mutation in "PTPN11 gene" on chromosome 12q24.1**. =

	Noonan syndrome is a genetic disorder that causes abnormal development of multiple parts of the body. It used to be called Turner-like syndrome because certain symptoms (webbing of neck and abnormally shaped chest) resembled those seen in Turner syndrome. Noonan syndrome maps to **chromosome 12q24.1**. It was reported that approximately half of a group of patients with Noonan syndrome carried a mutation of the PTPN11 gene at that location, which encodes protein tyrosine phosphatase SHP-2. The SHP2 protein is a component of several intracellular signal transduction pathways involved in embryonic development that modulate cell division, differentiation, and migration, including that mediated by the epidermal growth factor receptor. The latter pathway is important in the formation of the cardiac semilunar valves. Chromosomal abnormalities, such as a duplication of chromosome region 12q24 encompassing gene PTPN11 can result in an apparent Noonan syndrome. 4. Asthma = Linkage to **asthma** on chromosome **2q**. (Near the IL-1 family cluster), **6p, 9, and 12q**. Chromosome 12q harbors multiple genetic loci related to asthma and asthma-related phenotypes. The search for genes in asthma has now led to several locations on the genome, including genes on **chromosome 5, 11 and 12**. Like the Fc epsilon receptor for IgE on chromosome 11 and the cluster of cytokines on chromosome 5q. 5. t (12, 21) → acute lymphoblastic leukemia (AML) (pg 326) 6. Chronic lymphocytic leukemia (CLL)= "smudge cell", cytogenetic analysis maybe useful because some cases of chronic lymphocytic leukemia (CLL) are associated with trisomy 12 (= trisomy of chromosome 12). (Kaplan IM, p 183) 7. Phenylketonuria (PKU) =Autosomal recessive, mutation in the phenylalanine hydroxylase gene (PAH) on 12q. = Autosomal recessively inherited inborn error of metabolism of phenylalanine characterized by deficiency of 1) phenylalanine hydroxylase caused by mutation in the phenylalanine hydroxylase gene (PAH) on 12q; 2) occasionally, dihydropteridine reductase, caused by mutation in the dihydropteridine reductase gene (DHPR) on 4p; 3) rarely, dihydrobiopterin synthetase, caused by mutation in the pyruvoyl tetrahydropterin synthase gene (PTS) on 11q; or 4) even more rarely, guanidine triphosphate cyclohydrolase 1. The disorder is characterized by inadequate formation of L-tyrosine, elevation of serum L-phenylalanine, urinary excretion of phenylpyruvic acid and other derivatives, and accumulation of phenylalanine and its metabolites, which can

produce brain damage resulting in severe mental retardation, often with seizures, other neurologic abnormalities such as retarded myelination and deficient melanin formation leading to hypopigmentation of the skin and eczema. *Cf.* hyperphenylalaninemia. Syn: Folling disease, phenylpyruvate oligophrenia.

8. White sponge nevus= an autosomal dominant condition of the oral cavity characterized by soft, white or opalescent, thickened, and corrugated folds of mucous membrane; other mucosal sites are occasionally involved simultaneously; caused by mutation in either the mucosal keratin gene K4 on chromosome 12 or keratin-13 gene on 17. Syn: familial white folded dysplasia, oral epithelial nevus.
9. Von Willebrand disease= a hemorrhagic diathesis characterized by tendency to bleed primarily from mucous membranes, prolonged bleeding time, normal platelet count, normal clot retraction, partial and variable deficiency of factor VIIIR, and possibly a morphologic defect of platelets; **autosomal dominant inheritance** (first aid CK, p 149) with reduced penetrance and variable expressivity, caused by mutation in the von Willebrand factor gene (VWF) on chromosome 12p. Type III von Willebrand disease is a more severe disorder with markedly reduced factor VIIIR levels. There is a recessive version of this disease, which has the remarkable property that it represents a mutation at the same locus as the dominant form. (Kaplan peds, p204)
10. Familial hypophosphatemic rickets = Vitamin D-resistant rickets=a group of metabolic disorders characterized by renal tubular defect in phosphate transport and bone abnormalities resulting in hypophosphatemic rickets or osteomalacia; hypocalcemia and tetany are not features. There is an autosomal dominant form and an **X-linked dominant form** (Kaplan OB, p 6), the latter caused by mutation in the phosphate-regulating gene with homologies to endopeptidases (PHEX) on chromosome Xp. Both forms are not responsive to standard therapeutic doses of vitamin D but they may respond to very large doses of phosphate and/or vitamin D. There is also an autosomal recessive form caused by mutation in the vitamin D receptor gene (VDR) on 12q. familial hypophosphatemic rickets caused by vitamin D deficiency or vitamin D insentivity, laboratory abnormalities include hypophosphatemia, normal serum calcium and increased levels of PTH, vitamin D and alkaline phosphatase.
11. Nephrogenic diabetes insipidus= diabetes insipidus due to inability of the kidney tubules to respond to

	antidiuretic hormone; X-linked inheritance, caused by mutation in the vasopressin V2 receptor gene (AVPR2) on Xq. There is also an autosomal dominant form , caused by mutation in the (aquaporin) aquaphorin 2 gene (AQP2) on 12q. Syn: vasopressin-resistant diabetes. 12. Type II achondrogenesis= achondrogenesis with autosomal dominant inheritance, caused by mutation in the collagen type II gene (COL2A1) on chromosome 12q. Syn: Langer-Saldino syndrome. 13. Kniest syndrome= a chondrodysplasia characterized by round flat facies, enlargement and stiffness of joints, joint contractures, scoliosis, myopia with retinal detachment, cleft palate, deafness, and characteristic radiographic findings of metaphyseal flaring of long bones, flattening, and coronal clefting of vertebrae; autosomal dominant inheritance, caused by mutation in the type II collagen gene (COL2A1) on chromosome 12q. 14. Holt-Oram syndrome= atrial septal defect (ASD) in association with finger-like or absent thumb and other deformities of the forearm; autosomal dominant inheritance, caused by mutation in the T-box5 gene (TBX5) on chromosome 12q. Holt- Oram syndrome causes upper limb deformities. 15. Epidermolysis bullosa = a group of inherited chronic noninflammatory skin diseases in which large bullae and erosions result from slight mechanical trauma; a form localized to the hands and feet is called Weber-Cockayne syndrome, of autosomal dominant inheritance caused by mutation in either the gene encoding keratin-5 (KRT5) on chromosome 12q or the gene for keratin-14 (KRT14) on 17q. Syn: epidermolysis bullosa dystrophica, epidermolysis bullosa lethalis, epidermolysis bullosa simplex, mechanobullous disease. 16. Epidermolysis bullosa simplex = epidermolysis bullosa in which lesions heal rapidly without scarring; bulla formation is intraepidermal and microscopy reveals basal cell vacuolation and dissolution of tonofibrils; occurs most frequently on the feet of adults after unaccustomed trauma such as long marches; autosomal dominant inheritance caused by mutation in the keratin-5 gene (KRT5) on chromosome 12q or in the keratin-14 gene (KRT14) on 17q. Syn: epidermolysis bullosa, epidermolysis bullosa, epidermal type. 17. Spondyloepiphyseal dysplasia congenita (SEDC)= a skeletal dysplasia characterized by short-trunk dwarfism with short limbs, delayed ossification of the pubic

	rami and femoral and tibial epiphyses, flattening of the vertebral bodies, myopia, retinal detachment, and cleft palate; autosomal dominant inheritance caused by mutation in the type II collagen gene (COL2A1) on 12q. 18. Hereditary progressive arthroophthalmopathy= Stickler syndrome= Autosomal dominant inheritance caused by mutation in either the COL2A1 gene on 12q, COL11A1 gene on 1p or COL11A2 gene on 6p. 19. Trisomy 12= Trisomy 12 Syndrome= Trisomy of Chromosome 12 = some cases of chronic lymphocytic leukemia (CLL) are associated with trisomy 12 (= trisomy of chromosome 12). (Kaplan IM, p 183). Juvenile granulosa tumor of ovary, granulosa cell tumor of ovary and benign ovarian fibromas (=fibroma of ovary) are associated with trisomy 12 (= trisomy of chromosome 12) 20. Killian–Pallister syndrome = PKS= tetrasomy 12p = is a rare dysmorphic condition characterized by specific clinical manifestations and tetrasomy 12p (tetrasomy 12p =four copies of the short arm of. chromosome 12). Pallister-Killian syndrome (PKS) is a rare chromosome abnormality in which a person has four copies of the short arm of chromosome 12 instead of the normal two copies. Affected individuals have unusual facial features, mental retardation, seizures, patchy color differences in the skin, and various other physical abnormalities. Many fetuses with Pallister-Killian syndrome die during pregnancy or soon after birth. Inheritance is sporadic. PKS occurs sporadically. In other words, no other family member, brother and sister, is usually affected. [Inheritance: somatic mosaicism]. 21. Sanfilippo Syndrome= Mucopolysaccharidosis III =MPS-III= an error of the mucopolysaccharide metabolism, with excretion of large amounts of heparan sulfate in the urine; characterized by severe mental retardation with hepatomegaly; skeleton may be normal or may present mild changes similar to those in Hurler syndrome; several different types (A, B, C, and D) have been identified according to the enzyme deficiency; autosomal recessive inheritance. Syn: type III mucopolysaccharidosis. (Hunter syndrome is one of the disease of mucopolysaccharidosis which is X-linked recessive, other examples are hurler and Sanfilippo that are autosomal recessive) (Kaplan peds, p225). Sanfilippo syndrome is a rare **autosomal recessive** lysosomal storage disease caused by a deficiency in one of the enzymes needed to break down

	the glycosaminoglycan heparan sulfate (which is found in the extra-cellular matrix and on cell surface glycoproteins). Although undegraded heparan sulfate is the primary stored substrate, glycolipids such as gangliosides are also stored despite no genetic defect in the enzymes associated with their breakdown. The four types of MPS-III are due to specific enzyme deficiencies affecting the breakdown of heparan sulfate, which then builds up in various organs. **All four types have autosomal recessive inheritance**. 4) Sanfilippo syndrome type-D= MPS-III type-D : deficiency in enzyme N-acetylglucosamine-G-sulfate sulfatase , gene location on **chromosome 12q14**. 22. Pachyonychia congenita= a syndrome of ectodermal dysplasia of abnormal thickness and elevation of nail plates with palmar and plantar hyperkeratosis; the tongue is whitish and glazed owing to papillary atrophy; autosomal dominant inheritance caused by mutation in the keratin 16 gene (KRT16) on chromosome 17q or the keratin 6A gene (KRT6A) on 12q. Syn: Jadassohn-Lewandowski syndrome. 23. Weber-Cockayne syndrome = epidermolysis bullosa of the hands and feet; autosomal dominant inheritance, caused by mutation in the keratin 5 gene (KRT5) on chromosome 12q or keratin 14 gene (KRT14) on 17q.
13	1. Wilson disease gene= Mutation in the copper-transporting ATPase gene (ATP7B) on chromosome 13q (p 193). 2. Wilson disease = hepatolenticular degeneration = a disorder of copper metabolism, characterized by liver cirrhosis, basal ganglia degeneration, neurological manifestations, and deposition of green or golden brown pigment in the periphery of the cornea; the plasma levels of copper and ceruloplasmin are decreased, urinary excretion of copper is increased, and the amounts of copper in the liver, brain, kidneys, and lenticular nucleus are unusually high while cytochrome oxidase is reduced; autosomal recessive inheritance caused by mutation in the copper-transporting ATPase gene (ATP7B) on chromosome 13q. in Wilson disease get "**fixed smile", dysarthria, choreoathetosis, Kayser-Fleischer rings** (yellow brown deposit at the limbus of the cornea) (Kaplan Peds, p 224) . See Also: Kayser-Fleischer ring. [S.A.K. Wilson] **2.** Syn: exfoliative dermatitis. Syn: lenticular progressive disease. (Kaplan peds, p 224), (CK p 144), (IM p 27). Neurologic symptoms of Wilson's disease (loss of coordination, tremor, dysphagia) are secondary to copper deposition in the basal ganglia(CK p

144).

3. Human insulin receptor substrate-1 gene (IRS1): chromosomal localization to **chromosome 2 (2q35-q36.1)** and identification of a simple tandem repeat DNA polymorphism2) The human IRS-1 gene contains the entire 5'-untranslated region and protein coding region in a single exon and was localized on **chromosome 2 q36-37** by in situ hybridization. 3) IRS1 insulin receptor substrate 1 Gene on **Chromosome 13.** 4) The IRS-2 Gene on Murine **Chromosome 8** Encodes a Unique Signaling Adapter for Insulin and Cytokine Action. Insulin receptor substrate-1 = a cytoplasmic protein that is a direct substrate of the activated insulin receptor kinase. Insulin exposure results in its rapid phosphorylation at multiple tyrosine residues. Its phosphorylated sites associate with high affinity to certain cellular proteins. IRS-1 thus acts as an adaptor molecule that links the receptor kinase to various cellular activities regulated by insulin. IRS-1 is also phosphorylated after stimulation by insulinlike growth factor-1 and several interleukins.
4. Patau's syndrome (trisomy 13), (pg 48) life span less than 1 year. = Trisomy 13 syndrome = a chromosomal disorder that is usually fatal within 2 years; characterized by mental retardation, malformed ears, cleft lip or palate, microphthalmia or coloboma, small mandible, polydactyly, cardiac defects, convulsions, renal anomalies, umbilical hernia, malrotation of intestines, and dermatoglyphic anomalies. Syn: Patau syndrome, trisomy D syndrome trisomy 13 syndrome. **Holoprosencephaly** is usually associated with trisomy 13 ad less often trisomy 18. Incomplete separation of the cerebral hemisphere along the midline leads to a single ventricular cavity enclosed within the forebrain.
5. Panic Disorder = Substantial evidence supports that there is a genetic component to panic disorder (PD). Until recently, attempts at localizing genes for PD by using standard phenotypic data have not proven successful. Previous work suggests that a potential subtype of PD called the panic syndrome exists, and it is characterized by a number of medical conditions, most notably bladder/renal disorders. In the current study, a genome scan with 384 microsatellite markers was performed on 587 individuals in 60 multiplex pedigrees segregating PD and bladder/kidney conditions. Using both single-locus and multipoint analytic methods, we found significant linkage on chromosome 22 (maximum

heterogeneity logarithm of odds score = 4.11 at D22S445) and on chromosome 13q (heterogeneity logarithm of odds score = 3.57 at D13S793) under a dominant-genetic model and a broad phenotypic definition. Multipoint analyses did not support the observation on chromosome 22. The chromosome 13 findings were corroborated by multipoint findings, and extend our previous findings from 19 of the 60 families. Several other regions showed elevated scores by using when one analytic method was used, but not the other. These results suggest that there are **genes on chromosome 13q, and possibly on chromosome 22** as well, that influence the susceptibility toward a pleiotropic syndrome that includes PD, bladder problems, severe headaches, mitral valve prolapse, and thyroid conditions.

6. Gene (13q14) = retinoblastoma (Rb) gene = p110 , (pg 48) → retinoblastoma, osteosarcoma (pg 48) . Also note the human papilloma virus (HPV) viral gene E7 inhibits Rb tumor suppressor gene→ cause malignancy + endometrial cancer. (micro pg 397). Retinoblastoma= Malignant ocular neoplasm of childhood, with onset usually before the third year of life, composed of primitive retinal small round cells with deeply staining nuclei and elongated cells forming rosettes; there is an increased risk of developing osteosarcoma later in life. In familial cases, the disease is usually bilateral with multiple lesions within an eye, but in sporadic cases rarely so. **Autosomal dominant** inheritance caused by mutation in the tumor-suppressor **retinoblastoma gene (RB) on chromosome 13q**. Small Cell lung cancer(=SCLC) is associated with inactivating mutations of other tumor suppressor genes such as Rb (for retinoblastoma) and activating mutations in proto-oncogenes such as Myc. Knudson Two Hit Hypothesis of Tumorigenesis: The first hit is classically thought of as a point mutation that inactivates one copy of a tumor suppressor gene (TSG), such as Rb1. The classical example of such a loss of protecting genes is hereditary retinoblastoma, in which one parent's contribution of the tumor suppressor Rb1 is flawed. Although most cells will have a functional second copy, chance loss of heterozygosity (= LOH) events in individual cells almost invariably lead to the development of this retinal cancer in the young child.
7. (13q 12-13) = BRCA-2 gene (pg 83) → breast cancer
8. t (2, 13) = clear cell sarcoma = malignant melanoma of soft part arises from soft tissues rather than skin and found usually in tendon of extremities(pg 326)
9. Primary Nocturnal enuresis = bed-wetting = there is a

strong genetic predisposition for primary nocturnal enuresis (Kaplan peds, p 46) , A family history of nocturnal enuresis is found in most children with the condition. One study has shown that in families where both parents had enuresis, 77 percent of children will also have enuresis. In families where only one parent had enuresis, 44 percent of children will be affected; only 15 percent of children will have enuresis if neither parent had enuresis. **Heredity** as a causative factor of primary nocturnal enuresis has been confirmed by the identification of a gene marker associated with the disorder. The trait showed nearly **complete penetrance** in these families. This study seems to suggest the existence of a major **dominant gene** for **primary nocturnal enuresis**. This gene appears to be located on **chromosome 13**. However, no specific gene locus has yet been identified. The identification of this gene marker certainly lifts the burden of guilt from children who have enuresis and helps to dispel the theory that enuresis is behavioral in origin.

10. Chromosome 13 deletion = CHROMOSOME DELETION 13Q = CD 13= 13Q deletion syndrome is a chromosome disorder where one of the arms or the whole arm of the chromosome is missing at birth. This chromosome disorder was first diagnosed about 10 years ago. Depending on which band of the arm is missing, many symptoms can occur. Not all those diagnosed will have the below symptoms. : **Global Developmental Delay, Small stature(weight and height) , Low Muscle Tone , Seizures , Deafness , Blindness, Reflux, Cleft Palate, Retinoblastoma (tumors of the eye), Microcephaly (small head) , Factor VII and Factor X - Blood Clotting Issues (chromosome 13, q34)**
11. OTHER DISORDERS LINKED WITH chromosome 13 deletion (= CD13) = Autism (exact band of the arm unknown) , Sensory Processing Disorder (AKA Sensory Integration Dysfunction).
12. Möbius syndrome = congenital facial diplegia =a developmental bilateral facial paralysis usually associated with oculomotor or other neurological disorders. Möbius syndrome (also spelled Moebius) is an extremely rare congenital neurological disorder, which is characterized by facial paralysis and the inability to move the eyes from side to side. Most people with Möbius syndrome are born with complete facial paralysis, which means they cannot close their eyes or form facial expression. The syndrome is listed as Online Mendelian Inheritance in Man (OMIM) Number 157004, with a **gene map locus of 13q12.2-q13**. Scattered

	reports have described specific genetic localizations in Möbius syndrome. In 1977, Ziter et al reported a variant of Möbius syndrome co-segregating with a **reciprocal translocation between chromosomes 1 and 13**, i.e., **t(1p34;13q13)**, in at least 7 members of an affected family over 3 generations. In 1991, Slee et al described a 2.5-year-old girl with Möbius syndrome who had a deletion of band q12.2 on **chromosome 13.** Both reports suggested that a gene responsible for Möbius syndrome is located in region 13q12.2-q13. In 1996, Kremer et al described a large pedigree with autosomal dominant Möbius syndrome consisting largely of asymmetric bilateral facial paresis. After exclusion of the candidate region on **13q12.2-13**, they localized a gene to 3q21-22, raising the possibility of genetic heterogeneity of the syndrome. In 1997, Nishikawa et al reported a boy with a Möbius-like syndrome (i.e., facial diplegia and ptosis but with normal extraocular movements and no skeletal anomalies) with a **reciprocal translocation between chromosomes 1 and 2 (p22.3, q21.1)**. A dominantly inherited syndrome (with the clinical features of Möbius syndrome and clubfoot, digital abnormalities, and arthrogryposis) was described in a family with 15 affected members in 2 generations. Because of inconsistency in defining the condition, the role of inheritance in Möbius syndrome remains unclear. Pedigrees with autosomal dominant, autosomal recessive, and X-linked recessive inheritance patterns have been described. 13. Oguchi disease= a rare congenital nonprogressive night blindness with diffuse yellow or gray coloration of fundus; after two or three hours in total darkness, fundus resumes normal color; **autosomal recessive inheritance**, caused by mutation in either the arrestin gene (SAG) on 2q or the rhodopsin kinase gene (RHOK) on 13q.
14	1. Autoimmune lymphocytic hypophysitis = Autoimmune Hypophysitis (AH) = this region contained two novel candidate autoantigens: **chromosome 14** open reading frame 166 (C14orf166) and chorionic somatomammotropin. Autoimmune Hypophysitis is defined as below normal production of one or more hormones by the pituitary gland due to autoimmunity. 80% of patients with pituitary antibodies also have antibodies to thyroid gland or its hormones. Likewise, 20% of autoimmune thyroid patients also have pituitary antibodies. It follows that a subset of thyroid patients may have a disease related to autoimmune hypophysitis. Recent research has focused on a defect at the **CTLA-4 gene** which, coupled with other factors, may result

	in pan-autoimmunity primarily focusing on certain endocrine glands including the pituitary and thyroid. 2. Immunoglobulin heavy chain (Ig H) (pg 83,212,217,218) 3. C (C = constant region of the heavy chain of immunoglobulin) , C-gene for the gamma heavy chain (IgG) is on chromosome 14. C-gene for the alpha heavy chain (IgA) is on chromosome 14. The heavy chains determine the identity of the immunoglobulin isotypes: IgG, IgM, IgA, IgD, IgE 4. C- gene for the epsilon heavy chain (Ig E) is on chromosome 14. 5. C- gene for the mu heavy chain (Ig M) and delta heavy chain (IgD) are on chromosome 14. 6. V- gene for the heavy chain is on chromosome 14. 7. t (8,14) Burkitt lymphoma (C-myc) (genetics pg 341) 8. t (11, 14) mantle cell lymphoma (cyclin D) , translocation of Bcl-1 and heavy chain . BCL1 is on chromosome 11 , and heavy chain is on chromosome 14 (genetics pg 341) 1. t (14, 18) follicular lymphomas, = Small cleaved cell lymphoma = (translocation of bcl-2 that inhibits apoptosis) and activation of Bcl-2(genetics pg 341), translocation involving the immunoglobulin chain site and Bcl-2. **Heavy chain is on chromosome 14 and BCL-2 is on chromosome 18**. Follicular lymphoma = nodular lymphoma = malignant lymphoma arising from lymphoid follicular B cells which may be small or large, growing in a nodular pattern. Syn: giant follicular lymphoblastoma. 9. Antitrypsin deficiency= Alpha-1 Antitrypsin (= AAT) Deficiency = deficiency of alpha1 α_1-antitrypsin (= deficiency of elastase inhibitor), a serum protease inhibitor (PI), is associated with **emphysema** and/or **liver cirrhosis**. By isoelectric focusing, numerous variants have been identified, with different levels of normal activity; autosomal recessive inheritance, caused by mutation in the P1 gene on chromosomal 14q. Patients with AAT have emphysematous lung. Patients with AAT are at increase risk for liver diseases such as neonatal hepatitis, cirrhosis and liver failure. 10. Pi gene (produces alpha1-antitrypsin) (pg194) → alpha 1 antitrypsin deficiency = antitrypsin deficiency= deficiency of α_1-antitrypsin, a serum protease inhibitor (PI), is associated with emphysema and/or liver cirrhosis. By

	isoelectric focusing, numerous variants have been identified, with different levels of normal activity; **autosomal recessive** inheritance, caused by mutation in the P1 gene on chromosomal 14q. 11. Presenilin-1 gene (Alzheimer disease) (pg 307) 12. Krabbe disease = globoid cell leukodystrophy = deficiency of (galactocerebroside) lysosomal cerebrosidase (= **deficiency of galactosylceramide β-galactosidase**); **autosomal recessive** inheritance, caused by mutation in the gene encoding glycosylceramidase (GALC) on 14q. Can see presence of globoid cells in degenerating white matter in brain. Patient get **opisthotonus, optic atrophy and seizure**. (Kaplan peds, p 225). Globoid cell leukodystrophy a metabolic disorder of infancy or early childhood characterized by spasticity, seizures, and rapidly progressive cerebral degeneration, massive loss of myelin, severe astrocytic gliosis, and infiltration of the white matter with characteristic multinucleate globoid cells; metabolically there is gross deficiency of lysosomal cerebrosidase (galactosylceramide β-galactosidase). Syn: galactosylceramide lipoidosis, diffuse infantile familial sclerosis 13. Congenital ichthyosis = Lamellar Ichthyosis= Ichthyosis Congenita = a dry form of congenital ichthyosiform erythroderma, characterized by ectropion and large, coarse scales over most of the body with thickened palms and soles; may be fatal with complications of sepsis, protein, and electrolyte loss in the first year of life; histology shows hyperkeratosis, a prominent granular layer in the epidermis, slight acanthosis, many mitotic figures, and normal or reduced epidermal cell turnover. **Autosomal recessive inheritance**, caused by mutation in the gene encoding keratinocyte **transglutaminase** (TGM1) on chromosome 14q. See Also: collodion baby, harlequin fetus. (Kaplan OB, pg 2) 14. Oculopharyngeal Syndrome= a myopathic disorder with a slowly progressive blepharoptosis and dysphagia, beginning late in life; autosomal dominant inheritance, caused by mutation in the gene encoding poly(A)-binding protein-2 (PABP2) on chromosome 14q. 15. Machado-Joseph Disease = a rare form of hereditary ataxia, characterized by onset in early adult life of progressive, spinocerebellar and extrapyramidal disease with external ophthalmoplegia, rigidity dystonia symptoms, and, often, peripheral amyotrophy; found predominantly in people

	of Azorean ancestry; autosomal dominant inheritance, caused by a trinucleotide repeat expansion mutation in the Machado-Joseph gene (MJD1) on 14q. Syn: Azorean disease, Portuguese-Azorean disease. 16. Familial Hypertropic cardiomyopathy = Hereditary Hypertropic cardiomyopathy = Hereditary Hypertropic Obstructive Cardiomyopathy = HOCM = HHOCM although hypertropic cardiomyopathy can apparently develop sporadically, it is **hereditary** in more than **60% of cases** and is transmitted as an autosomal dominant trait. (Kaplan IM, p 151,152, 153). Familial occurrence of hypertrophic cardiomyopathy exhibiting an **autosomal dominant** pattern of inheritance. Familial cardiomyopathy of various kinds occurs with autosomal dominant inheritance. There is also an asymmetrical form affecting the ventricles and the interventricular septum. An **abnormality on chromosome 14** has been identified in the familial form of the disease. (Kaplan IM, p 151,152, 153). Hypertrophic cardiomyopathy (HCM)= thickening of the ventricular septum and walls of the left ventricle with marked myofibril disarray; often associated with greater thickening of the septum than of the free wall resulting in narrowing of the left ventricular outflow tract and dynamic outflow gradient; diastolic compliance is greatly impaired. (Kaplan IM, p 151,152, 153). 17. Idiopathic Hypertrophic Subaortic Stenosis (IHSS) = left ventricular outflow obstruction due to hypertrophy, usually congenital, of the ventricular septum. Syn: muscular subaortic stenosis. The congenital form of hypertrophic cardiomyopathy is know as idiopathic hypotrophic subaortic stenosis (IHSS) which is inherited as autosomal dominant in 50% of patient (1st aid for CK, p 40). 18. Trisomy 14 = Chromosome 14, Trisomy Mosaic= Trisomy 14 Mosaic =Trisomy 14 Mosaicism Syndrome = Chromosome 14, Trisomy Mosaic is a rare chromosomal disorder in which chromosome 14 appears three times (trisomy) rather than twice in some cells of the body. The term "mosaic" indicates that some cells contain the extra chromosome 14, whereas others have the normal chromosomal pair. The disorder may be characterized by growth delays before birth (intrauterine growth retardation); failure to grow and gain weight at the expected rate (failure to thrive) during infancy; delays in the

	acquisition of skills requiring the coordination of mental and physical abilities (psychomotor delays); and mental retardation. Affected infants also have distinctive abnormalities of the head and facial (craniofacial) region, such as a prominent forehead; deeply set, widely spaced eyes; a broad nasal bridge; and low-set, malformed ears. Additional craniofacial abnormalities may include an unusually small lower jaw (micrognathia); a large mouth and thick lips; and incomplete closure or abnormally high arching of the roof of the mouth (palate). Many affected infants also have structural malformations of the heart (e.g., tetralogy of Fallot). In some cases, additional physical abnormalities may also be present. 19. Hereditary elliptocytosis = A hematologic disorder in which 50–90% of the red blood cells consist of rod forms and elliptocytes; often associated with a hemolytic anemia. There are several autosomal dominant forms, with one form linked to the Rh blood group, caused by mutation in the gene encoding erythrocyte membrane protein band 4.1 (EPB41) on chromosome 1p, while the unlinked form is due to mutation either in the alpha-spectrin gene on 1q, or in the beta-spectrin gene on 14q or the band 3 gene on 17q. There is one autosomal recessive form known. Syn: ovalocytosis.
15	1. Tyrosinase positive oculocutaneous albinism (p-gene on chromosome 15) 2. Laurence-Moon-Bardet-Biedl Syndrome (LMBBS) = is an **autosomal recessive** genetic disorder characterized by obesity, retinal degeneration, extra digits on the hands and feet, and intellectual impairment. The gene responsible for LMBBS was located on chromosome **16q21** (type 2). Shortly thereafter, another gene on chromosome **11q13** (type 1) was identified. Since then, two others were found on chromosomes **3p12** (type 3) and **15q22** (type 4). The most common form of LMBBS is type 1 and the most rare form is type 3. It is expected, however, that another gene that causes the syndrome also exists because there are identified cases that have none of these four defects. Recently, however, the Laurence-Moon-Bardet-Biedl syndrome (LMBBS) was split into Laurence-Moon (LMS) and Bardet-Biedl (BBS), where LMS is characterized as the cases involving mental retardation and spastic paresis and BBS involved obesity, polydactyly, and learning disabilities. It has been shown that BBS represents the majority of published cases. Characteristics that have been seen in children with LMBBS are as follows, Not all children will exhibit all of these features: Rod-cone dystrophy (retinitis pigmentosa) , Strabismus , Nystagmus ,Myopia, Optic

	atrophy, Macular dystrophy, Glaucoma ,Cataracts , Polydactyly (extra fingers and toes), Brachydactyly (short, stubby fingers and toes), Syndactyly (webbing of the toes) , **Obesity** (excess weight gain begins around ages 1 to 2 years) (Kaplan peds, p 32) , Learning disabilities, Developmental delay (delay in sitting, standing, and walking) , Speech delay, Behavioral difficulties, Kidney abnormalities, Hepatic fibrosis, Hypertension (likely a consequence of obesity), Diabetes mellitus, Hypothyroidism, Hypogonadism, Small penis (hypogonadism), Undescended testes (cryptorchidism), Infertile males ,Unusually short tooth roots, Short stature, Ataxic gaits, Deep-set eyes, Premature frontal balding in adult males. 3. Aromatase deficiency syndrome = This syndrome is due to a mutation of gene CYP19 in **chromosome 15q21.1** and inherited in an **autosomal recessive** way. Accumulations of androgens during pregnancy may lead to virilization of a female at birth (males are not affected). Females will have primary amenorrhea. Individuals of both sexes will be tall as lack of estrogen does not bring the epiphyseal lines to closure. The gene CYP19, located on chromosome 15q21.1, encodes the aromatase enzyme. (Kaplan OB, p 151) 4. Tay-Sachs disease (HEXA gene) = infantile GM2 gangliosidosis = hexosaminidase A deficiency, autosomal recessive (pg 53), (genetics p 293), death by age three. Common in Ashkenazi Jews. = a lysosomal storage disease, resulting from hexosaminidase A deficiency. The monosialoganglioside is stored in central and peripheral neuronal cells. Infants present with hyperacusis and irritability, hypotonia, and failure to develop motor skills. Blindness with macular cherry red spots and seizures are evident in the first year. Death occurs within a few years. Autosomal-recessive transmission; found primarily in Jewish populations. (CK p 305), (Peds p 226). 5. Tyrosinemia= A group of **autosomal recessively** inherited disorders of tyrosine metabolism associated with elevated blood concentration of tyrosine, and enhanced urinary excretion of tyrosine and tyrosyl compounds. Type I tyrosinemia, due to deficiency of **fumarylacetoacetase (FAH)**, is characterized by hepatosplenomegaly, nodular liver cirrhosis, multiple renal tubular reabsorptive defects, and vitamin D–resistant rickets; caused by mutation in the FAH gene on **chromosome 15q**. Type II tyrosinemia, due to deficiency of **tyrosine aminotransferase (TAT),** is characterized by corneal ulcers and keratosis of digits, palms,

	and soles; caused by **mutation in the TAT gene on 16q**. Type III tyrosinemia is associated with intermittent ataxia and drowsiness without liver dysfunction and is due to **4-hydroxy-phenylpyruvate dioxygenase (4HPPD) deficiency**. Tyrosinemia is associated with increased risk of neonatal hepatitis and hepatocellular carcinoma. Up to 35% of patient with Tyrosinemia will develop hepatocellular carcinoma. Syn: hypertyrosinemia. 6. Marfan syndrome, Fibrillin gene (FBN1 = 15q21) , fibrillin is the major component of elastin-associated microfibril. Autosomal dominant with (80% penetrance??) (pg 56) = a connective tissue multisystemic disorder characterized by skeletal changes (arachnodactyly, long limbs, joint laxity, pectus), cardiovascular defects (aortic aneurysm which may dissect, mitral valve prolapse), and ectopia lentis; autosomal dominant inheritance, caused by mutation in the fibrillin-1 gene (FBN1) on chromosome 15q. Syn: Marfan disease. 7. Prader – Willi syndrome (father) / Angelman syndrome (mother) (imprinting) Microdeletion of (15q11–13), (genetics pg 307) . (Angelman give "**happy puppet"** syndrome in girls (pathology pg 58,59) but Rett syndrome causes "**Hand wringing**" and not happy puppet (1st aid, p 364). 1) Both male and female can get affected with Prader-Willi syndrome. But only get the Prader – Willi syndrome from the father. 2) Both male and female can get affected with Angelman syndrome. But only get the Angelman syndrome from the mother. 8. Prader-Willi syndrome = Syndrome of hypotonia-hypomentia-hypogonadism-obesity (HHHO) = a congenital syndrome characterized by short stature, "almond shape" eyes, mental retardation, polyphagia with marked obesity, and sexual infantilism (=hypogonadism = pseudo microphallus = small penis); severe muscular hypotonia and poor responsiveness to external stimuli decrease with age; a small deletion is demonstrable in the paternal-derived chromosome 15q11–13 in many cases; some cases are due to maternal uniparental disomy (i.e., both chromosomes 15 are derived from the mother). In Prader-Willi, Lesch Nyhan, get self-mutilation (= bite themselves = self injurious behavior= self destructive behavior). 1) Both male and female can get affected with Prader- Willi syndrome. But only get the Prader – Willi syndrome from the father. 2) Both male and female can get affected with Angelman syndrome. But only get the Angelman syndrome

	from the mother. 9. Angelman Syndrome= Happy Puppet Syndrome = microdeletion of 15q-13, of maternal origin, resulting in mental retardation, ataxia, **paroxysms of laughter**, seizures, characteristic facies, **Microbrachycephaly** and minimal speech. (Angelman give "**happy puppet"** syndrome in girls (pathology pg 58,59) but Rett syndrome causes "**Hand wringing**" and not happy puppet (1st aid, p 364). 1) Both male and female can get affected with Prader- Willi syndrome. But only get the Prader – Willi syndrome from the father. 2) Both male and female can get affected with Angelman syndrome. But only get the Angelman syndrome from the mother. 10. PML (polymorphonuclear leukocyte) gene → AML (acute myelogenous leukemia) type M3 (pg225) 11. t (15, 17) → acute myelogenous leukemia (translocation of retinoid receptor alpha on chromosome 17) → AML , M3 (genetics pg 341) 12. EYCL3 gene on chromosome 15 is responsible for brown or blue eye color 2) EYCL1 gene on chromosome 19 is responsible for blue or green eye color. 13. Autistic disorder = Autism = has been associated with **chromosome 15** (behavioral science, p 146). General medical condition (GMC) associated with autistic disorder include encephalitis, maternal rubella, phenylketonuria (PKU), tuberous sclerosis, fragile X syndrome, and perinatal anoxia. Autism occurs in 5:1 male to female ratio. (Kaplan psych, p 12). Autism= Single Chromosome Mutations, Deletion (1), duplication (2) and inversion (3) are all chromosome abnormalities that have been implicated in autism. Autism has been associated with chromosome 15. Genetic factors are the most significant cause for autism spectrum disorders. Early studies of twins estimated heritability to be more than 90%; in other words, that genetics explains more than 90% of autism cases. This may be an overestimate; new twin data and models with structural genetic variation are needed. When only one identical twin is autistic, the other often has learning or social disabilities. For adult siblings, the risk of having one or more features of the broader autism phenotype might be as high as 30%, much higher than the risk in controls. 14. Bloom syndrome = congenital telangiectatic erythema, primarily in butterfly distribution, of the face and occasionally of the hands and forearms, with sun sensitivity of skin lesions and dwarfism with normal body proportions except for a narrow face and dolichocephalic skull;

	chromosomes are excessively unstable and there is a predisposition to malignancy; autosomal recessive inheritance, caused by mutation in the Bloom syndrome gene (BLM) on chromosome 15q. 15. Bartter syndrome= **Autosomal recessive,** a disorder due to a defect in active chloride reabsorption in the loop of Henle; characterized by primary juxtaglomerular cell hyperplasia with secondary hyperaldosteronism, hypochloremia, high rennin and high aldosterone level, **hypokalemic alkalosis** (1st aid CK, p 360) , hypercalciuria, elevated renin or angiotensin levels, normal or low blood pressure, and growth retardation; edema is absent. **Autosomal recessive inheritance**, caused by mutation in either the **Na-K-2Cl cotransporter gene (SLC12A1) on chromosome 15q or the K (+) channel gene (KCNJ1) on 11q**. 16. Aggrecan= Candidate gene for otosclerosis located at 15q25 to q26.
16	1. PKD-1 (autosomal dominant, Adult polycystic kidney disease= APKD) (pg 144). Polycystic kidney = polycystic disease of kidneys = a progressive disease characterized by formation of multiple cysts of varying size scattered diffusely throughout both kidneys, resulting in compression and destruction of renal parenchyma, usually with hypertension, gross hematuria, and uremia leading to progressive renal failure. There are two major types: 1) with onset in infancy or early childhood, usually of autosomal recessive inheritance ; 2) with onset in adulthood, of autosomal dominant inheritance with genetic heterogeneity ; may be caused by mutation in either **polycystin-1 gene on chromosome 16p, polycystin-2 gene on 4q**, or gene(s) not identified yet. Approximately 50% of patients with ADPKD have **end-stage renal disease (ESRD)** by the age of 60, but those with ADPKD-2 tend to have later onset and slower progression. Hypertension is common and often precedes renal dysfunction. Hematuria may result from cyst rupture into the collecting system or from uric acid or **calcium oxalate kidney stones. Nephrolithiasis** occurs in about 20% of patients. Urinary tract infection occurs with increased frequency in ADPKD. Infection in a kidney or **liver cyst** is a particularly serious complication. It is most often due to Gram-negative bacteria and presents with pain, fever, and chills. Numerous extrarenal manifestations of ADPKD highlight the systemic nature of the disease and likely reflect a generalized abnormality in collagen and extracellular matrix. Patients with ADPKD have a risk of **cerebral hemorrhage from a ruptured**

	intracranial aneurysm as compared to the general population. **Saccular aneurysms** (berry aneurysm??) of the anterior cerebral circulation may be detected in up to 10% of asymptomatic patients on MRA screening. Other vascular abnormalities include **aortic root and annulus dilatation**. Cardiac valvular abnormalities occur in 25% of patients, most commonly **mitral valve prolapse** and **aortic regurgitation**. Although most valvular lesions are asymptomatic, some may progress over time and warrant valve replacement. **Abdominal hernia and inguinal hernia** also occur with a higher frequency than in the general population. 2. Alpha thalassemia = α-Thalassemia= Alpha thalassemia in **chromosome 16** (pg 203).thalassemia due to one of two or more genes that depress (severely or moderately) synthesis of α-globin chains by the chromosome with the abnormal gene. Heterozygous state: severe type, thalassemia minor with 5–15% of Hb Barts at birth, only traces of Hb Barts in adult; mild type, 1–2% of Hb Barts at birth, not detectable in adult. Homozygous state: severe type, erythroblastosis fetalis and fetal death, only Hb Barts and Hb H present; mild type not clinically defined. See Also: hemoglobin H. 3. Tyrosinemia= A group of **autosomal recessive**ly inherited disorders of tyrosine metabolism associated with elevated blood concentration of tyrosine, and enhanced urinary excretion of tyrosine and tyrosyl compounds. **Type I tyrosinemia, due to deficiency of fumarylacetoacetase (FAH)**, is characterized by hepatosplenomegaly, nodular liver cirrhosis, multiple renal tubular reabsorptive defects, and vitamin D–resistant rickets; caused by mutation in the **FAH gene on chromosome 15q**. **Type II tyrosinemia, due to deficiency of tyrosine aminotransferase (TAT)**, is characterized by corneal ulcers and keratosis of digits, palms, and soles; caused by mutation in the **TAT gene on 16q**. **Type III tyrosinemia** is associated with intermittent ataxia and drowsiness without liver dysfunction and is due to **4-hydroxy-phenylpyruvate dioxygenase (4HPPD)** deficiency. Tyrosinemia is associated with increased risk of neonatal hepatitis and hepatocellular carcinoma. Up to 35% of patient with Tyrosinemia will develop hepatocellular carcinoma. Syn: hypertyrosinemia 4. Laurence-Moon-Bardet-Biedl Syndrome (LMBBS) = is an **autosomal recessive** genetic disorder characterized by obesity, retinal degeneration, extra digits on the hands and feet, and intellectual impairment. The gene responsible for LMBBS was located on chromosome **16q21** (type 2). Shortly thereafter, another gene on chromosome **11q13** (type 1) was identified.

	Since then, two others were found on chromosomes **3p12** (type 3) and **15q22** (type 4). The most common form of LMBBS is type 1 and the most rare form is type 3. It is expected, however, that another gene that causes the syndrome also exists because there are identified cases that have none of these four defects. Recently, however, the Laurence-Moon-Bardet-Biedl syndrome (LMBBS) was split into Laurence-Moon (LMS) and Bardet-Biedl (BBS), where LMS is characterized as the cases involving mental retardation and spastic paresis and BBS involved obesity, polydactyly, and learning disabilities. It has been shown that BBS represents the majority of published cases. Characteristics that have been seen in children with LMBBS are as follows, Not all children will exhibit all of these features: Rod-cone dystrophy (retinitis pigmentosa) , Strabismus , Nystagmus ,Myopia, Optic atrophy, Macular dystrophy, Glaucoma ,Cataracts , Polydactyly (extra fingers and toes), Brachydactyly (short, stubby fingers and toes), Syndactyly (webbing of the toes) , **Obesity** (excess weight gain begins around ages 1 to 2 years) (Kaplan peds, p 32) , Learning disabilities, Developmental delay (delay in sitting, standing, and walking) , Speech delay, Behavioral difficulties, Kidney abnormalities, Hepatic fibrosis, Hypertension (likely a consequence of obesity), Diabetes mellitus, Hypothyroidism, Hypogonadism, Small penis (hypogonadism), Undescended testes (cryptorchidism), Infertile males ,Unusually short tooth roots, Short stature, Ataxic gaits, Deep-set eyes, Premature frontal balding in adult males. 5. Rubinstein-Taybi syndrome= mental retardation, broad thumb and great toe, antimongoloid slant to the eyes, thin and beaked nose, microcephaly, prominent forehead, low-set ears, high arched palate, and cardiac anomaly; there may be a submicroscopic chromosomal defect, but there is evidence that this syndrome is due to mutation in the gene encoding transcriptional coactivator CREB-binding protein (CREB) on chromosome 16p. 6. Familial paroxysmal polyserositis= transient recurring attacks of abdominal pain, fever, pleurisy, arthritis, and rash; the condition is asymptomatic between attacks; autosomal recessive inheritance, caused by mutation in the marenostrin gene on 16p. There is an autosomal dominant form in which amyloidosis in common. Syn: familial Mediterranean fever, Mediterranean fever(2), benign paroxysmal peritonitis, periodic peritonitis, familial recurrent polyserositis, periodic polyserositis. MEFV (Mediterranean fever) gene is a human gene that provides instructions for making a protein called pyrin (also known as marenostrin). Pyrin is produced in certain white blood cells

	(neutrophils, eosinophils and monocytes) that play a role in inflammation and in fighting infection. The MEFV gene is located on the short (p) arm of chromosome 16 at position 13.3. 7. EEM syndrome (or Ectodermal dysplasia, Ectrodactyly and Macular dystrophy syndrome) = is an **autosomal recessive** congenital malformation disorder affecting tissues associated with the ectoderm (skin, hair, nails, teeth), and also the hands, feet and eyes. EEM syndrome is caused by mutations in the P-cadherin gene (CDH3).Distinct mutations in **CDH3 (located on human chromosome 16)** are responsible for the macular dystrophy and spectrum of malformations found in EEM syndrome, due in part to developmental errors caused by the resulting inability of CDH3 to respond correctly to the P-cadherin transcription factor p63.The gene for p63 (TP73L, found on human chromosome 3) may also play a role in EEM syndrome. Mutations in this gene **(= P63 mutation)** are associated with the symptoms of EEM and similar disorders, particularly ectrodactyly. EEM syndrome is an **autosomal recessive** disorder, which means the defective gene is located on an autosome, and two copies of the defective gene - one from each parent - are required to inherit the disorder. The parents of an individual with an autosomal recessive disorder both carry one copy of the defective gene, but usually do not experience any signs or symptoms of the disorder. **P63 mutation is associated with ankyloblepharon-ectodermal dysplasia-clefting syndrome and ecodactyly-ectodermal dysplasia-clefting syndrome.** 8. Gitelman syndrome = a disorder seen in older children and young adults characterized by hypokalemia, hypomagnesemia, hypocalciuria, and sometimes tetany. Gitelman syndrome is a rare **inherited defect in the distal convoluted tubule** of the kidneys. It causes the kidneys to pass sodium, magnesium, chloride, and potassium into the urine, rather than allowing it to be resorbed into the bloodstream. Gitelman syndrome is not to be confused with Bartter syndrome, which is a rare inherited defect in the thick ascending limb of the loop of Henle. **Gitelman's syndrome is linked to inactivating mutations in the SLC12A3 gene resulting in a loss of function of the encoded thiazide-sensitive sodium-chloride co-transporter (NCCT)**. This cell membrane protein participates in the control of ion homeostasis at the distal convoluted tubule portion of the nephron. Gitelman's syndrome is an **autosomal-recessive disorder**: one defective gene has to be inherited from each parent. An attractive candidate gene for one form of Bartter syndrome is the thiazide-sensitive Na-Cl cotransporter of the distal convoluted tubule (SLC12A3), which is believed to be the principal mediator of sodium and

	chloride reabsorption in this segment of the nephron, accounting for a significant fraction of net renal sodium reabsorption. This cotransporter is the target of thiazide diuretics, one of the major classes of agents used in the treatment of hypertension. Simon et al. (1996) demonstrated complete linkage of Gitelman syndrome to the **thiazide-sensitive Na-Cl cotransporter gene on 16q13**. 9. Variants of the **caspase activating recruitment domain 15/nucleotide oligomerization domain 2 (CARD15/NOD2) gene** have been associated with susceptibility to **Crohn's disease** (CD). **CARD15/NOD2 is located on chromosome 16.** Inflammatory bowel diseased (IBD) = IBD includes **Crohn disease (CD)** and **ulcerative colitis (UC)**. Both are characterized by exacerbations and remission. It is more common in Jews and whites, and tends to run in families, indicating a genetic influence (Kaplan Peds, p 176). **Anti-saccharomyces cerevisiae antibodies (ASCA)** are associated with Crohn's disease and **antineutrophil cytoplasmic antibody (ANCA)** is associated with ulcerative colitis (Kaplan IM, p 12). (does this also have any thing to do with chromosome 6 and major histocompatibility complex (MHC) and human leukocyte antigens (HLA) in chromosome 6p??) 10. NOD2 (nucleotide-binding oligomerization domain containing 2) is a protein, also known as the caspase recruitment domain family, member 15 (CARD15), which plays an important role in the immune system. It is an intracellular pattern recognition receptor, which is similar in structure to resistant proteins of plants and recognizes molecules containing the specific structure called muramyl dipeptide (MDP) that is found in certain bacteria. The NOD2 gene is linked to inflammatory diseases such as inflammatory bowel disease/Crohn's Disease and Blau syndrome. **It is located on chromosome 16 in humans**. This gene is a member of the Nod1/Apaf-1 family and encodes a protein with two caspase recruitment (CARD) domains and six leucine-rich repeats (LRRs). The protein is primarily expressed in the peripheral blood leukocytes. It plays a role in the immune response to intracellular bacterial lipopolysaccharides (LPS) by recognizing the muramyl dipeptide (MDP) derived from them and activating the NFKB protein. Mutations in this gene have been associated with Crohn disease and Blau syndrome. 11. Blau syndrome = is a rare condition typically defined by granulomatous arthritis, skin eruption, and uveitis occurring in the absence of lung or other visceral involvement. Other

	characteristic physical findings include synovial cysts and camptodactyly. It's **autosomal dominant inheritance and anticipation**. Blau syndrome comprises granulomatous arthritis, iritis, and skin rash, and is an autosomal-dominant trait with **variable expressivity**. Blau syndrome is mutation of CARD 15/NOD 2 in sporadic early onset. Patients with sporadic early-onset granulomatous arthritis are clinically identical to Blau syndrome, but without the family history. Blau syndrome is an **autosomal dominant inherited** disease caused by mutations in the **CARD15 gene (also called NOD2). It is located on chromosome 16 in humans**. The nucleotide change (mutation) encodes an amino acid **substitution from arginine to tryptophan at position 334** of the protein. This mutation has been found in some Blau syndrome pedigrees reported in the literature. These data suggest that sporadic granulomatous arthritis may in fact be the sporadic form of Blau syndrome, but arising from a spontaneous neomutation (=new mutation). This would explain the profound clinical identity and the lack of disease history in the parents. 12. Tuberous sclerosis = Bourneville disease= epiloia = phacomatosis characterized by the formation of multisystem hamartomas producing seizures, mental retardation, and **angiofibromas (= fibroangioma = adenoma sebaceum)** of the face; the cerebral and retinal lesions are glial nodules; other skin lesions are hypopigmented macules, shagreen patches, and periungual fibromas; **autosomal dominant** inheritance with variable expression, caused by mutation in either the tuberous sclerosis Complex gene (T9SC1) which encodes for protein hamartin on chromosome 9q (9q34) or TSC2 which encodes for protein tuberin on chromosome 16 (16p13.3). (Kaplan peds, p232). TSC2 is contiguous with PKD1 , the gene involved in one from of polycystic kidney disease (PKD). Gross deletions affecting both genes may account for the 2% of individuals with TSC who also develop PKD in childhood. Spontaneous pneumothorax happens in people with tuberous sclerosis.
17	1. Osteogenesis imperfecta, type 2 (genetic pg 302). Osteogenesis imperfecta (OI) = a group of connective tissue disorders of type I collagen, characterized by **bone fragility, fractures on trivial trauma, skeletal deformity, blue sclerae, ligament laxity, and hearing loss**. The Sillence system, which is a clinical, radiographic, and genetic classification, shows four types; inherited as autosomal dominant, caused by mutation in either the collagen type I alpha-1 gene (COL1A1) on chromosome 17q or the alpha-2 gene (COL1A2) on 7q. Syn: brittle bones 2. Tumor suppressor gene (NF-1) for **neurofibromatosis** on

	(17q, 11.2) (neurofibromatosis is 17 letters → chromosome 17) = Neurofibromatosis Type 1= Von Recklinghausen disease, peripheral nerve tumors (pg 57) 3. Tylosis with esophageal cancer= nonepidermolytic palmoplantar keratoderma = A genetic disorder characterized by thickening (hyperkeratosis) of the palms and soles, white patches in the mouth (oral leukoplakia), and a very high risk of esophageal cancer. This is the only genetic syndrome known to predispose to squamous cell carcinoma of the esophagus. The risk of developing esophageal cancer is 95% by age 70. The syndrome is inherited in an autosomal dominant manner. The gene has been mapped to chromosome 17q25 but has not been identified. The syndrome is also called nonepidermolytic palmoplantar keratoderma. The causative locus, the tylosis esophageal cancer (TOC) gene, has been localized to a small region on chromosome 17q25. Recent loss of heterozygosity (LOH) studies have indicated a role for the TOC gene in sporadic squamous cell esophageal cancer and Barrett's adenocarcinoma. 4. Peroneal Muscular Atrophy= Charcot-Marie-Tooth disease (CMT)= Hereditary Motor-Sensory Neuropathy (HMSN) Type 1= a group of peripheral neuromuscular disorders, sharing the common feature of marked wasting of the distal parts of the extremities, particularly the peroneal muscle groups, resulting in long, thin legs; it usually involves the legs before the arms with pes cavus often the first sign. There are two forms of hereditary sensorimotor polyneuropathies, i.e., a demyelinating type and an axonal loss type. **Autosomal dominant** (Kaplan peds, p 228), autosomal recessive, and X-linked recessive forms exist. One of the most common forms of CMT is Type 1A. The gene for Type 1A CMT maps to chromosome 17 and is thought to code for a protein (PMP22) involved in coating peripheral nerves with myelin, a fatty sheath that is important for their conductance. Other types of CMT include Type 1B, autosomal-recessive, and X-linked. The same proteins involved in the Type 1A and Type 1B Charcot-Marie-Tooth disease (CMT) are also involved in a disease called Dejerine–Sottas Syndrome (DSS), in which similar clinical symptoms are presented, but they are more severe. Patient present with claw hands and storklike lower extremities. (Kaplan Peds, p 228)

	5. White sponge nevus= an autosomal dominant condition of the oral cavity characterized by soft, white or opalescent, thickened, and corrugated folds of mucous membrane; other mucosal sites are occasionally involved simultaneously; caused by mutation in either the mucosal keratin gene K4 on chromosome 12 or keratin-13 gene on 17. Syn: familial white folded dysplasia, oral epithelial nevus. 6. Smith-Magenis syndrome = interstitial delation of chromosome band (17p 11.2). Smith-Magenis syndrome is a developmental disorder that affects many parts of the body. The major features of this condition include mild to moderate mental retardation, delayed speech and language skills, distinctive facial features, sleep disturbances, and behavioral problems. Most people with Smith-Magenis syndrome have a broad, square-shaped face with deep-set eyes, full cheeks, and a prominent lower jaw. The middle of the face and the bridge of the nose often appear flattened. The mouth tends to turn downward with a full, outward-curving upper lip. These facial differences can be subtle in early childhood, but they usually become more distinctive in later childhood and adulthood. Dental abnormalities are also common in affected individuals. Disrupted sleep patterns are characteristic of Smith-Magenis syndrome, typically beginning early in life. Affected people may be very sleepy during the day, but have trouble falling asleep and awaken several times each night. People with Smith-Magenis syndrome have affectionate, engaging personalities, but most also have behavioral problems. These include frequent temper tantrums and outbursts, aggression, anxiety, impulsiveness, and difficulty paying attention. Self-injury, including biting, hitting, head banging, and skin picking, is very common. Repetitive self-hugging is a behavioral trait that may be unique to Smith-Magenis syndrome. People with this condition also compulsively lick their fingers and flip pages of books and magazines (a behavior known as "lick and flip"). Other signs and symptoms of Smith-Magenis syndrome include short stature, abnormal curvature of the spine (scoliosis), reduced sensitivity to pain and temperature, and a hoarse voice. Some people with this disorder have ear abnormalities that lead to hearing loss. Affected individuals may have eye abnormalities that cause nearsightedness (myopia) and other vision problems. Although less common, heart and kidney defects also have been reported in people with Smith-Magenis syndrome. **Smith-Magenis syndrome is related to chromosome 17. Mutations in the RAI1 gene cause Smith-Magenis syndrome**. Most people with Smith-Magenis

	syndrome have a deletion of genetic material from a specific region of **chromosome 17**. Although this region contains multiple genes, researchers believe that the loss of one particular gene, RAI1, in each cell is responsible for most of the characteristic features of this condition. The loss of other genes in the deleted region may help explain why the features of Smith-Magenis syndrome vary among affected individuals. A small percentage of people with Smith-Magenis syndrome have a mutation in the RAI1 gene instead of a chromosomal deletion. Although these individuals have many of the major features of the condition, they are less likely than people with a chromosomal deletion to have short stature, hearing loss, and heart or kidney abnormalities. The RAI1 gene provides instructions for making a protein whose function is unknown. Mutations in one copy of this gene lead to the production of a nonfunctional version of the RAI1 protein or reduce the amount of this protein that is produced in cells. Researchers are uncertain how changes in this protein result in the physical, mental, and behavioral problems associated with Smith-Magenis syndrome. **Smith-Magenis syndrome is typically NOT inherited**. This condition usually results from a genetic change that occurs during the formation of reproductive cells (eggs or sperm) or in early fetal development. Most often, people with Smith-Magenis syndrome have no history of the condition in their family. 7. Pachyonychia congenita= a syndrome of ectodermal dysplasia of abnormal thickness and elevation of nail plates with palmar and plantar hyperkeratosis; the tongue is whitish and glazed owing to papillary atrophy; autosomal dominant inheritance caused by mutation in the keratin 16 gene (KRT16) on chromosome 17q or the keratin 6A gene (KRT6A) on 12q. Syn: Jadassohn-Lewandowski syndrome 8. Hyperkalemic periodic paralysis=[type II]. a form of periodic paralysis in which the serum potassium level is elevated during attacks; onset occurs in infancy, attacks are frequent but relatively mild, and myotonia is often present; autosomal dominant inheritance caused by mutation in the sodium channel gene (SCN4A) on chromosome 17q. 9. Epidermolysis bullosa lethalis= a form of epidermolysis bullosa characterized by persistent and nonhealing perioral and perinasal crusted lesions with bullae often present in the oral mucosa and trachea, but not on the palms and soles, complicated by dermal sepsis and serum protein and electrolyte loss leading to death; autosomal recessive inheritance, caused by mutation in any one of the

	three distinct polypeptides of laminin-5; alpha-3 (LAMA3) on chromosome 18q, beta-3 (LAMB3) and gamma-2 (LAMC2) on 1q or the gene encoding integrin, beta-4 (ITGB4) on 17q. Syn: epidermolysis bullosa , epidermolysis bullosa, junctional type, Herlitz syndrome. 10. Epidermolytic Hyperkeratosis= Porcupine Skin = characterized by localized lesions, keratosis palmaris and plantaris, and elevated IgE, associated with hyperkeratosis, hypergranulosis, and reticular degeneration in the upper epidermis; **autosomal dominant inheritance**, caused by mutation in the epidermolytic palmoplantar keratoderma gene (EPPK) on chromosome 17q. Generalized epidermolytic hyperkeratosis is present in bullous congenital ichthyosiform erythroderma. Epidermolytic Hyperkeratosis is a rare autosomal dominant ichthyosis resulting from defects in keratin 1 and 10. it is manifest at birth as diffuse erythema with epidermal sloughing (Bullous congenital ichthyosiform erythroderma). 11. Epidermolysis bullosa= a group of inherited chronic noninflammatory skin diseases in which large bullae and erosions result from slight mechanical trauma; a form localized to the hands and feet is called Weber-Cockayne syndrome, of autosomal dominant inheritance caused by mutation in either the gene encoding keratin-5 (KRT5) on chromosome 12q or the gene for keratin-14 (KRT14) on 17q. Syn: epidermolysis bullosa dystrophica, epidermolysis bullosa lethalis, epidermolysis bullosa simplex, mechanobullous disease. 12. Cystinosis = A lysosomal storage disorder with various forms, all with **autosomal recessive** inheritance. The nephropathic form of early childhood is characterized by widespread deposits of cystine crystals throughout the body, including the bone marrow, cornea, and other tissues, with mild elevation of plasma cystine and cystinuria; associated with a marked generalized aminoaciduria, glycosuria, polyuria, chronic acidosis, hypophosphatemia with vitamin D-resistant rickets, and often with hypokalemia; other extrarenal manifestations include photophobia and hypothyroidism; due to a defect in the transport of cystine across lysosomal membranes caused by mutation in the **CTNS gene on 17p**. There is a milder form with onset in adolescence and one with onset in adulthood without kidney damage; the latter two forms are thought to be allelic to the nephropathic form of early childhood. Syn: cystine storage disease.

	13. Amaurosis congenita of Leber= a disorder of cone-rod abiotrophy causing blindness or severely reduced vision at birth; autosomal recessive inheritance with at least 3 different loci. Type I is caused by mutation in the gene for retinal guanylate cyclase (GUC2D) on chromosome 17p, type II by mutation in the gene for retinal pigment epithelium-specific 65-kD protein (RPE65) on 1p, and type III by mutation in the gene for photoreceptor-specific homeobox gene CRX on 19q. 14. p53 tumor suppressor gene on (17q, 13.1) = gene 17p → Li Fraumeni syndrome (genetic pg 360), lung, breast, colon cancer (pg 83). Also note the human papilloma virus (HPV) viral gene E6 inhibits p53 tumor suppressor gene→ cause malignancy + endometrial cancer. (micro pg 397). p53 chromosomal mutations is consistent with squamous cell carcinoma. p53 mutations are associated with the Li-Fraumeni syndrome, which carries an increased risk for gastric carcinoma and soft-tissue sarcomas, breast cancer, adrenocortical tumors, CNS tumors and others. Chemical present in cigarette smoking have been shown to cause specific mutations in the p53 tumor suppressor gene which seen in patient with small cell lung cancer (SCLC). 15. Tumor suppressor gene RAS 16. Retinoic acid receptor alpha gene (pg225) 17. t (15, 17) → acute myelogenous leukemia (translocation of retinoid receptor alpha on chromosome 17) → AML , M3 (genetics pg 341) 18. BRCA-1 gene (17q, 12-21) → breast cancer, ovarian cancers(pg 83,242) 19. Van Der Woude syndrome = Autosomal Dominant cleft lip/cleft palate = Van Der Woude syndrome is an autosomal dominant syndrome characterized by a cleft lip or cleft palate, distinctive pits of the lower lips, or both. It is the most common syndrome associated with cleft lip or cleft palate. The degree to which individuals who carry the gene are affected widely varies, even within families (= **variable expression**). These variable manifestations include lower lip pits alone, absent teeth, or isolated cleft lip and cleft palate of varying severity. Hypodontia (absent teeth) has been increasingly recognized as a frequently associated anomaly. Many other associated anomalies have also been described. Most cases of van der Woude syndrome have been linked to a deletion in **chromosome 1q32-q41**; however, a second chromosomal **locus at 1p34** has also been identified. The responsible mutation has been identified in the

	interferon regulatory factor-6 (IRF -6) gene, but the exact mechanism of this mutation on craniofacial development is uncertain. Demonstrating the presence or absence of an IRF-6 mutation can be helpful when distinguishing between uncomplicated cleft lip and/or cleft palate and van der Woude syndrome. A wide variety of chromosomal mutations that cause van der Woude syndrome and are associated with IRF-6 gene mutations have been described. A potential modifying gene has been identified at **17p11.2-p11.1**. 20. Galactokinase Deficiency= an inborn error of metabolism due to congenital deficiency of galactokinase (GALK), resulting in increased blood galactose concentration (galactosemia), **cataracts, hepatomegaly, and mental deficiency**; autosomal recessive inheritance, caused by mutation in the GALK gene on 17q. Galactose epimerase deficiency and galactose-1-phosphate uridyl transferase deficiency produce much the same clinical picture. (Kaplan Peds, p 6). 21. Glanzmann thrombasthenia = hereditary hemorrhagic thrombasthenia = Glanzmann disease, hereditary hemorrhagic thrombasthenia, constitutional thrombopathy = a hemorrhagic diathesis characterized by normal or prolonged bleeding time, normal coagulation time, defective clot retraction, normal platelet count but morphologic or functional abnormality of platelets; several different kinds of platelet abnormalities have been described; caused by defect in platelet membrane glycoprotein IIb-IIIa complex; **autosomal recessive** inheritance, caused by mutation in the platelet-membrane glycoprotein IIb-IIIa complex gene (ITGA2B) on chromosome 17. A disorder with a defect in the GPIIb-IIIa platelet receptor and decrease plate aggregation → defect clot formation (get clot retraction n, no clumping), platelet counts, PT, PTT are normal. Get abnormal result in platelet aggregation studies with ADP (CK p 403). 22. Congenital paramyotonia = Paramyotonia congenita = autosomal dominant inheritance caused by mutation in the sodium channel gene (SCN4A) on chromosome 17q 23. Another type of HIBM (Hereditary Inclusion Body Myopathies), inclusion body myopathy associated with Paget disease of bone and frontotemporal dementia (IBMPFD), is linked to a slightly different gene on chromosome 9 (located at 9p13-p12). d). Another type of HIBM (Hereditary Inclusion Body Myopathies), inclusion body myopathy-3

(IBM3) is linked to mutations in a gene encoding myosin heavy chain II proteins on chromosome 17 (located at 17p13.1).

24. Weber-Cockayne syndrome = epidermolysis bullosa of the hands and feet; autosomal dominant inheritance, caused by mutation in the keratin 5 gene (KRT5) on chromosome 12q or keratin 14 gene (KRT14) on 17q.
25. Dejerine-Sottas disease = a familial type of demyelinating sensorimotor polyneuropathy that begins in early childhood and is slowly progressive; clinically characterized by foot pain and paresthesias, followed by symmetrical weakness and wasting of the distal limbs; one of the causes of stork legs; patients are wheelchair-bound at an early age; peripheral nerves are palpably enlarged and non-tender; pathologically, onion bulb formation is seen in the nerves: whorls of overlapping, intertwined Schwann cell processes that encircle bare axons; usually autosomal recessive inheritance; an autosomal dominant form also exists; both forms can be caused by mutations in the peripheral myelin protein **gene 22** (PMP22) on **17q** or in the myelin protein zero gene (MPZ) on **1q**. Syn: Dejerine disease, hereditary hypertrophic neuropathy, progressive hypertrophic polyneuropathy.
26. Sanfilippo Syndrome= Mucopolysaccharidosis III =MPS-III= an error of the mucopolysaccharide metabolism, with excretion of large amounts of heparan sulfate in the urine; characterized by severe mental retardation with hepatomegaly; skeleton may be normal or may present mild changes similar to those in Hurler syndrome; several different types (A, B, C, and D) have been identified according to the enzyme deficiency; autosomal recessive inheritance. Syn: type III mucopolysaccharidosis. (Hunter syndrome is one of the disease of mucopolysaccharidosis which is X-linked recessive, other examples are hurler and Sanfilippo that are autosomal recessive) (Kaplan peds, p225). Sanfilippo syndrome is a rare **autosomal recessive** lysosomal storage disease caused by a deficiency in one of the enzymes needed to break down the glycosaminoglycan heparan sulfate (which is found in the extra-cellular matrix and on cell surface glycoproteins). Although undegraded heparan sulfate is the primary stored substrate, glycolipids such as gangliosides are also stored despite no genetic defect in the enzymes associated with their breakdown. The four types of MPS-III are due to specific enzyme deficiencies affecting the breakdown of heparan

	sulfate, which then builds up in various organs. **All four types have autosomal recessive inheritance**. 1) Sanfilippo syndrome type-A= MPS-III type-A: deficiency in enzyme heparan N-sulfatase, gene location on **chromosome 17q25.3** 2) Sanfilippo syndrome type-B = MPS-III type-B: deficiency in enzyme N-acetyl-alpha-D-glucosaminidase, gene location on **chromosome 17q21**. 3) Sanfilippo syndrome type-C = MPS-III type-C: deficiency in enzyme acetyl-CoA:alpha-glucosaminide acetyltransferase , gene location on **chromosome 8p11-q13** 4) Sanfilippo syndrome type-D= MPS-III type-D : deficiency in enzyme N-acetylglucosamine-G-sulfate sulfatase , gene location on **chromosome 12q14**. 27. Canavan disease= progressive degenerative disease of infancy; mostly affecting Ashkenazi Jewish babies; onset typically within the first 3–4 months of birth; characterized by megalencephaly, optic atrophy, blindness, psychomotor regression, hypotonia, and spasticity; there is increased urinary excretion of N-acetylaspartic acid. MRI shows enlarged brain, decreased attenuation of cerebral and cerebellar white matter, and normal ventricles; pathologically, there is increased brain volume and weight and spongy degeneration in the subcortical white matter. Autosomal recessive inheritance, caused by mutation in the aspartoacyclase A gene (ASPA) on chromosome 17p in Jewish and non-Jewish affected individuals. See Also: leukodystrophy. Syn: spongy degeneration of infancy, Canavan-van Bogaert-Bertrand disease, Canavan sclerosis 28. Sjögren-Larsson syndrome= congenital ichthyosis in association with oligophrenia and spastic paraplegia; autosomal recessive inheritance, caused by mutation in the fatty aldehyde dehydrogenase gene (FALDH) on chromosome 17p. 29. Hereditary elliptocytosis = A hematologic disorder in which 50–90% of the red blood cells consist of rod forms and elliptocytes; often associated with a hemolytic anemia. There are several autosomal dominant forms, with one form linked to the Rh blood group, caused by mutation in the gene encoding erythrocyte membrane protein band 4.1 (EPB41) on chromosome 1p, while the unlinked form is due to mutation either in the alpha-spectrin gene on 1q, or in the beta-spectrin gene on 14q or the band 3 gene on 17q. There is one autosomal recessive form known. Syn: ovalocytosis.

18	2. Edward's syndrome (trisomy 18) (pg47) ,life span less than 1 year (the average life span is 2-3 months) = trisomy 18 syndrome = a chromosomal disorder that is usually fatal within 2–3 years; characterized by mental retardation, abnormal skull shape, low-set and malformed ears, small mandible, cardiac defects, short sternum, diaphragmatic or inguinal hernia, Meckel diverticulum, abnormal flexion of fingers, rockerbottom feet, hammer toes, omphalocele, clenched hand, and dermatoglyphic anomalies. Syn: Edwards syndrome. 3. Epidermolysis bullosa lethalis= a form of epidermolysis bullosa characterized by persistent and nonhealing perioral and perinasal crusted lesions with bullae often present in the oral mucosa and trachea, but not on the palms and soles, complicated by dermal sepsis and serum protein and electrolyte loss leading to death; autosomal recessive inheritance, caused by mutation in any one of the three distinct polypeptides of laminin-5; alpha-3 (LAMA3) on chromosome 18q, beta-3 (LAMB3) and gamma-2 (LAMC2) on 1q or the gene encoding integrin, beta-4 (ITGB4) on 17q. Syn: epidermolysis bullosa , epidermolysis bullosa, junctional type, Herlitz syndrome. 4. Byler disease= progressive intrahepatic cholestasis, with early onset of loose, foul-smelling stools, jaundice, hepatosplenomegaly, dwarfism, and occasionally death; due to an error in conjugated bile salt metabolism; **autosomal recessive inheritance**, caused by mutation in the **familial intrahepatic cholestasis 1 gene (FIC1) on chromosome 18q**. Aagenaes syndrome = an idiopathic form of **familial intrahepatic cholestasis** associated with lymphedema of the lower extremities. 5. BCL-2 (inhibit apoptosis) → live forever (pg 10,83,217,212) 6. t (14, 18) follicular lymphomas, = Small cleaved cell lymphoma = (translocation of bcl-2 that inhibits apoptosis) and activation of Bcl-2(genetics pg 341), translocation involving the immunoglobulin chain site and Bcl-2. **Heavy chain is on chromosome 14 and BCL-2 is on chromosome 18**. Follicular lymphoma = nodular lymphoma = malignant lymphoma arising from lymphoid follicular B cells which may be small or large, growing in a nodular pattern. Syn: giant follicular lymphoblastoma. 7. Hereditary nonpolyposis syndrome = Hereditary

	nonpolyposis colon cancer = Hereditary nonpolyposis colorectal cancer = HNPCC = nonpolyposis inherited colon cancer (lynch syndrome): autosomal dominant, 1) lynch syndrome I : only associated with colon cancer 2) lynch syndrome II (family cancer syndrome) is associated with colorectal Cancer, endometrial Cancer, Ovarian Cancer, gastric Cancer and other types of cancer. Lynch Syndrome II is associated with extracolonic tumor development. (Surgery BRS, p 322), (IM p 20) 8. Synovial sarcoma= **t (X, 18)** = a rare malignant tumor of synovial origin, most commonly involving the knee joint and composed of spindle cells usually enclosing slits or pseudoglandular spaces that may be lined by radially disposed epithelial-like cells**.** It is due to **Translocation of some part of chromosome X with some part of chromosome 18.** (pg 326). 9. **(18q, 21)** = DCC = deleted in colon cancer gene → colon cancer and gastrointestinal carcinoma (pg 83) 10. **18q**, DPC = deleted in pancreatic cancer → pancreatic cancer = cancer of Pancreas. SMAD family member 4, also known as SMAD4, is a human gene. SMAD4 (also known as DPC4 or Mothers against decapentaplegic homolog 4) is a 552 amino acid polypeptide involved in cell signaling. It belongs to the Darfwin family of proteins which modulate members of the TGFβ protein superfamily. It binds receptor regulated SMADs such as SMAD1 or SMAD2 and forms a complex that binds to DNA and serves as a transcription factor. It is the only known mammalian coSMAD. It is a homolog of the Drosophila protein: "Mothers against decapentaplegic". SMAD4, is often found mutated in many cancers. It acts as a tumor suppressor that functions in the regulation of the TGF-β signal transduction pathway, which negatively regulates growth of epithelial cells and the extracellular matrix (ECM). SMAD4 alterations have been found in multiploid colorectal cancer and pancreatic carcinoma. It is found inactivated in at least 50% of pancreatic cancers. It is also found mutated in the autosomal dominant disease juvenile polyposis syndrome (JPS). JPS is characterized by hamartomatous polyps in the gastrointestinal (GI) tract. These polyps are usually benign, however they are at greater risk of developing gastrointestinal cancers, in particular colon cancer. Somatic mutations found in human cancers of the MH1 domain of Smad4 have been shown to inhibit the DNA-binding function of this domain.

19	1. Type II familial hyperlipoproteinemia = defect of the receptor or a modified LDL-apolipoprotein B-100, caused by mutation in the LDL receptor (LDLR) gene on chromosome 19p = Apo E4 allele = Familial hypercholesterolemia, mutation of LDL receptor= LDL receptor deficiency (pg 55), LDL receptor = apoB-100 receptor (biochem pg216). hyperlipoproteinemia characterized by increased plasma levels of β-lipoproteins and cholesterol, elevated or normal levels of triglycerides; heterozygotes have mild lipid changes and are susceptible to atherosclerosis in middle age, but homozygotes have severe changes—often with generalized xanthomatosis, xanthelasma, corneal arcus, and frank clinical atherosclerosis as young adults. This disorder is divided into two classes, both inherited as autosomal dominant with homozygotes more severely affected than heterozygotes: 1) type IIA, which is characterized by elevated LDL but normal triglycerides and is due to a deficiency of the LDL receptor, a defect of the receptor or a modified LDL-apolipoprotein B-100, caused by mutation in the LDL receptor (LDLR) gene on chromosome 19p. SYN familial hypercholesterolemia; 2) type IIB has elevated LDL, cholesterol, and triglycerides, due to dysregulation of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG CoA reductase), the rate-controlling enzyme in cholesterol biosynthesis. SYN familial hyperbetalipoproteinemia, familial hypercholesterolemic xanthomatosis. 2. Hereditary multiple exostoses (HME) = Hereditary multiple exostoses (HME) is a rare medical condition in which multiple bony spurs or lumps (also known as exostoses, or osteochondromas) develop on the bones of a child. HME is synonymous with Multiple hereditary exostoses and Multiple osteochondromatosis. HME can cause pain to people of all ages. To children, this can be especially painful. HME is an **autosomal dominant** hereditary disorder. HME has thus far been linked with mutations in three genes. 1) **EXT1 which maps to chromosome 8q24.1** 2) **EXT2 which maps to 11p13** 3) **EXT3 which maps to the short arm of Chromosome 19** (though its exact location has yet to be precisely determined). 3. Pseudoachondroplasia= A skeletal dysplasia characterized by short-limb dwarfism with leg deformities associated with genu varum or genu valgum and ligamentous laxity, allowing the joints to telescope; normal appearing head and face. Autosomal dominant inheritance caused by mutation in the cartilage oligomeric matrix protein gene

	(COMP) on 19p. Syn: pseudoachondroplastic spondyloepiphysial dysplasia. 4. Type III familial hyperlipoproteinemia = mutation in the APOE gene on chromosome 19q. Hyperlipoproteinemia characterized by increased plasma levels of LDL, β-lipoproteins, pre-β-lipoproteins, cholesterol, phospholipids, and triglycerides; hypertriglyceridemia induced by a high carbohydrate diet, and glucose tolerance is abnormal; frequent eruptive xanthomas and atheromatosis, particularly coronary artery disease; biochemical defect lies in apolipoproteins; there are many varieties; one variety is caused by mutation in the APOE gene on chromosome 19q. Syn: dysbetalipoproteinemia, familial hyperbetalipoproteinemia and hyperprebetalipoproteinemia, familial hypercholesterolemia with hyperlipemia, carbohydrate-induced hyperlipemia 5. Apolipoprotein E (Alzheimer dementia) (behavioral science pg 175). 6. Dicumarol resistance= an autosomal dominant disorder characterized by resistance to dicumarol, over and above general variability in tolerance to the drug; caused by mutation in the coumarin 7-hydroxylase gene (CYP2A6) on chromosome 19p. 7. Familial nephrosis= the nephrotic syndrome appearing in siblings in infancy, without nerve deafness; inherited as an autosomal recessive, the Finnish type of which is due to mutation in the nephrin gene on chromosome 19q. 8. Central core disease= a congenital myopathy characterized by **hypotonia**, delay of motor development in infancy, and nonprogressive or slowly progressive muscle weakness; on biopsy the central core of muscle fibers stains abnormally, myofibrils are abnormally compact, and there is virtual absence of mitochondria and sarcoplasmic reticulum; histochemically, the cores are devoid of oxidative enzyme, phosphorylase, and ATPase activity; **autosomal dominant inheritance**, often subclinical, caused by **mutation in the ryanodine receptor-1 gene (RYR1) on 19q**. 9. Myotonic Muscular Dystrophy = MMD = Steinert Disease = adult muscular dystrophy, **autosomal dominant**. Abnormal trinucleotide repeat expansion(**CTG repeat** in 3' UTR) in the gene coding for the **dystrophia myotonin protein kinase gene (DMPK)** on **chromosome 19q** . Myotonic dystrophy is associated with **cataracts and heart conduction defects**, the disease is chronic, slowly progressive multisystem disease primarily characterized by

	muscle wasting. The sensory findings clearly suggest a neurologic process, rather than a musculoskeletal one. (Genetics pg 305). The disease manifests with sustained contraction and stiffness of skeletal muscles. **Baldness**, cataracts, and cardiomyopathy are associated abnormalities. Myotonic Dystrophy = the most common adult muscular dystrophy, characterized by progressive muscle weakness and wasting of some of the cranial innervated muscles, as well as the distal limb muscles; other clinical features include **myotonia, cataracts, hypogonadism, cardiac abnormalities (such as dilated (congestive cardiomyopathy) (IM, p 150), "V- shape mouth, V shape lips" and frontal balding, frontal baldness, temporal wasting**; onset usually in the third decade; autosomal dominant inheritance caused by abnormal trinucleotide repeat expansion in the dystrophia myotonica protein kinase gene (DMPK) on chromosome 19q. This disorder demonstrates **anticipation (increase in severity in successive generations because of successive amplification of the trinucleotide repeats)**; the severe congenital form is **almost always confined to the offspring of affected women**. **In myotonic dystrophy, mother of the affected child also had difficulty releasing object once grasp**. Syn: dystrophia myotonica, myotonia atrophica, myotonia dystrophica. 10. Maple Syrup Urine Disease = MSUD = an inborn error of metabolism caused by defective oxidative decarboxylation of **α-keto acids of leucine, isoleucine, and valine; these branched-chain amino acid**s are present in the blood and urine in high concentrations; manifestations of disease include feeding difficulties, physical and mental retardation, and a urine odor similar to that of maple syrup; neonatal death is common. **Autosomal recessive** inheritance, caused by **mutation in the E1, E2 or E3 subunit of the branched-chain α-keto acid dehydrogenase gene (BCKDH) on 19q**. There are various forms differentiated by the subunit of BCKDH mutated. Syn: ketoacidemia, branched chain ketoaciduria, branched chain ketonuria. MSUD is a familial cerebral degenerative disease caused by a defect in branched chain amino acid metabolism. MSUD is characterized by sever mental and motor retardation and by urine with a maple syrup-like odor. 11. Congenital hypoplastic anemia= congenital nonregenerative anemia = Diamond-Blackfan anemia= familial hypoplastic anemia = pure red

	cell anemia= erythrogenesis imperfect= Diamond-Blackfan syndrome= a **macrocytic anemia** resulting from congenital hypoplasia of the bone marrow, which is grossly deficient in erythroid precursors while other elements are normal; (macrocytic) anemia is progressive and severe, but leukocyte and platelet counts are normal or slightly reduced; survival of transfused erythrocytes is normal; minor congenital anomalies are found in some patients. Both autosomal dominant and recessive forms have been described, caused by mutation in the gene encoding ribosomal protein S19 (RBS19) on chromosomal 19q. Diamond-Blackfan anemia is associated with physical abnormalities in approximately 25% of patients. Anomalies include **short stature, webbed neck, cleft lip, shielded chest, dysmorphic facial features, micrognathia, flattening of the thenar eminences, and triphalangeal thumbs** (Kaplan peds, p200). 12. Leprechaunism= A congenital form of dwarfism characterized by extreme growth retardation, endocrine disorders, and emaciation, with elfin facies and large, low-set ears; autosomal recessive inheritance; caused by mutation in the insulin receptor gene (INSR) on 19p. Syn: Donohue disease, Donohue syndrome. 13. EYCL3 gene on chromosome 15 is responsible for brown or blue eye color 2) EYCL1 gene on chromosome 19 is responsible for blue or green eye color 14. Peutz-Jeghers syndrome = generalized hamartomatous multiple polyposis of the intestinal tract, consistently involving the jejunum, associated with melanin spots of the lips, buccal mucosa, and fingers; **autosomal dominant** inheritance, caused by mutation in the serine/threonine kinase gene (STK11) on chromosome 19p. Peutz-Jeghers syndrome is associated with breast cancer. (1st aid surgery, p 143). Acral and **periorificial pigmented macules = perioral pigmentation** (blue- gray or **brownish spots on the lips**) occur together with hamartomatous polys and adenocarcinoma of the colon in Peutz- Jeghers syndrome. Clubbing of the finger may occasionally be seen. (Kaplan IM, p 21)(Kaplan Peds, p 252). 15. Familial goiter = a group of heritable thyroid disorders in which goiter is commonly apparent first during childhood; often associated with skeletal and/or mental retardation, and with other signs of hypothyroidism that may develop with age. Various types of familial goiter have been identified: 1) iodide transport defect ; of autosomal recessive inheritance

	caused by mutation in the sodium iodide symporter gene (SLC5A5) on 19p, in which the gland is unable to concentrate iodide; 2) organification defect , in which the iodination of tyrosine is defective; 3) Pendred syndrome ; autosomal recessive inheritance caused by mutation in the Pendred syndrome gene (PDS) on 7q; 4) coupling defect, in which cretinism results from defective coupling of iodotyrosines to form iodothyronine ; 5) iodotyrosine deiodinase defect, in which deiodination of iodotyrosine is defective, considerable glandular loss of these hormonal precursors occurs, and cretinism may be present 6) plasma iodoprotein disorder , in which an abnormal iodinated serum protein that is insoluble in acidic butanol is present; 7) hereditary hyperthyroidism. 16. Mannosidosis = Congenital deficiency of α-mannosidase; associated with **coarse facial features, enlarged tongue, mental retardation, kyphosis, radiographic skeletal abnormalities, and vacuolated lymphocytes**, with accumulation of mannose in tissues; autosomal recessive inheritance, caused by mutation in the alpha-mannosidase gene (MANB) on chromosome 19p. 17. Multiple epiphyseal dysplasia (EDM)= a disorder of epiphyses characterized by difficulty in walking, pain and stiffness of joints, stubby fingers, and often short stature; on X-ray examination, the epiphyses are irregular and mottled, the ossification centers are late in appearance and may be multiple, but the vertebrae are normal. There are at least 3 forms of autosomal dominant inheritance: EDM1 due to mutation in the cartilage oligomeric matrix protein gene (COMP) on chromosome 19p; EDM2 , due to mutation in the type IX collagen gene (COL9A2) on 1p; and EDM3 , which is linked to an unknown locus. There is also an autosomal recessive form . Syn: dysplasia epiphysealis multiplex. 18. **1p19q codeletion in anaplastic oligodendrogliomas**= Neuronal differentiation in oligodendrogliomas with 1p19q codeletion and support the hypothesis that the cell of origin for gliomas with 1p19q codeletion could be a bi-potential progenitor cell, able to give rise to both neurons and oligodendrocytes. Anaplastic oligodendrogliomas with **1p19q codeletion** have a proneural gene expression profile. A recent study analyzed survival based on chromosomal deletions and the effects of radiation or chemotherapy as treatment, with the following results (both low-grade and anaplastic oligodendrogliomas): 1p/19q deletion with radiation = 121 months (mean), 1p/19q deletion with chemotherapy = over 160 months (mean not yet reached), no 1p/19q deletion with radiation = 58 months (mean), and no 1p/19q deletion with

	chemotherapy = 75 months (mean). Another study divided anaplastic oligodendrogliomas into the following four clinically relevant groups of histology with the following results: combined 1p/19q loss = median survival was >123 months (not yet reached), 1p loss only = median survival was 71 months, 1p intact with TP53 mutation = median survival 71 months, and 1p intact with no TP53 mutation = median survival was 16 months. 19. Amaurosis congenita of Leber= a disorder of cone-rod abiotrophy causing blindness or severely reduced vision at birth; autosomal recessive inheritance with at least 3 different loci. Type I is caused by mutation in the gene for retinal guanylate cyclase (GUC2D) on chromosome 17p, type II by mutation in the gene for retinal pigment epithelium-specific 65-kD protein (RPE65) on 1p, and type III by mutation in the gene for photoreceptor-specific homeobox gene CRX on 19q.
20	1. Mutations at the SALL4 locus on chromosome 20 result in a range of clinically overlapping phenotypes, including Okihiro syndrome, Holt-Oram syndrome, acro-renal-ocular syndrome, and patients previously reported to represent thalidomide embryopathy. 2. Alagille Syndrome = Alagille Syndrome = Alagille - Watson Syndrome (=AWS) = Arteriohepatic Dysplasia (=AHD) = Cholestasis With Peripheral Pulmonary Artery Stenosis= Syndromatic Hepatic Ductular Hypoplasia = **get arteriohepatic dysplasia, lack of bile ducts, butterfly vertebrae, eye abnormalities, pulmonic stenosis (either pulmonary valve stenosis or branched artery, pulmonary artery stenosis) is also seen.** Alagille syndrome is a genetic disorder that affects the liver, heart, and other systems of the body. Problems associated with the disorder generally become evident in infancy or early childhood. The disorder is inherited in an **autosomal dominant** pattern, and the estimated prevalence of Alagille syndrome is 1 in every 70,000 live births. The syndrome has recently been mapped to the **chromosome 20 (20p12-jagged-1) locus (JAG1)**, which encodes a ligand critical to the **notch gene–signaling cascade** that is important in fetal development. A minority (6-7%) of patients have complete deletion of JAG1, and approximately 15-50% of mutations are spontaneous. Diagnosis of Alagille syndome (AGS) is marked reduction of intrahepatic bile ducts on biopsy in association with other

	cardiac, ocular, skeletal and facial abnormalities. 3. Trisomy 20 syndrome = a chromosomal disorder characterized by profound mental retardation, coarse facies, macrostomia and macroglossia, minor anomalies of the ears, pigmentary dysplasia of the skin, dorsal kyphoscoliosis, and other skeletal defects. 4. Familial Benign neonatal convulsions = a familial, self-limited epilepsy, beginning at 2, 3, or 6 days of age and resolving spontaneously by six months of age; **autosomal dominant inheritance**. The familial benign neonatal convulsion is linked to **chromosome 8 and chromosome 20**. 5. Tissue transglutaminase =TG2 = tTG= human tTG gene is located chromosome 20. Tissue transglutaminase is an enzyme (EC 2.3.2.13) of the transglutaminase family. Like other transglutaminases, it crosslinks proteins between an ε-amino group of a lysine residue and a γ-carboxamide group of glutamine residue, creating an inter- or intramolecular bond that is highly resistant to proteolysis (protein degradation). It is particularly notable for being the autoantigen in celiac disease, but is also known to play a role in apoptosis, cellular differentiation and matrix stabilization. The human tTG gene is located on the 20th chromosome (20q11.2-q12). 6. Pseudohypoparathyroidism= A disorder resembling hypoparathyroidism, with high serum phosphate and low calcium levels but with normal or elevated serum parathyroid hormone levels; the defect is due to lack of end-organ responsiveness to parathyroid hormone. There are two types: type I shows lack of renal tubular response to exogenous parathyroid hormone with increase in urinary cAMP, type Is has type I skeletal defects (SYN Albright hereditary osteodystrophy), and type II is associated with a defect at a locus after cAMP production. X-linked dominant inheritance caused by **mutation in the gene encoding guanine nucleotide-binding protein α-stimulating activity polypeptide 1 (GNAS1),** which regulates adenyl cyclase on chromosome 20q **(=The genetic defect is in the hormone receptor adenylate cyclase system)** . *Cf.* thyrotropin resistance 7. Hunter-Thompson dwarfism= a severe form of acromesomelic dwarfism, characterized by shortening of the distal segments of the limbs; lower extremities are more severely affected than the upper limbs; often associated with dislocations of elbows, knees, and hips. Autosomal recessive inheritance, caused by mutations in the cartilage-derived morphogenetic protein 1 (CDMP1) gene on chromosome 20q.

	8. Posterior Polymorphous Corneal Dystrophy in Czech Families Maps to VSX1 on chromosome 20. 9. Creutzfeldt- Jakob disease (CJD) , caused by a prion protein (PrP) and is encodes by a single-exon geno on chromosome 20. Mutation of PrP result in hereditary cases of Creutzfeldt- Jakob disease (CJD). (Path p 297) 10. Kuru disease (prion disease) = kuru plaques are deposits of amyloid of altered prion protein (PrP). Kuru is seen in tribes with cannibalism. (path p 297) 11. CJD is caused by a prion protein (an abnormal isoform of amyloid protein) that serves as a nucleating factor, inducing abnormalities in other proteins. This protein is detectable by Western blot early in the course of clinical disease. Prion diseases besides CJD include Gerstmann-Sträussler-Scheinker syndrome, fatal familial insomnia, and kuru in humans; scrapie in sheep and goats; bovine spongiform encephalopathy (mad cow disease) in cattle; and similar encephalopathies and wasting syndromes in other species. 12. Albright syndrome = Albright hereditary osteodystrophy = an inherited form of hyperparathyroidism associated with ectopic calcification and ossification and skeletal defects, notably the small fourth metacarpals; intelligence may be normal or subnormal. Inheritance is heterogeneous; the autosomal form is caused by mutation in the guanine nucleotide-binding protein gene (GNAS1) on 20q. There are also the recessive and X-linked forms.
21	1. Amyotrophic lateral sclerosis (ALS) = progressive spinal amyotrophy= progressive muscular atrophy= Aran-Duchenne disease, Charcot disease= Duchenne-Aran disease=Lou Gehrig disease = a fatal degenerative disease involving the corticobulbar, corticospinal, and spinal motor neurons, manifested by progressive weakness and wasting of muscles innervated by the affected neurons; fasciculations and cramps commonly occur. The disorder is 90–95% sporadic in nature (although a number of cases are inherited as an **autosomal dominant** trait), affects adults (typically, older adults), and usually is fatal within 2–5 years of onset. It is the most common subgroup of motor neuron disease, and the only one manifested by a combination of upper and lower abnormalities (= a disease of both upper motor neuron and lower motor neuron disease). Variants include: 1) progressive bulbar palsy, in which isolated or predominant lower

	brainstem motor involvement occurs; 2) primary lateral sclerosis, in which only upper motor neuron abnormalities are seen; and 3) progressive spinal muscle atrophy, in which only lower motor neuron dysfunction is noted.. **Copper-Zinc superoxide dismutase gene (SOD1) (for Leu Gehrig disease** = ALS = amyotrophic lateral sclerosis, **autosomal dominant** (pg 308) 2. Down syndrome (trisomy 21) (pg 47), life span of about 40 years. A chromosomal dysgenesis syndrome consisting of a variable constellation of abnormalities caused by triplication or translocation of chromosome 21. The abnormalities include mental retardation, retarded growth, flat hypoplastic face with short nose, prominent epicanthic skin folds, small low-set ears with prominent antihelix, fissured and thickened tongue, laxness of joint ligaments, pelvic dysplasia, broad hands and feet, stubby fingers, and transverse palmar crease. Lenticular opacities and heart disease are common. The incidence of leukemia is increased and Alzheimer disease is almost inevitable by age 40. also get cardiac problem such as endocardial cushion defects (A-V canal/ atrioventricular canal) Syn: trisomy 21 syndrome. (Kaplan peds, p 156). The higher the maternal age (= when mother is too old) in pregnancy, especially in pregnant female after age 35, the higher the risk of the fetus to have Down syndrome. P**atients with Down syndrome, neurofibromatosis, or sickle cell disease can develop Moyamoya malformations**. Moyamoya disease is more common in women than in men. Brain radiation therapy in children with neurofibromatosis increases the risk of its development. Moyamoya can be either congenital or acquired 3. Unverricht disease= a progressive myoclonic epilepsy; one of the degenerative gray matter disorders characterized by myoclonus and generalized seizures, with progressive neurologic and intellectual decline; age of onset between 8–13 years of age; autosomal recessive inheritance, caused by mutation in the cystatin B gene (CSTB) on 21q22. 4. Alzheimer disease = **amyloid** β-protein (Aβ) is a characteristic of **Alzheimer's disease** . (BAPP = Beta amyloid precursor protein) (pg 74, 307). Virtually all Down syndrome patients are destined to develop Alzheimer disease in theirs forties. Down patients have triple copies of the APP gene. (p 307). At least half of all patients with early-onset familial AD show mutations in the presenilin-1 gene on chromosome 14. Mutations in the presenilin-2 gene on chromosome 1 or the amyloid precursor protein gene on chromosome 21 have been found in smaller kindreds with

	familial disease. Late-onset familial disease has been traced to mutations in an apolipoprotein E (APOE) locus on chromosome 19. All of these mutations are associated with increased production of Aβ42. It has been suggested that incorporation of Presenilin proteins into neurons programs them for death through apoptosis. Cognitive decline in AD has been attributed in part to a deficiency of the neurotransmitter acetylcholine, and therapy with reversible cholinesterase inhibitors (donepezil, galanthamine, metrifonate, tacrine) has improved cognition and slowed progression of dementia in some patients. Numerous other agents (including nicotine, ginkgo extract, vitamin E, selegiline, ergoloid mesylates, and ibuprofen) have shown slight efficacy in some studies. Experimental evidence suggests that administration of estrogen to postmenopausal women retards onset and progression of nonfamilial AD. 5. P- APP gene (pg 308). APP = amyloid precursor protein 6. t (8,21) translocation is seen in M2 leukemia, also known as acute myeloid leukemia (AML) with maturation and some M4 (AML with granulocytic and monocytic maturation). 7. t (12, 21) → acute lymphoblastic leukemia (AML) (pg 326) 8. Jervell and Lange-Nielsen syndrome= Jervell - Lange-Nielsen syndrome =is a form of congenital long QT syndrome = a prolonged Q-T interval recorded in the electrocardiogram of certain congenitally deaf children subject to attacks of unconsciousness resulting from Adams-Stokes seizures and ventricular fibrillation; patient with this syndrome are predisposed to a particular type of ventricular tachycardia called torsades De pointes. Torsades De pointes causes syncopal episodes and sudden death. Jervell and Lange-Nielsen syndrome is **autosomal recessiv**e inheritance, caused by homozygosity for a mutation in the potassium channel gene (KVLQT1) on chromosome 11 or minimal potassium ion channel gene (KCNE1) on 21. Syn: surdocardiac syndrome. 9. Polyglandular Autoimmune (PGA) Syndromes = PAS= PGAS= Polyglandular Failure Syndromes= Autoimmune Polyendocrine Syndrome = (= APS) Autoimmune Polyglandular syndromes = Polyglandular autoimmune diseases= Autosomal Recessive inheritance (1st Aid CK, p 101)= are constellations of multiple endocrine gland insufficiencies. Other descriptive terminologies, such as autoimmune polyendocrine syndrome (APS). PGA is inherited as a **Autosomal recessive trait** such that a child with the disease has received 2 changed (mutant)

	AIRE genes, one from each parent. Although PGA is generally rare, **it is more frequent in 3 genetically isolated populations: the Finnish, Iranian Jews, and Sardinians**. PGA (polyglandular autoimmune syndrome): A genetic autoimmune disease with an extraordinary array of clinical features but characterized most often by at least 2 of the following 3 findings: hypoparathyroidism -- under-function of the parathyroid glands which control calcium, candidiasis (yeast infection), and adrenal insufficiency (under-function of the adrenal gland). PGA was the first systemic (body wide) autoimmune disease found due to a defect in a single gene. In 1997 a novel gene was identified that mapped to chromosome region 21q22.3. The gene was named AIRE for autoimmune regulator. Changes in the AIRE gene are responsible for PGA. The child with PGA develops problems in numerous glands (polyglandular) including hypoparathyroidism, hypogonadism (with sex gland failure), adrenal insufficiency, type 1 (insulin-dependent) diabetes with insufficient insulin production by the pancreas gland, and latent hypothyroidism (under-function of the thyroid gland). Other features of APS are total baldness (alopecia totalis), inflammation of the cornea and whites of the eye (keratoconjunctivitis), underdevelopment (hypoplasia) of the enamel of the teeth, childhood-onset moniliasis (yeast infection), juvenile-onset pernicious anemia, gastrointestinal problems (malabsorption, diarrhea), and chronic active hepatitis. The laboratory studies attest to an immune disease with an abnormally low level of gamma globulin antibodies (= decrease IgG level) in blood (hypogammaglobulinemia) and an abnormally low T4/T8 white blood cell ratio (as in AIDS). There is specific evidence for autoimmunity with antibodies directed against the adrenal and thyroid glands and against cell nuclei (antiadrenal, antithyroid and antinuclear antibodies). Polyglandular autoimmune (PGA) syndromes type 1 (= PGA-I)= Autoimmune Polyendocrine syndrome Type I= (= APS-I) = PGA-I is unique among autoimmune endocrine disorders, because it has no HLA antigen association. However, an increased frequency of HLA-A28 and HLA-A3 has been documented in PGA-I, more so than in normal controls. The genetic locus responsible for the disease has been localized to the short arm of chromosome 21 near markers D21s49 and D21s171 on band 21p22.3. A Finnish study concluded that the mutation R257X is responsible for 82% of cases. A monogenic mutation of AIRE (AutoImmune REgulator), which codes for a putative transcription factor

	featuring 2 zinc motifs, is believed to be the likely pathogenic paradigm for PGA-I.7 . PAS I, also known as APECED (autoimmune polyendocrinopathy, candidiasis and ectodermal dystrophy = autoimmune polyglandular endocrinopathy, candidiasis and ectodermal dysplasia) or MEDAC (multiple endocrine deficiency autoimmune candidiasis syndrome), usually appears in childhood at age 3–5 yr is a Monogenic **autosomal-recessive inheritance** due to **Mutations in AIRE gene on chromosome 21**. Mutations in an autoimmune-suppressor gene (AIRE, for autoimmune regulator), which encodes a transcription factor, cause the syndrome. Persons with any two of several specific conditions — **mucocutaneous candidiasis, hyperparathyroidism, and Addison's disease — almost always have AIRE mutations**. Mutations in the AIRE gene cause many autoimmune diseases, and affected patients are at risk for the development of multiple additional autoimmune diseases over time, including type 1A diabetes, hypothyroidism, pernicious anemia, alopecia, vitiligo, hepatitis, ovarian atrophy, and keratitis. Affected patients may also have diarrhea or obstipation that may be related to the destruction of gastrointestinal endocrine cells (enterochromaffin and enterochromaffin-like cells). 10. Homocystinuria = **Autosomal recessive** inheritance, but carriers have an increased risk of occlusive vascular disease; caused by mutation in the cysthathione beta-synthase gene (CBS) on chromosome 21q. **Remember: [Marfan's features +mental retardation + thromboembolic events (deep venous thrombosis/DVT, pulmonary embolism/PE, cerebrovascular accident/stroke) + downward dislocation of lens= lens dislocation = homocystinuria]**. Patients with homocystinuria have **marfanoid appearance** with associated **mental retardation** or psychiatric illness (Kaplan Peds, p 30). Homocystinuria is a metabolic disorder characterized by sparse blond hair, long limbs, pectus excavatum, dislocation of lens, failure to thrive, mental retardation, psychiatric disturbances, megaloblastic anemia, and thromboembolic episodes; some patients have alleviation of symptoms with pyridoxine (= vitamin B6) while others are not responsive; associated with increased urinary excretion of homocystine and methionine. Autosomal recessive inheritance, but carriers have an increased risk of occlusive vascular disease; caused by mutation in the cysthathione beta-synthase gene (CBS) on chromosome 21q. In addition, there are seven other causes of homocystinuria: (1) defect in vitamin B12 metabolism, (2) deficiency of N-methylene-tetrahydrofolate reductase , (3)

	selective intestinal malabsorption of vitamin B12, (4) vitamin B12 responsive homocystinuria, cblE type, (5) methylcobalamin deficiency, cblG type, (6) vitamin B12 metabolic defect type 2 , and (7) transcobalamin II deficiency.
22	1. Tumor suppressor gene (NF-**2**) on (**22**q 12) neurofibromatosis type **2** (**bi**lateral acoustic neurofibromatosis) , acoustic neuroma, meningioma, glioma, schwannoma, merlin (**notice all the 2's**)(pg 57, 83) 2. **DiGeorge syndrome**, chromosome 22q11; autosomal dominant inheritance (microdeletion of a specific DNA sequence from chromosome 22q11.2 is found in the majority of cases) (pg 65), (Kaplan peds, p 120). With Di George syndrome get truncus arteriosus (=conotruncal heart defect). Some features of patients with DiGeorge syndrome include epicanthal folds to the eyes, hypertelorism, low set ears, a bifid uvula, a short philtrum, micrognathia, a fish mouth and congenital heart disease (atrial septal defect (ASD), ventricular septal defect (VSD). Congenital hypoplasia of parathyroid gland is seen in patients with DiGeorge syndrome. 3. Velocardiofacial syndrome (= VCFS)= in **Velocardiofacial** syndrome get **Velo** (=velar = palate??) + **cardiac** + **facial** abnormalities = a syndrome with **cardiac** abnormalities and conotruncal heart defect with hypernasal speech, dysmorphic **facial** features (long midface, cylindrical nose, downward turned corners of mouth); Velocardiofacial syndome has the same chromosomal abnormality as seen in DiGeorge syndrome (a microdeletion in chromosome 22q11); dominant inheritance. Syn: Shprintzen syndrome. (Kaplan peds, p 121). 4. Conotruncal anomaly face syndrome (CTAFS) and velocardiofacial syndrome (VCFS) share similarities with DiGeorge syndrome (i.e., 22q deletions and conotruncal heart defects= truncus arteriosus). (Kaplan peds, p 121). 5. Psychosis = A microdeletion at chromosome 22q11 is the most frequently known interstitial deletion found in humans, occurring in approximately one of every 4000 live births. Its occurrence is associated with a characteristic facial dysmorphology, a range of congenital abnormalities, and psychiatric problems, especially schizophrenia. The prevalence of psychosis in those with 22q11 deletion syndrome is high (30%), suggesting that haploinsufficiency of a gene or genes in this region may confer a substantially increased risk. In addition, several studies provide evidence for linkage to schizophrenia on 22q, suggesting that a gene in

	this region could confer susceptibility to schizophrenia in nondeleted cases. 6. Panic Disorder = Substantial evidence supports that there is a genetic component to panic disorder (PD). Until recently, attempts at localizing genes for PD by using standard phenotypic data have not proven successful. Previous work suggests that a potential subtype of PD called the panic syndrome exists, and it is characterized by a number of medical conditions, most notably bladder/renal disorders. In the current study, a genome scan with 384 microsatellite markers was performed on 587 individuals in 60 multiplex pedigrees segregating PD and bladder/kidney conditions. Using both single-locus and multipoint analytic methods, we found significant linkage on chromosome 22 (maximum heterogeneity logarithm of odds score = 4.11 at D22S445) and on chromosome 13q (heterogeneity logarithm of odds score = 3.57 at D13S793) under a dominant-genetic model and a broad phenotypic definition. Multipoint analyses did not support the observation on chromosome 22. The chromosome 13 findings were corroborated by multipoint findings, and extend our previous findings from 19 of the 60 families. Several other regions showed elevated scores by using when one analytic method was used, but not the other. These results suggest that there are **genes on chromosome 13q, and possibly on chromosome 22** as well, that influence the susceptibility toward a pleiotropic syndrome that includes PD, bladder problems, severe headaches, mitral valve prolapse, and thyroid conditions. 7. V-gene for the lambda light chain gene is on chromosome 22 8. BCR (break point cluster) region in CML (chronic myelogenous leukemia) (pg 226) 9. t (9, 22) = abl –BCR hybrid = chronic myelogenous leukemia (CML) (pg 326) (genetic pg 341) , have Abl-BCR hybrid (bcr-c-abl) 10. Metachromatic leukodystrophy (MLD) =Autosomal recessive inheritance, caused by mutation in either the arylsulfatase A gene (ARSA) on 22q or the prosaposin gene (PSAP) on 10q. (Kaplan peds, p225) 11. Retrotransposon element on chromosome 22 cause insertion of L1 of Long Interspersed Repetitive Elements (=LINE)1 in some hemophilia A patient. 12. Burkitt's lymphoma = common variant t (8,14) (q24, q32), involving the oncogene myc on chromosome 8 and the heavy immunoglobulin chain on chromosome 14. The other two variants of Burkitt's lymphoma are t (8,22) (q24, q11) involving myc and the lambda light chain immunoglobulin

	site and t (2,8)(p12, 24) involving the kappa light chain and myc. 13. Dejerine-Sottas disease = a familial type of demyelinating sensorimotor polyneuropathy that begins in early childhood and is slowly progressive; clinically characterized by foot pain and paresthesias, followed by symmetrical weakness and wasting of the distal limbs; one of the causes of stork legs; patients are wheelchair-bound at an early age; peripheral nerves are palpably enlarged and non-tender; pathologically, onion bulb formation is seen in the nerves: whorls of overlapping, intertwined Schwann cell processes that encircle bare axons; usually autosomal recessive inheritance; an autosomal dominant form also exists; both forms can be caused by mutations in the peripheral myelin protein **gene 22** (PMP22) on **17q** or in the myelin protein zero gene (MPZ) on **1q**. Syn: Dejerine disease, hereditary hypertrophic neuropathy, progressive hypertrophic polyneuropathy.
23	**Chromosome 23 are X and Y-chromosomes!** Sex chromosomes = W chromosome, X chromosome, Y chromosome, Z chromosome = the pair of chromosomes responsible for sex determination. In humans and most animals, the sex chromosomes are designated X and Y; females have two X chromosomes, males have one X and one Y chromosome In certain birds, insects, and fishes the sex chromosomes are designated Z and W; males have two Z chromosomes, females may have one Z and one W chromosome, or one Z and no W chromosome. Syn: gonosome.
X	1. Fragile X syndrome = marker X syndrome= Martin-Bell syndrome = FMR1 (familial mental retardation) = FMR-1 (familial mental retardation) gene on (X q27.3) → Fragile X syndrome, **X-linked dominant** with 100% penetrance in male and 60% penetrance in females (pg 58), (genetics pg 297). (Triplet repeat expansion), Expanded trinucleotide repeat = (cytosine-Guanine- Guanine)= CGG repeat in 5'UTR (genetics pg 305). fragile X syndrome is an X-linked recessive syndrome consisting of mental retardation, a characteristic facies, and macroorchidism (= large testicles) (peds p 251) (CK p 304); DNA analysis shows abnormal trinucleotide repeats on the X chromosome near the end of its long arm, at Xq27.3; a constriction is demonstrable at this site on karyotyping after culture in folate-deficient medium. The incidence of fragile X syndrome (about 1:2000 in males) is second only to that of

	Down syndrome among genetically identifiable sources of mental retardation. Phenotypic expression is variable, but mental retardation is the most commonly observed feature. The face is long and narrow, with large ears, a prominent mandibular symphysis, and a high-arched palate. Absolute or relative macrocephaly is common. Macroorchidism appears at puberty or before; histologic study shows only edema of the testis. Connective tissue abnormality may be manifested by hypermobility of fingers and other joints, pes planus, dilation of the aorta, and mitral valve prolapse. Besides intellectual impairment, neuropsychiatric findings include hyperactivity, short attention span, poor eye contact, autistic-like behavior, jocular speech, echolalia, and motor incoordination. The IQ may deteriorate with advancing age. A few males with this genetic defect, and about two-thirds of females, are phenotypically normal. Expression depends on a mutation that occurs in two or more steps and that is both meiotically and mitotically unstable. Transmission is complex and varies with the gender of both the proband and the transmitting parent. The fragile chromosomal locus represents a site of abnormal amplification with a variable number of CGG repeats. These block transcription of the FMR1 (familial mental retardation) gene, which normally encodes FMR1 protein; **clinical expression is due to failure to synthesize FMR1 protein and to abnormal methylation of DNA sequences distal to the fragile site**. 2. Vitamin D-resistant rickets=a group of metabolic disorders characterized by renal tubular defect in phosphate transport and bone abnormalities resulting in hypophosphatemic rickets or osteomalacia; hypocalcemia and tetany are not features. There is an autosomal dominant form and an **X-linked dominant** form, the latter caused by mutation in the phosphate-regulating gene with homologies to endopeptidases (PHEX) on chromosome Xp. Both forms are not responsive to standard therapeutic doses of vitamin D but they may respond to very large doses of phosphate and/or vitamin D. There is also an autosomal recessive form caused by mutation in the vitamin D receptor gene (VDR) on 12q. Syn: familial hypophosphatemic rickets. 3. Nephrogenic diabetes insipidus= diabetes insipidus due to inability of the kidney tubules to respond to antidiuretic hormone; X-linked inheritance, caused by mutation in the vasopressin V2 receptor gene (AVPR2) on Xq. There is also an autosomal dominant form , caused by mutation in the (aquaporin ?) aquaphorin 2 gene (AQP2) on 12q. Syn: vasopressin-resistant diabetes.

	4. Dermatochalasis=A congenital or acquired condition characterized by deficient elastic fibers of the skin, which may hang in folds; vascular anomalies may be present; inheritance is either autosomal dominant or recessive, the latter sometimes in association with pulmonary emphysema and diverticula of the alimentary tract or bladder. The dominant form is caused by mutation in the elastin gene (ELN) on 7q. There is also an X-linked form that is due to mutation in the Menkes gene (MNK), encoding copper-transporting ATPase on Xq. Syn: cutis laxa , generalized elastolysis, loose skin. 5. Choroideremia = Progressive degeneration of the choroid in males, occasionally in females, beginning with peripheral pigmentary retinopathy, followed by atrophy of the retinal pigment epithelium and of the choriocapillaris, night blindness, progressive constriction of visual fields, and finally complete blindness; X-linked inheritance caused by mutation in the Rab escort protein-1 (REP1) gene on Xq; heterozygous females show a pigmentary retinopathy but without visual defect or peripheral progression. Syn: progressive choroidal atrophy, progressive tapetochoroidal dystrophy. 6. Centronuclear myopathy= slowly progressive generalized muscle weakness and atrophy beginning in childhood; on biopsy of skeletal muscle, the nuclei of most muscle fibers are seen to be located near the center of a small fiber (the normal position for a 10-week embryo) rather than at the periphery of the fiber; familial incidence. Autosomal dominant recessive and X-linked forms occur. The X-linked form is caused by mutation in the myotubular myopathy gene (MTM1) on Xq28. Syn: myotubular myopathy. 7. Anhidrotic ectodermal dysplasia= a disorder characterized by absent or defective sweat glands, saddle-shaped nose, hyperpigmentation around the eyes, malformed or missing teeth, sparse hair, dysplastic nails, smooth, finely wrinkled skin, syndactyly, absent breast tissue, and occasionally mental retardation; X-linked recessive inheritance, caused by mutation in the ED1 gene on chromosome Xq. There is also an autosomal recessive form. Syn: hypohidrotic ectodermal dysplasia. 8. Hypophosphatemic rickets, X-linked dominant, (genetics pg 297). X-linked dominant = affected males can transmit x-linked dominant mutations to their daughters. 9. Klinefelter syndrome = (47,XXY) = abnormal male, male hypogonadism, infertility, eunuchoid body habitus, gynecomastia and lack of male secondary sexual

	characteristics = one extra X chromosome (pg 59), normal life span, failure of separation (nondisjunction of sex chromosomes) → get gynecomastia, small gonads and failure of development of secondary sexual characteristics. (47,XXY), the classic karyotype of Klinefelter's syndrome is defined as male hypogonadism due to the presence of a Y chromosome and two or more X's . as in normal females, one of the X chromosomes, become a Barr body in Klinefelter's syndrome. Compare Kallmann syndrome (= Hypogonadotropic hypogonadism= get decrease in both LH and decrease in FSH) with **Klinefelter Syndrome (=Hypergonadotropic hypogonadism = get increase in both LH and increase in FSH)** (IM, p 57), (OB, p 154) 10. Klinefelter syndrome = (48,XXXY) = abnormal male = two extra X chromosome (genetic pg 335) = abnormal Klinefelter male +intellectual impairment 11. Turner syndrome = (45, XO) = gonadal dysgenesis (Kaplan OB, p 154) = (45, X) deletion on one X. (genetic pg 335), life span of 30-40 years = a syndrome with chromosome count 45 and only one X chromosome; buccal and other cells are usually sex chromatin-negative; anomalies include dwarfism, webbed neck, **Pterygium coli (= webbed neck)**, valgus of elbows, pigeon chest, infantile sexual development, and amenorrhea; the ovary has no primordial follicles and may be represented only by a fibrous streak; some individuals are chromosomal mosaic, with two or more cell lines of different chromosome constitution; seen in many animal species, in the meadow vole it is the normal female state. Syn: XO syndrome. 12. 47, XXX = female, mild intellectual impairment (slightly mentally retarded) with menstrual irregularities, normal phenotype with normal life span 13. 48, XXXX = female, intellectual impairment (increase in number of x-chromosome causes increase in mental retardation and menstrual irregularities due to increase in number of inactivated x chromosomes (= increase in number of Barr bodies). The Barr body or X chromatin body is an inactivated X chromosome seen as a small, perinuclear, dark staining dot in somatic cells with two or more X chromosomes. Barr bodies are seen in any individuals born with at least two X chromosomes, including normal females. 14. 47, XYY = double Y syndrome = XYY syndrome = XYY males = double Y males (CK, p 304) = double Y males, some intellectual impairment + behavioral problem. Normal life span, affected individuals often go undetected but are taller than average, and may be

more likely to exhibit aggressive, antisocial behavior. a chromosomal anomaly with chromosome count 47, with a supernumerary Y chromosome; controversial evidence associates tallness, aggressiveness, and severe **acne** with this condition. Double Y male is observed with ↑ frequency among inmates of penal institutions. **Phenotypically normal**, v**ery tall, severe acne, antisocial behavior** (seen in 1–2% of XYY males) (CK, p 304).

15. Dystrophin gene (X p21) → muscular dystrophy (pg 291). Dystrophin gene is coding for a plasma membrane protein of muscle fibers. A protein found in the sarcolemma of normal muscle; it is missing in individuals with pseudohypertrophic muscular dystrophy and in other forms of muscular dystrophy; its role may be in the linkage of the cytoskeleton of the muscle cell to extracellular protein. Dystrophin is located on the plasma membrane of muscle fibers. It function is to stabilize the muscle membrane, thereby protecting it from degradation. Its absence results in degeneration of muscle fibers, causing progressive weakness in the individual.
16. Adrenoleukodystrophy (ALD) = X-ALD = An **X-linked recessive** disorder affecting young **males**, characterized by chronic **adrenocortical insufficiency (and adrenal insufficiency)**, **skin hyperpigmentation (due to increase in MSH= melanocyte stimulating hormone), progressive dementia, spastic paralysis**, and other intellectual and neurologic disturbances; due to **myelin degeneration in the white matter** of the brain. The gene that is defective in X-ALD is called ABCD1, and encodes a protein called **ALDP (=adrenoleukodystrophy protein).** The causative gene maps to Xq and encodes adrenoleukodystrophy protein (ALDP), an ATP-binding transporter located in the peroxisomal membrane. (Kaplan peds, p225). Get **elevated level of hexocasanote** (=HA) level in blood, can't break down **long chain fatty acids (LCFA).** X-linked Adrenoleukodystrophy (ALD) is characterized by an increase of **very long chain fatty acids (VLCFA)** in particular of hexacosanoic acid (HA), in tissues and fluids. The biochemical abnormality is due to the **dysfunction of peroxisomal degradation of Very Long-Chained Fatty Acid (=VLCFA) → (is a peroxisomal disorder)**. To-date it is unclear if the demyelination which characterizes this disease is the direct consequence of HA accumulation. Other clinical names your might encounter of X-ALD include: Schilder's disease and sudanophilic leukodystrophy.
17. Becker's Muscular Dystrophy (BMD) = X-linked

recessive (genetics pg 296, 393), "in-frame" mutation, milder presentation.

18. Duchenne's muscular dystrophy (DMD) = X-linked recessive (genetics pg 296), frame shift mutation, worse presentation. Dystrophin gene is coding for a plasma membrane protein of muscle fibers. Dystrophin is located on the plasma membrane of muscle fibers. It function is to stabilize the muscle membrane, thereby protecting it from degradation. Its absence results in degeneration of muscle fibers, causing progressive weakness in the individual.
19. Synovial sarcoma= **t (X, 18) =** a rare malignant tumor of synovial origin, most commonly involving the knee joint and composed of spindle cells usually enclosing slits or pseudoglandular spaces that may be lined by radially disposed epithelial-like cells**.** It is due to **Translocation of some part of chromosome X with some part of chromosome 18.** (pg 326).
20. Hemophilia A = X-linked recessive (genetics pg 296), deficiency of factor 8 (VIII) activity (Kaplan peds, p 203). = Hemophilia due to deficiency of factor VIII; an X-linked recessive condition, occurring almost exclusively in human males and also affecting several breeds of dogs, characterized by prolonged clotting time, decreased formation of thromboplastin, and diminished conversion of prothrombin. Syn: classic hemophilia.
21. Hemophilia B = X-linked recessive (genetics pg 296) , deficiency of factor 9 (IX) activity (Kaplan peds, p 204). = a clotting disorder resembling hemophilia A, caused by hereditary deficiency of factor IX; also seen as an X-linked recessive condition in the Cairn terrier breed of dogs. Syn: Christmas disease.
22. Lesch – Nyhan syndrome, HGPRT deficiency in purine salvage pathway, X –linked recessive, self-mutilation + aggressive destructive behavior ,self mutilation (= bite themselves = self injurious behavior= self destructive behavior). (genetics pg 296, 253) = a disorder of purine metabolism due to deficiency of **hypoxanthine-guanine phosphoribosyltransferase (HPRT)**; characterized by hyperuricemia, uric acid renal stones, mental retardation, spasticity, choreoathetosis, and self-mutilation of fingers and lips by biting; X-linked inheritance, caused by mutation in the HPRT gene on Xq.
23. Glucose 6-phosphate dehydrogenase deficiency (G6PDH deficiency = G6PD deficiency), in HMP shunt (hexose monophosphate pathway) **X-linked recessive**

(genetics pg 296) → cause hemolytic anemia and formation of Heinz bodies. A deficiency of glucose-6-phosphate dehydrogenase, an enzyme important for maintaining cellular concentrations of reduced nucleotides. An X-linked disorder with various polymorphic forms, it can cause a variety of anemias including favism, primaquine sensitivity and other drug sensitivity anemias, anemia of the newborn, and chronic nonspherocytic hemolytic anemia. Can see " Bite Cell" in blood. (CK p 160), (IM p 180), (Peds p 198)

26. Alport syndrome= type 1 = The **X-linked** form is caused by mutation in the collagen type IV alpha-5 gene (COL4A5) on chromosome Xq, **X-linked dominant disorder**. (Kaplan peds, p 184) = a genetically heterogeneous disorder characterized by nephritis associated with microscopic hematuria and slow progression of renal failure, sensorineural hearing loss, and ocular abnormalities such as lenticonus and maculopathy; **autosomal dominant, autosomal recessive, and X-linked recessive forms exist**. The X-linked form is caused by mutation in the collagen type IV alpha-5 gene (COL4A5) on chromosome Xq; the autosomal recessive form is due to mutation in the collagen type IV alpha-3 gene (COL4A3) or alpha-4 gene (COL4A4) on 2q. **(Don't mix Apert syndrome (chromosome 10q) with Alport syndrome (X-liked, chromosome 2q)** (Kaplan peds, p184).

24. Fabry Disease = Diffuse angiokeratoma = angiokeratoma corporis diffusum (ACD) = glycolipid lipidosis= X-linked recessive inheritance caused by mutation the α-galactosidase gene (GLA) on Xq = due to **deficiency of α-galactosidase** and characterized by abnormal accumulations of neutral glycolipids (e.g., globotriaosylceramide) in endothelial cells in blood vessel walls; clinical findings include **angiokeratomas** on the thighs, buttocks, and genitalia, hypohidrosis, paresthesia in extremities, **cornea verticillata, corneal opacities, burning extremities pain and involvement of kidney, heart and brain**, also get spoke-like posterior subcapsular cataracts; death results from renal, cardiac, or cerebrovascular complications; X-linked recessive inheritance caused by mutation the α-galactosidase gene (GLA) on Xq. In Fabry disease get dilated (congestive) cardiomyopathy (IM, p 150).

25. Hunter syndrome = (Hunter syndrome is one of the disease of mucopolysaccharidosis, other examples are hurler and Sanfilippo disease that are autosomal recessive) (Kaplan peds, p225). = An error of mucopolysaccharide metabolism characterized by deficiency of iduronate sulfatase, with

	excretion of dermatan sulfate and heparan sulfate in the urine; clinically similar to Hurler syndrome but distinguished by less severe skeletal changes, no corneal clouding, and **X-linked recessive** inheritance; caused by mutation in the iduronate sulfatase gene (IDS) on chromosome Xq. Syn: type II mucopolysaccharidosis. 26. Nyctalopia (= night blindness) with congenital myopia = X-linked inheritance, characterized by low visual acuity, strabismus, or nystagmus. 27. Ocular albinism 1 = Nettleshop-Falls albinism = type of ocular albinism characterized by depigmentation of the fundus and prominent choroidal vessels, nystagmus, and titubation; vision is usually impaired; caused by mutation in the OA1 gene on chromosome Xp; X-linked inheritance.. 28. Ocular ALBINISM with late-onset sensorineural deafness = x-linked inheritance. 29. X-Linked Polyendocrinopathy, Immune Dysfunction, and Diarrhea = XPID = XLAAD (X-linked autoimmunity and allergic dysregulation) = IPEX (immune dysfunction, polyendocrinopathy, and enteropathy, X-linked) = XPID is an extremely rare disorder characterized by fulminant, widespread autoimmunity and type 1A diabetes, which usually develops in neonates; it is often fatal. The disorder is also known as XLAAD (X-linked autoimmunity and allergic dysregulation) and IPEX (immune dysfunction, polyendocrinopathy, and enteropathy, X-linked). XPID is due to mutation of "Scurfin or FOXP3 gene "on chromosome X. X-linked inheritance. X-Linked Polyendocrinopathy is the X-linked form of the :Polyglandular Autoimmune (PGA) Syndromes = PAS= PGAS= Polyglandular Failure Syndromes= Autoimmune Polyendocrine Syndrome = (= APS) = Autoimmune Polyglandular syndromes = Polyglandular autoimmune diseases. 30. Menkes disease = Ehlers – Danlos syndrome type 9 = kinky hair syndrome, X-linked recessive. Mutation in gene ATP7A which encodes an ATP-dependent copper efflux protein in the intestine get defect in copper metabolism (biochem, pg 62), (pg 56) = kinky-hair disease= kinky hair disease= **decreased uptake of copper => defected LYSYL OXIDASE** = an inborn error of copper metabolism with onset within a few weeks of birth; manifested by short, sparse, poorly pigmented kinky hair; failure to thrive; development of seizures; spasticity; and progressive mental

	deterioration leading to death. X-linked recessive inheritance due to a defect of copper transport, caused by mutation in the Menkes gene (MNK), which encodes a copper-transporting ATPase on Xq. Menkes syndrome is a disorder relating to copper metabolism. This is a disorder caused by an enzymatic defect (lysyl oxidase), which requires Copper (=Cu) to function normally. Syn: Menkes syndrome, trichopoliodystrophy. 31. Ornithine transcarbamoylase (OTC) deficiency, in Urea cycle = X-linked recessive (biochem pg 253) = ornithine transcarbamoylase = ornithine carbamoyltransferase = an enzyme catalyzing formation of L-citrulline and orthophosphate from L-ornithine and carbamoyl phosphate; a part of the urea cycle; a deficiency of this enzyme will result in ammonia intoxication and impaired urea formation. 32. Occipital horn syndrome= an X-linked recessive disorder in which there is defective biliary excretion of copper, resulting in a deficiency of lysyl oxidase causing skin and joint laxity. 33. Severe combined immunodeficiency (SCID) = absence of both humoral and cellular immunity with lymphopenia (of both B-type and T-type lymphocytes), death may occur in the first year of life. Both **autosomal recessive** and **X-linked** forms occur; about one-half of those with autosomal recessive SCID have **adenosine deaminase deficiency**. The X-linked form is caused by mutation in the interleukin-2 receptor gamma gene (IL2RG) on Xq. Both B-cells and T-cells numbers are very low. 34. Wiskott-Aldrich syndrome = X-linked recessive inheritance, caused by mutation in the Wiskott-Aldrich syndrome protein (WASP) on chromosome Xp. An immunodeficiency disorder occurring in male children and characterized by thrombocytopenia, eczema, melena, and susceptibility to recurrent bacterial infections; death occurs from severe hemorrhage or overwhelming infection; X-linked recessive inheritance, caused by mutation in the Wiskott-Aldrich syndrome protein (WASP) on chromosome Xp. Syn: Aldrich syndrome. 35. Chronic Granulomatous Disease (CGD) = a congenital defect in the killing of phagocytosed bacteria by polymorphonuclear leukocytes, which cannot increase their oxygen metabolism either because of defective cytochrome or other specific factor deficiencies. As a result there is an increased susceptibility to severe infection by catalase-positive microorganisms; inheritance is usually autosomal

recessive or X-linked. Syn: granulomatous disease, congenital dysphagocytosis. NBT Test= Nitroblue Tetrazolium Test = Nitro blue tetrazolium = is used for dx of chronic granulomatous disease (CGD). In chronic granulomatous disease, patient suffer from numerous pyogenic (pus forming) infections and abscesses. A nitroblue tetrazolium test checks for the presences of functional catalase (Kaplan peds, p 118). In CGD, there is a **defect in NADPH oxidase**; therefore the phagocyte is unable to make the reactive oxygen species or radicals required for bacterial killing and results in bacteria thriving within the phagocyte. To test for CGD do "phagocytic assay" (peds p 118).

36. Bruton X-linked hypogammaglobulinemia= X-linked= an X-linked condition, with hypo- or agammaglobulinemia; the immune deficiency becomes apparent as maternally transmitted immunoglobulin levels decline in early infancy. Syn: X-linked agammaglobulinemia (= XLA). The abnormal gene in Bruton is q22 on the long arm of the X chromosome (Kaplan peds, p 119).
37. X-linked infantile hypogammaglobulinemia =X-linked recessive inheritance caused by mutation in the Bruton tyrosine kinase gene (BTK) on Xq = a congenital, primary immunodeficiency characterized by decreased numbers (or absence) of circulating B lymphocytes with corresponding decrease in immunoglobulins of the five classes; associated with marked susceptibility to infection by pyogenic bacteria (notably, pneumococci and *Haemophilus influenzae*) beginning after loss of maternal antibodies; X-linked recessive inheritance.
38. X-linked Ichthyosis = **X-linked recessive inheritance**, caused by mutation in the steroid sulfatase gene (STS) on Xp= a form of ichthyosis, with onset at birth or in early infancy and affecting males; characterized by scaling predominantly on the scalp, neck and trunk and progressing centripetally; the palms and soles are spared; histologic manifestations are hyperkeratosis, a granular layer in the epidermis, and normal epidermal cell turnover. X-linked recessive inheritance. X-linked ichthyosis the scaling of skin is similar to that of ichthyosis vulgaris but tends to favor flexor and intertriginous surface, but ichthyosis vulgaris favors the extensor surface of the extremities.
39. X-linked lymphoproliferative syndrome= X-linked recessive immunodeficiency and lymphoproliferative disease caused by mutation in the SH2 domain protein 1A gene (SH2D1A) on Xq characterized by defective cellular or

humoral immune response to Epstein-Barr virus; manifestations include fulminant infectious mononucleosis, B-cell malignancies, and hypogammaglobulinemia. Syn: Duncan disease, X-linked lymphoproliferative disease, Duncan syndrome.

40. X-linked recessive bulbospinal neuronopathy= Kennedy disease = X-linked recessive, an X-linked recessive disorder characterized by progressive spinal and bulbar muscular atrophy; associated features include distal degeneration of sensory axons, and signs of endocrine dysfunction, including diabetes mellitus, gynecomastia, and testicular atrophy. The term spinal muscular atrophy thus refers to atrophy of muscles due to loss of motor neurons within the spinal cord. Hereditary Bulbo-Spinal spinal muscular atrophy (SMA) Kennedy's disease is X linked and due to defect in **Androgen receptor.**
41. **X-Linked** infantile spinal muscular atrophy (SMA) due to mutation of (**gene UBE1**). Spinal muscular atrophy (SMA)= a heterogeneous group of degenerative diseases of the anterior horn cells in the spinal cord and motor nuclei of the brainstem; all are characterized by weakness. Upper motor neurons remain normal. These diseases include Werdnig-Hoffmann disease (SMA type 1), SMA type 2, and Kugelberg-Welander disease (SMA type 3).
42. Hereditary hearing impairment= hereditary deafness, X- linked form of inheritance (has different mode of inheritance) = hearing impairment occurring in syndromic forms (in which there are other anomalies in addition to the hearing impairment) and nonsyndromic forms (in which hearing impairment is the only unusual finding) with autosomal dominant and recessive, X-linked, and mitochondrial modes of transmission; may be congenital, of early onset in childhood, or late onset in mid-life and advanced age.
43. Alopecia congenitalis= absence of all hair at birth. May be associated with psychomotor epilepsy; autosomal dominant or X-linked inheritance. Syn: congenital baldness, hypotrichiasis
44. Rett syndrome = **X-linked dominant disorder,** seen in **girls** only (= sex linked), affected males die in utero, **Hand wringing** (1^{st} aid, p 364). Absence of MeCP2 leads to failure of silencing multiple gene. A pervasive developmental disorder characterized by the development of several specific deficits after an apparently normal prenatal and perinatal period, including deceleration in head growth, loss of

	purposeful hand skills with deterioration into stereotypical hand movements, impairment in expressive and receptive language, and significant psychomotor retardation. Rett Syndrome results from a mutation in the **X-linked** gene - **methyl-cytosine binding protein 2 (= MeCP2)**. Rett syndrome is an x-linked dominant disorder, affecting exclusively girls. Pt present with acquired microcephaly, **hand wringing** and singing, they develop **autistic behavior** . (Kaplan Peds, p 47, p 225). Rett syndrome (also called Rett disorder) is a neurodevelopmental disorder that is classified as a pervasive developmental disorder by the DSM-IV. The clinical features include a deceleration of the rate of head growth (including microcephaly in some) and small hands and feet. Stereotypic, repetitive hand movements such as mouthing or wringing are also noted. Symptoms of the disorder include cognitive impairment and problems with socialization, the latter during the regression period. Socialization typically improves by the time they enter school. Girls with Rett syndrome are very prone to gastrointestinal disorders and up to 80% have seizures. They typically have no verbal skills, and about 50% of females are not ambulatory. Scoliosis, growth failure, and constipation are very common and can be problematic. Many argue that it is misclassified as a pervasive developmental disorder, just as it would be to include such disorders as fragile X syndrome, tuberous sclerosis, or Down syndrome where one can see autistic features. The symptoms of this disorder are most easily confused with those of Angelman syndrome, cerebral palsy and autism. Rett syndrome (symbolized RTT) is caused by sporadic mutations in the gene **MECP2 (=methyl-CpG-binding protein-2)** located on the X chromosome. It almost exclusively affects girls -- male fetuses with the disorder rarely survive to term. Development is typically normal until 6-18 months, when language and motor milestones regress, purposeful hand use is lost and acquired deceleration in the rate of head growth (resulting in microcephaly in some) is seen. Hand stereotypies are typical and breathing irregularities such as hyperventilation, breath holding, or sighing are seen in many. Early on, autistic-like behavior may be seen. Rett syndrome is usually caused (95% or more) by a de novo mutation in the child (so it is inherited from a genotypically normal mother, i.e. without a MECP2 mutation). It can also be inherited from phenotypically normal mothers who have a germline mutation in the gene encoding **methyl-CpG-binding protein-2= MECP2**. MECP2 is found near the end of the long arm of the **X**

	chromosome at Xq28. An atypical form of Rett syndrome, characterized by infantile spasms or early onset epilepsy, can also be caused by a mutation to the gene encoding **cyclin-dependent kinase-like 5 (CDKL5)**. Rett syndrome affects one in every 12,500 female live births by age 12 years. Most individuals with Rett syndrome are female. Because the disease-causing gene is located on the X chromosome, a female born with a MECP2 mutation on her X chromosome has another X chromosome with an ostensibly normal copy of the same gene, while a male with the mutation on his X chromosome has no other X chromosome, only a Y chromosome; thus, he has no normal gene. Without a normal gene to provide normal proteins in addition to the abnormal proteins caused by a MECP2 mutation, the XY karyotype male fetus is unable to staunch the development of the disease, hence the failure of many male fetuses with a MECP2 mutation to survive to term. Females with a MECP2 mutation, however, have a non-mutant chromosome that provides them enough normal protein to survive at least to birth. Research shows that males with Rett's syndrome almost all have Klinefelter's syndrome as well (in which the male has an XXY karyotype). Thus, a non-mutant MECP2 gene is necessary for a Rett's-affected embryo to survive in most cases, and the embryo, male or female, must have another X chromosome. There have, however, been several cases of 46,XY Karyotype males with a **MECP2 mutation (associated with classical Rett syndrome in females**) carried to term, who were affected by neonatal encephalopathy and died before 2 years of age. The incidence of Rett syndrome in males is unknown, partly due to low survival of male fetuses with the Rett syndrome associated MECP2 mutations, and partly to differences between symptoms caused by MECP2 mutations and those caused by Rett's. The severity of Rett syndrome in females can vary depending on the type and position of the mutation of MECP2 and the pattern of X-chromosome inactivation. It is generally assumed that 50% of a female's cells use the maternal X chromosome while the other 50% uses the paternal X chromosome (see X-inactivation). However, if most cells in the brain activate the X chromosome with the functional MECP2 allele, the individual will have very mild Rett syndrome; likewise, if most neurons activate the X chromosome with the mutated MECP2 allele, the individual will have very severe Rett syndrome just as males with MECP2 mutations do (as they only have one X chromosome). 45. Hypokalemic periodic paralysis = a form of periodic

paralysis in which the serum potassium level is low during attacks; onset usually occurs between the ages of 7–21 years; attacks may be precipitated by exposure to cold, high carbohydrate meal, or alcohol, may last hours to days, and may cause respiratory paralysis; autosomal dominant caused by mutation in the muscle dihydropyridine (DHP)-sensitive calcium channel)-1-subunit (CACNL1A3) on chromosome 1q, or X-linked inheritance.

46. Leigh disease =subacute encephalomyelopathy affecting infants, causing seizures, spasticity, optic atrophy, and dementia; the genetic causation is heterogeneous; may be associated with deficiency of cytochrome c oxidase or NADH-ubiquinone oxidoreductase or other enzymes involved in energy metabolism. Autosomal recessive, X-linked recessive and mitochondrial inheritance have been described; mutations have been identified in the surfeit-1 gene (SURF) on chromosome 9, in a mtDNA-encoded subunit of ATP synthase , in the X-linked E1-alpha subunit of pyruvate dehydrogenase , and in several subunits of mitochondrial complex I . Syn: necrotizing encephalomyelopathy , necrotizing encephalopathy.(path, p50)

47. Incontinentia pigmenti = Bloch-Sulzberger disease, Bloch-Sulzberger syndrome= a rare genodermatosis characterized by hyperpigmented lesions in linear, zebra stripe, and other bizarre configurations following the lines of Blaschko; occasionally accompanied by other developmental anomalies of the eyes, teeth, nails, skeleton, nails, heart. The dermatologic features involve four stages: stage I is characterized by erythema, vesicles, and pustules; stage II by papules, verrucous lesions, and hyperkeratosis; stage III by hyperpigmentation; and stage IV by pallor, atrophy, and scarring. Historically, there were thought to be two forms: 1) the sporadic type of incontinentia pigmenti (IP1), which is now known to be hypomelanosis of Ito and 2) the familial type (IP2), which is **X-linked dominant** (Kaplan OB, p 6) and a genetic lethal in males. Subtle, fiant, hypochromic or atrophic Blaschko-linear lesion on the extremities are seen in the fourth and last stage of incontinentia pigmenti, an X-linked dominant disease that is believed to be lethal in utero in boys. It appears in girls during the first weeks of life and evolves through a vesicular (inflammatory), verrucous, and pigmentary stage. A fourth, hypopigmented and/or atrophic stage, may be seen in some adult women (Q book3, p 230). See Also: hypomelanosis of Ito.

	48. Focal dermal hypoplasia= Goltz syndrome = inherited as an **X-linked dominant** (Kaplan OB, p 6) with in utero lethality in males; characterized by linear areas of dermal atrophy or hypoplasia, herniation of fat through the dermal defects, and papillomata of the mucus membranes or skin; may be associated with digital, ocular, and oral anomalies; mental retardation; and bony striations. 49. Orofaciodigital syndrome= orodigitofacial dysostosis, OFD syndrome, Papillon-Léage and Psaume syndrome= an inherited syndrome, lethal in males, with varying combinations of defects of the oral cavity, face, and hands, including lobulated or bifid tongue, cleft or pseudo-cleft palate, tongue tumors, missing or malpositioned teeth, hypoplastic nasal alar cartilage, depressed nasal bridge, brachydactyly, clinodactyly, incomplete syndactyly, and, frequently, mental retardation; autosomal recessive or **X-linked dominant** inheritance. (Kaplan OB, p 6) 50. Dyskeratosis congenita= nail dystrophy, oral leukoplakia, and reticular pigmentation of the skin, testicular atrophy with anemia progressing most commonly to pancytopenia; **X-linked recessive** inheritance, caused by mutation in the DKC1 gene encoding dyskenin on Xq. 51. Amelogenesis imperfecta=a group of hereditary ectodermal disorders in which the enamel is defective in structure or deficient in quantity. Three major groups are recognized: hypoplastic types, with defective enamel matrix deposition but normal mineralization; hypomineralization types, with normal matrix but defective mineralization; and hypomaturation type, in which the enamel crystallites remain immature. The several types may be inherited as autosomal dominant, recessive or X-linked . Syn: enamel dysplasia, enamelogenesis imperfecta. 52. Albright syndrome = Albright hereditary osteodystrophy = an inherited form of hyperparathyroidism associated with ectopic calcification and ossification and skeletal defects, notably the small fourth metacarpals; intelligence may be normal or subnormal. Inheritance is heterogeneous; the autosomal form is caused by mutation in the guanine nucleotide-binding protein gene (GNAS1) on 20q. There are also the recessive and X-linked forms. 53. Peroneal muscular atrophy= a group of peripheral neuromuscular disorders, sharing the common feature of marked wasting of the distal parts of the extremities, particularly the peroneal muscle groups, resulting in long,

thin legs; it usually involves the legs before the arms with pes cavus often the first sign. There are two forms of hereditary sensorimotor polyneuropathies, i.e., a demyelinating type and an axonal loss type. Autosomal dominant, autosomal recessive, and X-linked recessive forms exist. One of the most common forms of CMT is Type 1A. The gene for Type 1A CMT maps to chromosome 17 and is thought to code for a protein (PMP22) involved in coating peripheral nerves with myelin, a fatty sheath that is important for their conductance. Other types of CMT include Type 1B, autosomal-recessive, and X-linked. The same proteins involved in the Type 1A and Type 1B Charcot-Marie-Tooth disease (CMT) are also involved in a disease called Dejerine–Sottas Syndrome (DSS), in which similar clinical symptoms are presented, but they are more severe. Syn: Charcot-Marie-Tooth disease (CMT), Hereditary motor sensory neuropathy (HMSN) type1. (Kaplan peds, p228)

54. Pseudohypoparathyroidism = A disorder resembling hypoparathyroidism, with high serum phosphate and low calcium levels but with normal or elevated serum parathyroid hormone levels; the defect is due to lack of end-organ responsiveness to parathyroid hormone. There are two types: type I shows lack of renal tubular response to exogenous parathyroid hormone with increase in urinary cAMP, type Is has type I skeletal defects (SYN Albright hereditary osteodystrophy), and type II is associated with a defect at a locus after cAMP production. X-linked dominant inheritance caused by mutation in the gene encoding guanine nucleotide-binding protein α-stimulating activity.
55. Faciodigitogenital dysplasia = a syndrome of ocular hypertelorism, anteverted nostrils, broad upper lip, saddle-bag or shawl scrotum, protruding umbilicus, and laxity of ligaments resulting in genu recurvatum, flat feet, and hyperextensible fingers; the X-linked form is caused by mutation in the FGD1 gene on Xp; autosomal dominant and recessive forms also exist. Syn: Aarskog-Scott syndrome.
56. Emery-Dreifuss muscular dystrophy = a generally benign type of muscular dystrophy, with onset in childhood or early adulthood. Weakness begins with the pectoral girdle and proximal upper extremity muscles and spreads to the pelvic girdle and distal lower extremity muscles. Contractures of the elbow, flexors, neck flexors, and calf muscles often occur; muscle pseudohypertrophy and mental retardation do not occur. A cardiomyopathy is common. An **X-linked inherited disorder**, nonallelic to Duchenne

muscular dystrophy.

57. Cornelia de Lange Syndrome aka CdLS is a little known genetic disorder that can lead to severe developmental anomalies. It affects both the physical and intellectual development of a child. genes responsible for **CdLS** are: **NIPBL on Chromosome 5**, a second gene— **SMC1A on the X chromosome**— and **gene SMC3 is on chromosome 10**. The latter two genes(on chromosome X and chromosome 10) seem to correlate with a milder form of the syndrome. The vast majority of cases are due to spontaneous mutations, although the defected gene can be inherited from either parent, making it **autosomal dominant**.
58. Fanconi Anemia = Constitutional Fanconi Pancytopenia (Kaplan Peds, p 201) = **is autosomal recessive inheritance. Fanconi anemia should not be confused with Fanconi syndrome, a kidney disorder also named after Fanconi**. Fanconi Anemia is associated with aplastic anemia and congenital musculoskeletal and cutaneous abnormalities (Kaplan Peds, p 201) . Approximately 80% of patients with Fanconi anemia can exhibit a variety of congenital anomalies. The characteristic **aplastic anemia** is usually not evident before the age of 5 years. Other key features which can help distinguish this disorder are: **hyperpigmentation of skin, café au lait spots spots, short stature, upper limb anomalies (which can include absent thumbs, hypoplastic thumbs, supernumerary or bifid thumbs and aplasia of the first metacarpal or the radius, absent radius), hypogonadism, Microcephaly, microphthalmia, hearing loss, absent radii, horseshoe kidney, absent thumbs**. **Diepoxybutane** (DEB) is used for diagnosis of Fanconi anemia; get increased chromosomal breakage in the presence of diepoxybutane in patients with Fanconi anemia (peds p 201). The only potential cure for Fanconi anemia is bone marrow transplant and early diagnosis is a key element in prognosis. Fanconi anemia (FA) is a genetic disease that affects children and adults from all ethnic backgrounds. The disease is named after the Swiss pediatrician who originally described this disorder, Guido Fanconi. It should not be confused with Fanconi syndrome, a kidney disorder also named after Fanconi. FA is characterized by short stature, skeletal anomalies, increased incidence of solid tumors and leukemias, bone marrow failure, hypocellular bone marrow with decrease all cell lines (pancytopenia) (aplastic anemia), and cellular sensitivity to DNA damaging agents such as

	mitomycin C. FA is primarily an **autosomal recessive** genetic disorder. There are at least 13 genes of which **mutations are known to cause Fanconi Anemia (=FA): FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM and FANCN. FANCB is the one exception to FA being autosomal recessive, as this gene is on the X chromosome**. The carrier frequency in the **Ashkenazi Jewish** population is about 1/90. Bone marrow transplantation is the accepted treatment to repair the hematological problems associated with FA. However, even with a bone marrow transplant, patients face an increased risk of acquiring cancer and other serious health problems throughout their lifetime. 59. Chondrodysplasia punctata =a developmental disorder characterized by epiphyseal stippling, coronal clefting of the vertebrae, dwarfism with rhizomelic shortening of the limbs, joint contractures, congenital cataracts, ichthyosis, and mental retardation. **Autosomal dominant and recessive** and **X-linked** forms exist. Syn: hypoplastic fetal chondrodystrophy, dysplasia epiphysialis punctata, stippled epiphysis. 60. Perilymphatic gusher= abnormal flow of perilymph when the footplate of the stapes is perforated; occurs in X-linked mixed deafness (DFN 3) due to a mutation of the POU3F4 gene and in other conditions. 61. Coffin-Lowry syndrome= characterized by coarse facial features with bulbous nose, large ears, and thick lips; short stature; tapered fingers; skeletal anomalies and mental retardation. X-linked recessive inheritance, caused by mutation in the ribosomal S6 kinase gene (RSK) on chromosome Xp 62. Oculocerebrorenal syndrome= a congenital syndrome with hydrophthalmia, cataracts, mental retardation, aminoaciduria, reduced ammonia production by the kidney, and vitamin D–resistant rickets; X-linked recessive inheritance, caused by mutation in the oculocerebrorenal gene (OCRL) on Xq. Syn: Lowe syndrome, Lowe-Terrey-MacLachlan syndrome. 63. Norrie disease=congenital bilateral masses of tissue arising from the retina or vitreous and resembling glioma (pseudoglioma), usually with atrophy of iris and development of cataract; associated mental retardation and deafness; X-linked recessive inheritance, caused by mutation in the Norrie disease gene (NDP) on Xp.

64. **Pelizaeus-Merzbacher disease** = a sudanophilic leukodystrophy with a tigroid appearance of the myelin resulting from patchy demyelination. Type 1, classic, nystagmus and tremor appearing in the first few months of life, followed by slow motor development sometimes with choreoathetosis, spasticity, optic atrophy and seizures, with death in early adulthood, X-linked recessive inheritance caused by mutation in the proteolipid protein gene (PLP) on Xq; there is an autosomal recessive form as well; type 2, contralateral form with death in months to years after birth, X-linked recessive inheritance; type 3, transitional, with death in the first decade; type 4, adult form associated with involuntary movements, ataxia and hyperreflexia, but without nystagmus; autosomal dominant inheritance; type 5, variant forms. Cockayne is sometimes included as a sixth form. Syn: Merzbacher-Pelizaeus disease. Pelizaeus-Merzbacher disease is a well-established, autosomal, dominant, mendelian disorder.
65. Reifenstein syndrome= partial androgen sensitivity; a familial form of male pseudohermaphroditism characterized by varying degrees of ambiguous genitalia or hypospadias, postpubertal development of gynecomastia, and infertility associated with seminiferous tubular sclerosis; cryptorchidism may be present, and Leydig cell hypofunction may lead to impotence in later years; chromosomal studies show 46,XY karyotype; X-linked recessive inheritance, caused by mutation in the androgen receptor gene (AR) on Xq.
66. Familial Hypogonadotropic Hypogonadism = a group of disorders characterized by failure of sexual development, owing to inadequate secretion of pituitary gonadotropins; perhaps X-linked, but probably autosomal dominant and recessive modes of inheritance also exist (IM, p 57).
67. Kallmann syndrome (= Hypogonadotropic hypogonadism)= Hypogonadism with anosmia= isolated gonadotropin deficiency or familial hypogonadotropic hypogonadism = anovulation, anosmia , color blindness = failure of sexual development secondary to inadequate secretion of pituitary gonadotrophins, associated with **anosmia** due to agenesis of the olfactory lobes of the brain. Autosomal dominant , autosomal recessive , and X-linked recessive forms exist; the X-linked form is caused by mutation in the

Kallmann gene (KAL1) on Xp. (Kaplan OB, p 154) (IM, p 57). Hypogonadotropic hypogonadism= 1) hypogonadotropism = get low level of gonadotropins (= decrease LH and decrease FSH), 2) hypogonadism= lack of development of secondary sexual characteristics such as amenorrhea. Compare Kallmann syndrome (= Hypogonadotropic hypogonadism= get decrease in both LH and decrease in FSH) with **Klinefelter Syndrome (=Hypergonadotropic hypogonadism = get increase in both LH and increase in FSH)** (IM, p 57), (OB, p 154)

68. Cleft lip = harelip = a congenital facial abnormality of the lip (usually of the upper lip) resulting from failure of union of the medial and lateral nasal prominences and maxillary process; frequently but not necessarily associated with cleft alveolus and cleft palate. In many families and in various forms there seems to be **autosomal dominant** inheritance; likewise for **X-linked inheritance**. But generally, as with the supposed autosomal recessive forms, the genetics is more confusing and may represent a variable feature of a syndrome. Cleft lip is an example of Multifactorial inheritance = polygenic in origin (Kaplan OB, p 7 and8).
69. Dyschondrosteosis=. A skeletal dysplasia, more severe in females and with a female preponderance, characterized by bowing of radius, dorsal dislocation of the distal ulna with limited movement of the elbow and wrist (wrist deformity is called Madelung deformity), and mesomelic dwarfism; dominant inheritance, caused by mutation in the short stature homeobox gene (SHOX) on the pseudoautosomal region of Xp. Langer mesomelic dysplasia, the homozygous form of dyschondrosteosis, is also caused by homozygous mutations in the SHOX gene. Syn: Leri-Weill disease, Leri pleonosteosis, Leri-Weill syndrome.
26. Testicular Feminization Syndrome (46, XY)= Androgen Insensitivity Syndrome (OB p 154)= **X-linked recessive inheritance, caused by mutation in the androgen receptor gene (AR) on chromosome Xq.** In these genetically male (46, XY) individuals, with complete lack of androgen receptor function, their bodies do not respond to the high levels of androgens present without androgen stimulation, internal wolffian duct structures atrophy. With **testicular mullerian inhibitory factor (MIF) present**, the mullerian duct derivatives involute. Without body recognition of dihydrotestosterone (DHT), external genitalia differentiate

	in a female direction. These patients function psychologically and physically as females (=female phenotype) and are brought up as girls (OB p 154) . 46X"Y" but "Y" chromosome doesn't work because of insensitivity of androgen receptors (so Y is useless), but "Y" produce testosterone, so get raised testosterone level in these individuals= a type of male pseudohermaphroditism characterized by female external genitalia (may be ambiguous if the syndrome is incomplete), incompletely developed vagina often with rudimentary uterus and fallopian tubes, female habitus at puberty but with scanty or absent axillary and pubic hair and amenorrhea, and testes present within the abdomen or in the inguinal canals or labia majora; epididymis and vas deferens are usually present; androgens and estrogens are formed, but target tissues are largely unresponsive to androgens; individuals have a normal male karyotype; **X-linked recessive inheritance, caused by mutation in the androgen receptor gene (AR) on chromosome Xq. Tx of androgen insensitivity syndrome is bilateral abdominal gonadectomy (= testicular resection at puberty) and creation of a neovagina** (OB p 154). Note: **Female pseudohermaphrodism = it means ovaries are present) is due to Congenital adrenal hyperplasia and Male pseudohermaphrodism = it means testis are present) is due to 5-alpha reductase deficiency as one of its etiologies**. Androgen stimulation (from testicular source) causes mesonephric (wolffian duct) in male to differentiate to vas deference, seminal vesicles, epididymis and efferent ducts. In females without the androgen stimulation, the wolffian ducts undergoes regression. If a genetic male has an absence of androgen receptors, the Wolffian duct will also undergo regression (OB, p 9). 70. X =female sex chromosome -chromosome carrying gene for intelligence (I.Q.) 71. Spondyloepiphyseal dysplasia tarda = a skeletal dysplasia of later onset, usually in the second decade, characterized by short stature, flattening of the vertebrae, epiphyseal involvement with bony fusion of the hip joint, premature osteoarthritis, and distinctive radiographic findings. **Autosomal dominant** and **X-linked recessive** forms exist. 72. Rud syndrome = ichthyosiform erythroderma associated with acanthosis nigricans, dwarfism, hypogonadism, and epilepsy; mostly sporadic, but may be an X-linked recessive trait. 73. Aicardi syndrome = an X-linked dominant disorder

	with lethality in hemizygous males; characterized by agenesis of corpus callosum, chorioretinal abnormality with "holes," cleft lip with or without cleft palate, seizures, and characteristic EEG changes. 74. Dyggve-Melchior-Clausen syndrome = a skeletal dysplasia that has some clinical resemblance to Morquio syndrome but without mucopolysaccharidiuria; characterized by mental retardation, short-trunk dwarfism, progressive sternal bulging, restricted joint mobility, waddling gait, and radiographic findings of irregular iliac crests and flattening of vertebral bodies; **autosomal recessive inheritance**. There is an **X-linked** form. 75. Retinitis pigmentosa =a progressive retinal degeneration characterized by bilateral nyctalopia, constricted visual fields, electroretinogram abnormalities, and pigmentary infiltration of the inner retinal layers; may be sporadic or demonstrate autosomal dominant, autosomal recessive, or X-linked inheritance. Syn: pigmentary retinopathy. 76. Congenital cataract = cataract, usually bilateral, present at birth. It occurs as an autosomal recessive condition in calves of the Jersey breed. In humans approximately 25% of bilateral congenital cataracts are **autosomal dominant; X-linked** forms also exist. Most congenital cataracts are sporadic, some the result of prematurity, intrauterine infection, drug-related toxicity, injury, or chromosomal or metabolic disorders. 77. Panhypopituitarism (PHP) = A state in which the secretion of all anterior pituitary hormones is inadequate or absent; caused by a variety of disorders that result in destruction or loss of function of all or most of the anterior pituitary gland. Rare forms of PHP are inherited as autosomal recessive or as X-linked recessive. Syn: hypophyseal cachexia, hypophysial cachexia, ateliotic dwarfism. 78. Familial bipolar mood disorder= bipolar mood disorder commonly inherited as an **autosomal dominant** trait and also occasionally as an **X-linked** one.
Y	1. Disappearing testes syndrome= genetic male with (46,XY), male genotype, female phenotype. They have no breast, no ovaries, no mullerian duct and no wolffian duct. This is NOT a genetic abnormality. It's just that the male embryo fails to differentiate to male fetus and as a result it follows the default pathway of female phenotype. 2. The gene for testes determining factor (TDF) is on the Y

	chromosome; TDF will cause the indifferent gonad to develop into a testis containing sertoli cells. Sertoli cells, during early fetal life, will secret Mullerian inhibitory factor (= MIF), a substance that suppresses the paramesonephric ducts, preventing formation of the female internal reproductive organs. In males the Y chromosome induces gonadal secretion of mullerian inhibitory factor (MIF) , which causes the mullerian duct (= paramesonephric duct) to involutes. In females, without MIF, development continues to form the fallopian tubes, corpus of the uterus, cervic and proximal vagina. (Kaplan OB, p 9) 3. Y-linkage= The state of a genetic factor (gene) being borne on the Y chromosome. This idea is analogous with X-linkage, but since the Y chromosome does not fully take part in chiasma formation and recombination, it is not amenable to analysis by conventional linkage methods. Little is known about its content. There is a gene for the H-Y antigen, and indirect arguments suggest that there is a principle that determines the formation of the testis and masculinization of the fetus but its localization, though narrowing the limits, remains elusive. 4. H-Y antigen =an antigen factor, dependent on the Y chromosome, responsible for the differentiation of the human embryo into the male phenotype by inducing the initially bipotential embryonic gonad to develop into a testis; in the absence of this antigen, the indifferent gonad develops into an ovary. There are at least two loci involved, an autosomal gene that generates the antigen and one that makes the receptor . 5. 47, XYY = double Y syndrome = XYY syndrome = XYY male = double Y male = incidence 1:1000, some intellectual impairment + behavioral problem. Normal life span, affected individuals often go undetected but be taller than average, and may be more likely to exhibit aggressive, antisocial behavior. a chromosomal anomaly with chromosome count 47, with a supernumerary Y chromosome; controversial evidence associates tallness, aggressiveness, and acne with this condition. [Phenotypically normal, very tall, sever acne, antisocial behavior, seen in 1-2 % of XYY males. observed with high frequency among inmates of penal institutions.] (1^{st} aid, p 401) 6. Y- Linked inheritance = holandric inheritance = [G. *holos,* entire, + *aner,* human male] = the pattern of inheritance that may result from a mutant gene located on a Y chromosome = affected males would transmit the mutation and would transmit it only to their sons.

	7. Y- chromosome mosaicism = Mosaicism refers to the presence of two or more cytogenetically distinct cell lines in the same individual. Mosaicism can involve the placenta, the fetus or both. Gonadal mosaicism can result in premature ovarian failure and predispose the gonad to malignancy (Kaplan OB, p 3, 155). A positive EPCT (estrogen-Progesterone challenge test) with an elevated FSH suggested ovarian failure. If this occurs before age 25 years, the cause could be Y chromosome mosaicism that is associated with malignancy, so order a karyotype (Kaplan OB, 156). Secondary amenorrhea with hypergonadotropic (= increase FSH and increase LH) can suggest ovarian follicular failure (Kaplan OB, p 155). Ovarian failure syndrome occurs before age 30 years and may be associated with autoimmune disease or Y chromosome mosaicism (Kaplan OB, p165).
Mitochondria/ maternal inheritance diseases	**Mitochondria/ maternal inheritance diseases=** affected males never produce affected children, but affected females do produce affected children of both sexes when they mate with unaffected male (Kaplan Peds, p 249) = with mitochondrial inheritance, only an affected mother can transmit the disease phenotype, the offspring of affected males are always unaffected = mitochondrial disorders = a group of diverse hereditary disorders caused by genetic mutation of mitochondrial DNA; includes ragged red fiber myopathy; progressive external ophthalmoplegia; Leigh syndrome; myoclonic epilepsy with ragged red fiber myopathy (MERRF); mitochondrial myopathy, encephalopathy, lactic Acidosis (= lactacidosis), and stroke (MELAS); and Lieber optic neuropathy. 1. Leber hereditary optic neuropathy (LHON) = point mutation in subunit 4 of NADH dehydrogenase. (genetics pg 299). Leber hereditary optic atrophy= degeneration of the optic nerve and papillomacular bundle with resulting loss of central vision and blindness, progressive for several weeks, then usually becoming stationary with permanent central scotoma; the age of onset is variable, most often in the third decade; more males than females are affected. Mitochondrial or cytoplasmic inheritance via the maternal lineage, caused by mutation in the mitochondrial gene(s) acting autonomously or in association with each other. 2. MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke –like episodes = point mutation in tRNA leucine (genetics pg 299). MELAS =

	acronym for *m*itochondrial myopathy, *e*ncephalopathy, *l*actic *a*cidosis, and *s*trokelike episodes. One of the mitochondrial disorders, this condition is usually hereditary, with a mutation at the mitochondrial genome at locus 3243. **2.** An acronym for mitochondrial myopathy, encephalopathy, lactacidosis, and stroke; an inherited disorder of the respiratory chain, either a deficiency of NADH: ubiquinone oxidoreductase (complex I of the chain) or of cytochrome *c* oxidase. 3. May-White syndrome = progressive myoclonus epilepsy with lipomas, deafness, and ataxia; probably a familial form of mitochondrial encephalomyopathy. 4. Myoclonus epilepsy= a clinically diverse group of epilepsy syndromes, some benign, some progressive. Many are hereditary with Mendelian and nonmendelian mitochondrial inheritance. All are characterized by the occurrence of myoclonus, which may be limited or predominate in the condition. Specific syndromes include cherry red spot myoclonus syndrome, ceroid lipofuscinosis, myoclonic epilepsy with ragged red fibers, and Baltic myoclonus. Syn: localization-related epilepsy. 5. **M**yoclonic **E**pilepsy with **R**agged **R**ed muscle **F**ibers disease (MERRF) = ragged red muscle fiber disease = point mutation in tRNA lysine (genetics pg 186, 299) **6.** Kearns-Sayre syndrome (KSS) = oculocraniosomatic syndrome = **Kearns-Sayer** Syndrome= **is a sporadic condition and not inherited),** test for KSS is the **"DNA analysis" =** type of mutation is "**deletion**" = Kearns-Sayre syndrome (abbreviated KSS) or oculocraniosomatic syndrome is a disease **caused by a 5,000 base deletion in the mitochondrial DNA.** As such, it is a rare genetic disease in that it can be hetero-plasmic, that is, more than one genome can be in a cell at any given time. Unlike most mitochondrial diseases, it is not maternally inherited. Rather, it occurs sporadically. Kearns -Sayre syndrome starts before the age of 20.Its expression is systemic, but many of the most common expressions are in the eyes, with ophthalmoplegia and retinal degeneration, specifically retinitis pigmentosa, as common features. Other characteristic features of KSS are dysphagia, proximal weakness, hearing loss, cerebellar ataxia and cardiac conduction defects. White matter lesions are usually seen. The **deletion event in KSS is sporadi**c (i.e. a stochastic event), and occurs either in oogenesis or early in embryogenesis (pre-blastocyst stage). Some mutated

	mitochondria can enter the zygote when the ovum's 150000 mtDNA copies are reduced to a much smaller set. Once in the embryo, the giant-deletion mutants can enter the ectoderm, mesoderm and endoderm, causing systemic disorders. There is no treatment for Kearns-Sayre syndrome as of now. In general, only palliative medications are available to sufferers in order to help relieve the symptoms of the disease. It is named for Thomas Kearns and George Sayre. **Kearns–Sayre syndrome = External ophthalmoplegia, retinal degeneration, diabetes, thyroiditis, hypoparathyroidism** 7. Chronic external ophthalmoplegia plus (CEOP) = [chronic progressive external ophthalmoplegia (CPEO)??] = deletion 8. Hereditary hearing impairment, mitochondrial form of inheritance (has different mode of inheritance) 9. Leigh disease =subacute encephalomyelopathy affecting infants, causing seizures, spasticity, optic atrophy, and dementia; the genetic causation is heterogeneous; may be associated with deficiency of cytochrome c oxidase or NADH-ubiquinone oxidoreductase or other enzymes involved in energy metabolism. Autosomal recessive, X-linked recessive and mitochondrial inheritance have been described; mutations have been identified in the surfeit-1 gene (SURF) on chromosome 9, in a mtDNA-encoded subunit of ATP synthase , in the X-linked E1-alpha subunit of pyruvate dehydrogenase , and in several subunits of mitochondrial complex I . Syn: necrotizing encephalomyelopathy , necrotizing encephalopathy.(path, p50)
DNA Repair Problem	1. Xeroderma Pigmentosa (biochem, pg 27) = an eruption of exposed skin occurring in childhood and characterized by photosensitivity with severe sunburn in infancy and the development of numerous pigmented spots resembling freckles, larger atrophic lesions eventually resulting in glossy white thinning of the skin surrounded by telangiectases, and multiple solar keratoses that undergo malignant change at an early age; results from several rare autosomal recessive complementation groups in which DNA repair processes are defective, so that they are more liable to chromosome breaks and cancerous change when exposed to ultraviolet light. Severe ophthalmic and neurologic abnormalities are also found. See Also: De Sanctis-Cacchione syndrome. 2. De Sanctis-Cacchione syndrome = Xeroderma pigmentosum with mental deficiency, dwarfism, and gonadal hypoplasia; autosomal recessive inheritance associated with defective DNA repair following damage by ultraviolet

	irradiation. 3. Hereditary Nonpolyposis Colon Cancer = Hereditary Nonpolyposis Colorectal Cancer = HNPCC (= Lynch Syndrome), hMLH (loss of heterogenicity) 2, hMSH2 (microsatellite) (biochem, pg 27) . hMLH and hMSH are a mismatch repair gene associated with Hereditary Nonpolyposis Colorectal Cancer (HNPCC), hereditary endometrial cancer, and microsatellite instability in the tumor cells. Lynch syndrome= Lynch type I, familial colorectal cancer, generally occurring at an early age; Lynch type II, familial colorectal cancer occurring at an early age in conjunction with female genital cancer (= adenocarcinomas of the uterus, ovary, cervic and breast) or cancers at other sites proximal to the bowel. (1st aid surgery, p242). Lynch syndrome II (family cancer syndrome) is associated with colorectal Cancer, endometrial Cancer, Ovarian Cancer, gastric Cancer and other types of cancer. Lynch Syndrome II is associated with extracolonic tumor development. (Surgery BRS, p 322), (IM p 20). Cancer most commonly occurs in the proximal colon in hereditary non-polyposis colorecta caner (HNPCC, Lynch syndrome), which results from mutations in DNA mismatch repair genes inherited in an autosomal dominant manner. Patient who have HNPCC are also predisposed to other forms of caner, such as urinary tract or endometrial malignancies.

Other disease/syndromes/anomalies, which I couldn't find information on the web about their specific gene, that is responsible for it:

1. Absence (petit mal) seizure: being in childhood, subside before adulthood, often **familial**. (1st aid CK, p 228)
2. Acrochordons = Skin Tags = Acrochordons are benign cutaneous polyp (= pedunculated lesion) that do not require treatment unless they are symptomatic . The color is varied from flesh-colored to slightly hyperpigmented. There is a **familial predisposition** and an association with obesity and insulin resistance.
3. Acrodermatitis enteropathica = a progressive hereditary defect of zinc metabolism in young children (onset 3 weeks to 18 months), often manifests first as a blistering, oozing, and crusting eruption on an extremity or around one of the orifices of the body, followed by loss of hair and diarrhea or other gastrointestinal disturbances; relieved by lifelong oral zinc supplementation; **autosomal recessive trait.**
4. Acropachy = Hereditary clubbing = simple hereditary clubbing of the digits without associated pulmonary or other progressive disease, often more severe in males; most common in black patients; **autosomal dominant** inheritance.

5. Acute Recurrent Rhabdomyolysis= Familial Paroxysmal Rhabdomyolysis = repeated paroxysmal attacks of muscle pain and weakness followed by passage of dark red-brown urine, often precipitated by intercurrent illness and diagnosed by demonstration of myoglobin in the urine (myoglobinuria); it is attributed to **abnormal phosphorylase activity** in skeletal muscle, but there may be more than one biologic type; probably **autosomal recessive inheritance**. In some cases, at least, there is **deficiency of carnitine palmitoyl transferase**.
6. Alagille syndrome= an **autosomal dominant** syndrome that becomes apparent in childhood and is associated with jaundice due to a paucity of intrahepatic bile ducts; characteristics include a narrow face and pointed chin, broad forehead, long, straight nose, deep-set eyes, posterior embryotoxon in the eye, cardiovascular abnormalities, vertebral defects, and nephropathy.
7. Alpha 1-proteinase inhibitor Deficiency = Alpha-1 Proteinase Inhibitor are used for tx of Alpha-1 Proteinase Inhibitor Deficiency (genetic disease). (is this disease the same as alpha-1-antitrypsin deficiency??)
8. A.R.M =Advancement of Research for Myopathies, **IBM2, the Autosomal Recessive** form of Hereditary Inclusion Body Myopathies (HIBM). HIBM (Hereditary Inclusion Body Myopathies) are a group of genetic disorders that cause progressive muscle wasting and weakness. The **autosomal recessive form (IBM2 or DMRV)** is very common among people of Middle Eastern & Persian Jewish heritage. Recessively inherited hereditary inclusion body myopathy (HIBM) with quadriceps sparing was initially described only in Jews originating from the region of Persia. The recent identification of the gene responsible for this myopathy and the common **"Persian Jewish mutation" (M712T)** enabled the re-evaluation of atypical phenotypes and the epidemiology of HIBM in various communities in the Middle East. Hereditary Inclusion Body Myopathies (HIBM) are a group of muscle wasting disorders, which are uncommon in the general world population. An autosomal recessive form of HIBM is known as **IBM2**, which is a common genetic disorder amongst people of I**ranian-Jewish descent**. IBM2 has also been identified in other minorities throughout the world. Patients of Asian (Japanese and others), European, and South American origin, as well as Muslim patients in the Middle Eastern, Palestinian, and Iranian origin, have been identified. In Japan and many East Asian countries, this disorder is known as **Distal Myopathy with Rimmed Vacuoles (DMRV)**. Types of hereditary inclusion body myopathy: a). An **autosomal dominant form (IBM1)** where the quadriceps are one of the first muscles to become weak. i). An autosomal recessive form (IBM2), common among people of Middle Eastern and Jewish heritage. This form mainly affects leg muscles, but with an unusual distribution that spares the quadriceps: a so-called **quadriceps-sparing myopathy (QSM)**, the quadriceps are among the last muscles to become weak. b) ii). Nonaka distal myopathy with rimmed vacuoles, essentially a form of IBM2. c). Another type of HIBM (Hereditary Inclusion Body Myopathies), I**nclusion** B**ody** M**yopathy** associated with P**aget disease** of bone and F**rontotemporal** D**ementia** (IBMPFD), is linked to a slightly different gene on **chromosome 9 (located at 9p13-p12)**. d).

Another type of HIBM (Hereditary Inclusion Body Myopathies), inclusion body myopathy-3 (IBM3) is linked to mutations in a gene encoding myosin heavy chain II proteins on **chromosome 17** (located at 17p13.1).

9. Alopecia areata= a common condition of undetermined etiology characterized by circumscribed, nonscarring, usually asymmetrical areas of baldness on the scalp, eyebrows, and bearded portion of the face. Hairy skin anywhere on the body may be affected; occasionally follows autosomal dominant inheritance. Peribulbar lymphocytic infiltration and association with **autoimmune disorders suggest an autoimmune etiology**. **(Dose this have to do with HLA and MHC in chromosome 6??)** .
10. Alopecia congenitalis= absence of all hair at birth. May be associated with psychomotor epilepsy; autosomal dominant or X-linked inheritance. Syn: congenital baldness, hypotrichiasis.
11. Amylopectinosis = Andersen disease = type 4 glycogenosis = type 4 glycogen storage disease = due to **deficiency of glycogen branching enzyme** = familial cirrhosis of the liver with storage of abnormal glycogen; glycogenosis due to deficiency of **1,4-α-glucan branching enzyme**, resulting in accumulation of abnormal glycogen with **long inner and outer chains** in **liver, kidney, muscle**, and other tissues.
12. Aplasia cutis congenita = congenital absence or deficiency of a localized area of skin, with the base of the defect covered by a thin translucent membrane; most often a single area near the vertex of the scalp, but may occur in other areas; underlying structures may also be affected; autosomal inheritance, either dominant or recessive.
13. Arachnodactyly = A condition in which the hands and fingers, and often the feet and toes, are abnormally long and slender; a characteristic of Marfan syndrome, Achard syndrome, the MASS syndrome [= *m*itral valve prolapse, *a*ortic anomalies, skeletal changes, and skin changes.], and kindred hereditary disorders of connective tissue. Syn: spider finger.
14. Arnold-Chiari Malformation = Arnold-Chiari Deformity= Arnold-Chiari syndrome= Cerebellomedullary Malformation Syndrome = malformed **posterior fossa** structures associated with caudad traction and displacement of the rhombencephalon as caused by tethering of the spinal cord; may or may not be accompanied by **spina bifida** and associated anomalies such as **meningomyelocele** (Kaplan peds, p 219); this malformation is usually **multifactorial in inheritance**; very weak evidence of **autosomal recessive inheritance**. 1) In **Arnold-Chiari type 1** malformation consists of downward displacement of the **cerebellar tonsils (= Tonsils of Cerebellum)** through the **foramen magnum**. 2) **Arnold-Chiari type 2 malformation**: the small posterior fossa is a crucial diagnostic feature of Arnold-Chiari type 2. This anatomical defect is responsible for downward displacement of the cerebellar vermis **(= Vermis of Cerebellum)** and medulla through the foramen magnum. This lead to **obstruction** of the CSF flow and **hydrocephalus (= Obstructive Hydrocephalus)**. Important associated abnormalities include **lumbar myelomeningocele** and **syringomyelia**.

15. Athrombia = A hereditary bleeding disorder characterized by prolonged bleeding time, decreased platelet adhesion and aggregation but normal plasma clotting and clot retraction, normal platelet count with platelet factor 3 availability; probably **autosomal recessive** inheritance.
16. Articular chondrocalcinosis= a disease characterized by deposits of calcium pyrophosphate crystals free of urate in synovial fluid (= CPPD = calcium pyrophosphate dihydrate deposition disease), articular cartilage, and adjacent soft tissue; causes various forms of arthritis commonly characterized by goutlike attacks of pain, swelling of joints, and radiologic evidence of calcification in articular cartilage (pseudogout); inherited as an **autosomal dominant trait** in some cases, and associated with certain diseases in others.
17. Attention Deficit Hyperactivity disorder (ADHD) = ADHD has a **strong genetic basis** in the majority of cases, experts believe. It is much more common among people who have a close relative with the disorder. At the moment, researchers are investigating many different genes, particularly ones involved with the brain chemical dopamine. People with ADHD seem to have lower levels of dopamine in the brain. Occur 9:1 male to female ratio. (Kaplan psych, p 13)
18. Bardet-Biedl syndrome= mental retardation, pigmentary retinopathy, polydactyly, **obesity** (Kaplan peds p 32), and hypogenitalism; **autosomal recessive inheritance**. **Due to mutation in multiple genes in multiple chromosomes**. See Also: Laurence-Moon syndrome.
19. Bare Lymphocyte Syndrome = The failure to express class 2 molecules is inherited as an **Autosomal Recessive characteristic**. Affected infants have recurrent infections especially of the GI tract. Patients have a deficiency of Th cells and thus antibodies as well since the development of CD4+ cells depends on positive selection by class 2 molecules in the thymus. Patients **lack expression of MHC class 2 molecules**. The defect is the gene encoding an activator required for transcription of class 2. Circulating T & B cell numbers may be normal, but in the absence of class 2 molecules, foreign antigen cannot be presented. Collaboration does not occur between any of the antigen presenting cells (B cells, Macrophages, Dendritic cells).
20. Benign Familial Hematuria= autosomal dominant due to mutation in type 4 collagen. Diffuse thinning of glomerular **basement membrane (collagen type 4)** seen on biopsy. Tx: reassurance, excellent prognosis.
22. Rolandic Epilepsy = Benign partial epilepsy of childhood = (Centrotemporal epilepsy) with alternative […] = Benign rolandic epilepsy (BRE) = benign rolandic epilepsy of childhood (BREC) = benign epilepsy with centro-temporal spikes (BECTS) = a benign, **autosomal dominant** form of epilepsy occurring in children, characterized clinically by arrest of speech, muscular contractions of the side of the face and arm, and epileptic discharges electroencephalographically. 'Rolandic' means the seizures begin in the part of the brain called the **rolandic area**. The seizures are classified as a **partial seizure** because only this one part of the brain is involved. Benign focal

(rolandic) are focal motor seizures with generalized spread. They being by 5-10 years and disappear by adolescence (peds, p 222).

23. Bernard-Soulier disease = an **autosomal recessive** disorder of absent or decreased platelet membrane glycoproteins Ib (= GP Ib), IX, and V (the receptor for factor VIII R). This deficiency can lead to a failure to bind von Willebrand factor (=vWF), causing moderate bleeding. Get giant/large platelets, thrombocytopenia and bleeding disorder. Platelet from these patients do not aggregate in the presence of normal VWF and **ristocetin** because of the decrease abnormality in GP-IB. (CK p 403).
24. Biotinidase deficiency = a rare, **autosomal recessive** disease causing loss of excessive biotin; clinical manifestations may be absent, but extreme manifestations include seizures, alopecia, dermatitis, hypotonia, optic atrophy, ataxia, developmental delay, hearing deficits, and occasionally immunodeficiency; trait has a prevalence of 1 in 60,000.
25. Bixler type hypertelorism= accompanying features are microtia and clefting of the lip, palate, and nose, mental deficiency, atresia of the auditory canals, ectopic kidneys, and thenar hypoplasia; **autosomal recessive inheritance.**
26. Björnstad syndrome = pili torti associated with sensorineural hearing loss, the severity of distortion and brittleness of the hair correlated with the degree of hearing impairment; **autosomal dominant** inheritance.
27. Camptomelic dwarfism. = Dwarfism with shortening of the lower limbs due to anterior bending of the femur and tibia. camptomelic dwarfism is due to camptomelia of the lower limbs, often accompanied by cleft palate and other abnormalities. We have studied two female newborns with camptomelic dwarfism, XY-gonadal dysgenesis and chromosome anomalies. The preponderance of "females" among the hitherto reported cases of this allegedly **autosomal recessive** form of lethal dwarfism may be due to an increased incidence of an associated XY-gonadal dysgenesis. Camptomelic syndrome = also associated with flat facies, short vertebrae, hypoplastic scapula, and bowed tibia. Syn: osteochondrodysplasia.
28. Carbonic anhydrase II deficiency syndrome = osteopetrosis with renal tubular acidosis = **autosomal recessive**, an inherited deficiency of carbonic anhydrase II that results in osteopetrosis and metabolic acidosis. Get Type 2 (Proximal) Renal Tubular acidosis (RTA) because there is no proximal tubular bicarbonate absorption which leads to **hyperchloremic-Hypokalemic non-anion gap metabolic acidosis** (1st aid CK, p 370), (Kaplan IM, p 253,255).
29. Carney complex = an autosomal dominant condition of Cushing syndrome due to immunoglobulin-mediated ACTH receptor inhibition, cardiac and cutaneous myxomas, lentigines, melanotic schwannomas, and pituitary and testicular tumors.
30. Carnosinemia = An **autosomal recessive** congenital disease, characterized by the presence of excess amounts of carnosine in the blood and urine and caused by a genetic deficiency of the enzyme carnosinase. Clinically characterized by progressive neurologic damage, severe mental retardation, and myoclonic seizures. Origin: [carnosine + G. *haima*, blood + -ia]

31. Centrofacial lentiginosis= uncommon **autosomal dominant** syndrome of small hyperpigmented macules in a horizontal band across the center of the face at one year, increasing in number up to ten years, and associated with skeletal and neural defects.
32. Chondrodysplasia calcificans congenita= **autosomal dominant** inheritance characterized by asymmetric calcifications and dysplastic skeletal changes, less frequent occurrence of congenital cataracts and ichthyosis compared to other forms, and relatively good prognosis. Syn: Conradi disease, Conradi-Hünermann disease.
33. Chondrodystrophy= A disturbance in the development of the cartilage primordia of the long bones, especially the region of the epiphysial plates, resulting in arrested growth of the long bones and dwarfism in which the extremities are abnormally short, but the head and trunk are essentially normal; **autosomal recessive** inheritance. Syn: chondrodysplasia.
34. Clinodactyly = Permanent deflection of one or more fingers. Clinodactyly is a medical term describing a bend or curvature of the fifth fingers (the "little fingers") toward the adjacent fourth fingers. It is a fairly common isolated anomaly, which often goes unnoticed, but also occurs in combination with other abnormalities in many genetic syndromes, such as Russell-Silver syndrome, Feingold Syndrome or Down syndrome. When identified in prenatal ultrasound, it is considered statistically correlated with increased risk of chromosome aberration in the fetus and may be an indication for intrauterine sampling for fetal chromosome analysis.
35. Color blindness = color blindness is usually red-green and **sex-linked recessive** (seen mostly in men) (Kaplan peds p 123) = Color blindness is misleading term for anomalous or deficient color vision; complete color blindness is the absence of one of the primary cone pigments of the retina. Color blindness can be deuteranopia, protanopia, and tritanopia. 1) Protanopia = A form of dichromatism characterized by absence of the red-sensitive pigment in cones, decreased luminosity for long wavelengths of light, and confusion in recognition of red and green. 2) Deuteranopia = A congenital abnormality of the retina in which there are two rather than three retinal cone pigments (dichromatism) and complete insensitivity to middle wavelengths (green). 3) Tritanopia = Deficient color perception in which there is an absence of blue-sensitive pigment in the retinal cones.
36. Conduct Disorder = **Genetic influences** play a role by affecting temperament. Occurs at a 9:1 male to female ratio. a mental disorder of childhood or adolescence characterized by a persistent pattern of violating societal norms and the rights of others; children with the disorder may exhibit physical aggression, bullying, fighting, cruelty to people or animals, and rape, fire-setting, running away and or school truancy, vandalism and robbery, along with truancy, cheating, and lying. (Kaplan psych, p 14).
37. Congenital Hip Dysplasia= developmental hip dysplasia =developmental dysplasia of the hip (DDH) = a developmental abnormality in which a neonate's hips easily become dislocated, children have

uneven gluteal fold; etiology is complex, with mechanical, **familial**, first born babies, Cesarean section babies, hormonal, and birthing presentation all contributing; **female** predominance is 9:1. Treatment is the usage of "Frejka pillow splint". (Kaplan Surgery, p 13)

38. Congenital Hypothyroidism = Macroglossia (large tongue) can be seen with congenital hypothyroidism, which can be **familial** or sporadic (**is this a genetic disease?**).
39. Congenital Methemoglobinemia= **1.** Methemoglobinemia due to formation of any one of a group of abnormal α chain or β chain hemoglobins collectively known as hemoglobin M. Slate-gray cyanosis occurs in early infancy, without pulmonary or cardiac disease, and is resistant to ascorbic acid or methylene blue therapy; **autosomal dominant** inheritance; an autosomal dominant trait that manifests as structural alteration in the hemoglobin making it more susceptible to oxidation. **2.** Methemoglobinemia due to deficiency of cytochrome *b*5 reductase or methemoglobin reductase, the enzyme responsible for reduction of intra-erythrocyte methemoglobin; cyanosis is improved by ascorbic acid or methylene blue; **autosomal recessive** inheritance. An autosomal recessive trait that results in insufficient NADH dependent reductase enzyme production; Syn: hereditary methemoglobinemic cyanosis, hereditary methemoglobinemia, and primary methemoglobinemia.
40. Conradi-Hünermann syndrome= one of the syndromes of chondrodysplasia punctata (q.v.), **autosomal dominant,** with variable skin keratinization disorders and facial, cardiac, optic, and central nervous system abnormalities; epiphyseal stippling is also present.
41. Cori Disease = Type 3 Glycogenosis = debranching deficiency limit dextrinosis = Forbes disease = Type 3 glycogen storage disease = due to **deficiency of glycogen debranching enzyme** = glycogenosis due to **amylo-1, 6-glucosidase deficiency**, resulting in accumulation of abnormal **glycogen with short outer chains** in **liver and muscle**. Hepatic adenoma can be due to type 1 (=Von Gierke Disease) and type 3 glycogen storage disease.
42. Coronary cataract = peripheral cortical developmental cataract occurring just after puberty; transmitted as a **hereditary dominant** characteristic.
43. Costello syndrome (CS) = Costello Syndrome is a genetic disorder , **Autosomal Dominant inheritance**, that affects many parts of the body. This condition is characterized by delayed development and mental retardation, distinctive facial features, loose folds of extra skin (especially on the hands and feet), and unusually flexible joints. Heart abnormalities are common, including a very fast heartbeat (tachycardia), structural heart defects, and overgrowth of the heart muscle (hypertrophic cardiomyopathy). Infants with Costello syndrome may be large at birth, but have difficulty feeding and grow more slowly than other children. Later in life, people with this condition have relatively short stature and many lack growth hormone. Beginning in early childhood, people with Costello syndrome have an increased risk of developing certain cancerous and noncancerous tumors. Small growths called papillomas are the most common noncancerous tumors seen with this condition. They usually develop around the nose and mouth or

near the anus. The most frequent cancerous tumor associated with Costello syndrome is a soft tissue tumor called a rhabdomyosarcoma. Other cancers also have been reported in children and adolescents with this disorder, including a tumor that arises in developing nerve cells (neuroblastoma) and a form of bladder cancer (transitional cell carcinoma). **The Costello syndrome (CS) gene ,the HRAS gene**, along with mutations linked to cardio-facio-cutaneous syndrome (CFC). Mutations in the HRAS gene cause Costello syndrome. The HRAS gene provides instructions for making a protein that helps control cell growth and division. Mutations that cause Costello syndrome lead to the production of an HRAS protein that is permanently active. Instead of triggering cell growth in response to particular signals from outside the cell, the overactive protein directs cells to grow and divide constantly. This unchecked cell division may predispose to the development of benign and malignant tumors. It remains unclear how mutations in the HRAS gene cause the other features of Costello syndrome, but many of the signs and symptoms may result from cell overgrowth and abnormal cell division. Costello syndrome is inherited in an **autosomal dominant** manner, which means one copy of the altered gene is sufficient to cause the disorder.

44. Craniocarpotarsal Dystrophy= a syndrome characterized by specific facial features with sunken eyes, hypertelorism, long philtrum, small nose, and small mouth with pursing of lips as in whistling, and skeletal malformations with ulnar deviation of hands, camptodactyly, talipes equinovarus, and frontal bone defects; autosomal dominant inheritance. Syn: craniocarpotarsal dysplasia, Freeman-Sheldon syndrome, whistling face syndrome.
45. Cronkhite–Canada syndrome (CCS) = Cronkhite–Canada syndrome is a rare syndrome characterized by multiple polyps of the digestive tract. It is sporadic (i.e. it does not seem to be a hereditary disease), and it is currently considered acquired and idiopathic (i.e. cause remains unknown). About two-thirds of patients are of Japanese descent and the male to female ratio is 2:1. Cronkhite–Canada syndrome is association of juvenile type polyp and ectodermal abnormalities like alopecia, hyperpigmentation and nail loss (onycholysis).
46. Dentinogenesis imperfecta = an **autosomal dominant** disorder of the teeth characterized clinically by **translucent gray to yellow-brown teeth** involving both primary and permanent dentition; the **enamel fractures** easily, leaving exposed dentin, which undergoes rapid attrition; radiographically, the pulp chambers and canals appear obliterated and the roots are short and blunted; sometimes occurs in association with **osteogenesis imperfecta**; **autosomal dominant** inheritance. Syn: hereditary opalescent dentin
47. Denys-Drash syndrome = syndrome comprising nephropathy, Wilms tumor, and genital abnormalities. Patient with Denys-Drash syndrome present with pseudohermaphrodism, early onset of renal failure characterized by mesangial sclerosis.
48. Dermatofibrosis Lenticularis Disseminata= Small papules or discs of increased dermal elastic tissue appearing in early life; when osteopoikilosis is also present, the condition is called osteodermatopoikilosis or Buschke-Ollendorf syndrome; autosomal dominant inheritance.

49. DNA repair-deficiency disorder= is a medical condition due to reduced functionality of DNA repair. It is sometimes considered synonymous with the term accelerated aging disease, which is a genetic disorder in which various tissues, organs or systems of the human body age prematurely. Because the accelerated aging diseases display different aspects of aging, but never every aspect, they are often called segmental progerias by biogerontologists. This is in contrast to Progeria (Hutchinson-Gilford Progeria syndrome), which affects a broader spectrum of functions. Some of the examples include: **Bloom syndrome, Cockayne's syndrome, Werner syndrome, Xeroderma pigmentosum, Trichothiodystrophy**
50. Doose syndrome = a rare familial type of primary, generalized myoclonic astatic epilepsy characterized by a 2–3- or 4–6-Hz spike and wave complexes in the EEG; the condition usually responds to medication.
51. Dysfibrinogenemia = An **autosomal dominant** disorder of qualitatively abnormal fibrinogens of various types; each type is named for the city in which the abnormal fibrinogen was discovered. Examples include: 1) Amsterdam, Bethesda II, Cleveland, Los Angeles, Saint Louis, Zurich I and II: major defect, aggregation of fibrin monomers; thrombin time prolonged; inhibitory effect on normal clotting; asymptomatic; 2) Bethesda I and Detroit: major defect, fibrinopeptide release; thrombin time prolonged; inhibitory effect on normal clotting; abnormal bleeding; 3) Baltimore: major defect, fibrinopeptide release; thrombin time prolonged; no inhibitory effect on normal clotting; bleeding and thrombosis; 4) Leuven: major defect, questionable aggregation of fibrin monomers; thrombin time prolonged; slight inhibitory effect on normal clotting; abnormal bleeding; 5) Metz: major defect unreported; thrombin time infinite; effect on normal clotting unreported; abnormal bleeding; 6) Nancy: major defect, aggregation of fibrin monomers; thrombin time prolonged; slight inhibitory effect on normal clotting; asymptomatic; 7) Oklahoma: major defect unreported; thrombin time normal; no effect on normal clotting; abnormal bleeding; 8) Oslo: major defect unreported; thrombin time shortened; effect on normal clotting unreported; abnormal thrombosis; 9) Parma: major defect unreported; thrombin time infinite; no inhibitory effect on normal clotting; abnormal bleeding; 10) Paris I: major defect unreported; thrombin time infinite; inhibitory effect on normal clotting; asymptomatic; 11) Paris II: major defect unreported; thrombin time prolonged; inhibitory effect on normal clotting; asymptomatic; 12) Troyes: major defect unreported; thrombin time prolonged; effect on normal clotting unreported; asymptomatic; 13) Vancouver: major defect unreported; thrombin time prolonged; no effect on normal clotting; abnormal bleeding; 14) Wiesbaden: major defect, aggregation of fibrin monomers; thrombin time prolonged; inhibitory effect on normal clotting; bleeding and thrombosis.
52. Dystonia musculorum deformans = a genetic, environmental, or idiopathic disorder, usually beginning in childhood or adolescence, marked by muscular contractions that distort the spine, limbs, hips, and sometimes the cranial-innervated muscles. The abnormal movements are increased by excitement and, at least initially, abolished by sleep. The musculature is hypertonic when in action, hypotonic when at rest. Hereditary forms usually begin with involuntary posturing of the foot or hand (**autosomal recessive** form) or of the neck or trunk (**autosomal**

dominant form); both forms may progress to produce contortions of the entire body. Syn: torsion disease of childhood, Ziehen-Oppenheim disease, torsion dystonia.

53. Ehlers-Danlos syndrome type 3 = autosomal dominant, unknown defect. Most common type, (pg 56)
54. Ehlers-Danlos syndrome type 4 = autosomal dominant, defect in the type 3 collagen gene (pg 56)
55. Ehlers-Danlos syndrome type 6 = autosomal dominant, defect in lysyl hydroxylase gene (pg 56)
56. Enchondromatosis =A rare disorder characterized by hamartomatous proliferation of cartilage in the metaphyses of several bones, most commonly of the hands and feet, causing distorted growth in length and pathological fractures; chondrosarcoma may develop. When enchondromatosis is associated with hemangiomas in the cutaneous or visceral regions, the condition is called Maffucci syndrome. Most cases are sporadic but a few instances demonstrate autosomal dominant inheritance with reduced penetrance. Syn: asymmetric chondrodystrophy, hereditary deforming chondrodystrophy, Ollier disease, dyschondroplasia
57. Erythema palmare hereditarium = a hereditary condition, which may be precipitated by pregnancy, characterized by asymptomatic symmetrical redness of the palms; autosomal dominant inheritance. Syn: Lane disease.
58. Escobar's syndrome = (Associated persons: Victor Escobar). Description: Escobar's syndrome is A rare disturbance manifested by orthopaedic and cranial anomalies. Characteristic features include short stature, craniofacial anomalies, joint contractures, vertebral fusion anomalies, rocker-bottom feet, and pterygia of the neck, antecubital, digital, popliteal, and intercrural areas. Abnormalities of the head usually consist of epicanthal microcephaly, skin folds, long philtrum, antimongoloid palpebral slant, low-set ears, pointed and receding chin, ptosis, down-turned angles of the mouth, cleft lip and palate, and hemangiomas of the forehead. Associated anomalies may include rib defects, scoliosis or lordosis, vertical talus, cryptorchism, hypoplastic labia majora, and mental retardation. Most cases are transmitted as an **autosomal recessive trait, some as a dominant trait, and a few are sporadic**. First description of disease picture in 1902 originates with J. A. Boussière. A compilation of the symptoms and entity was done in 1978 by **Victor Escobar** and associates.
59. Essential fructosuria = a benign, asymptomatic inborn error of metabolism due to deficiency of fructokinase, the first enzyme in the specific fructose pathway; fructose appears in the blood and urine, but is simply excreted unchanged; autosomal recessive inheritance. A fructokinase deficiency. See Also: hereditary fructose intolerance. Syn: fructokinase deficiency, benign fructosuria
60. Facioscapulohumeral muscular dystrophy= a highly variable hereditary disorder with onset in childhood or adolescence, characterized by weakness and wasting, sometimes asymmetrical, mainly of the muscles of the face, shoulder girdle, arms, and later, pelvic girdle and legs; **autosomal dominant** inheritance. Syn: facioscapulohumeral atrophy, Landouzy-Dejerine dystrophy.

61. Factor V Leiden = Factor V Leiden mutation = Factor 5 Leiden = Factor V Leiden thrombophilia = Factor V Leiden thrombophilia is an inherited disorder of blood clotting. Factor V Leiden is the name of a specific mutation (genetic alteration) that results in thrombophilia, or an increased tendency to form abnormal blood clots in blood vessels. People who have the factor V Leiden mutation are at somewhat higher than average risk for a type of clot that forms in large veins in the legs (deep venous thrombosis, or DVT) or a clot that travels through the bloodstream and lodges in the lungs (pulmonary embolism, or PE). A mutation in the factor V gene (F5) increases the risk of developing factor V Leiden thrombophilia. The protein made by F5 called factor V plays a critical role in the formation of blood clots in response to injury. The Factor V protein is involved in a series of chemical reactions that hold blood clots together. A molecule called activated protein C (APC) prevents blood clots from growing too large by inactivating factor V. In people with the factor V Leiden mutation, APC is unable to inactivate factor V normally. As a result, the clotting process continues longer than usual, increasing the chance of developing abnormal blood clots. **(Note: Factor V Leiden is not the same as factor V deficiency. Factor 5 Leiden causes a hypercoagulable state (=thrombophilia = increase risk of clotting and DVT) whereas factor 5 deficiency causes an increase risk of bleeding).**
62. Familial amyloid neuropathy= a disorder in which various peripheral nerves are infiltrated with amyloid and their functions disturbed, an abnormal prealbumin is also formed and is present in the blood; characteristically, it begins during midlife and is found largely in persons of Portuguese descent; autosomal dominant inheritance. Other rare clinical types occur. Syn: familial amyloidosis, hereditary amyloidosis.
63. Familial Transthyretin Amyloidosis = [Synonym: Familial TTR Amyloidosis. Includes: Familial Amyloid Cardiomyopathy, Familial Amyloid Polyneuropathy Type I (Portuguese-Swedish-Japanese Type), Familial Amyloid Polyneuropathy Type II (Indiana/Swiss or Maryland/German Type), Leptomeningeal Amyloidosis, Familial Oculoleptomeningeal Amyloidosis (FOLMA)] = **Familial amyloidosis, or ATTR**, is a rare form of inherited amyloidosis. The amyloid deposits in familial amyloidosis are composed of the protein **transthyretin, or TTR**, which is made in the liver. Familial amyloidosis is an inherited autosomal dominant in genetics terminology. This means that for the offspring of a person with the condition, there is a 50% chance of inheriting it.= Familial transthyretin (TTR) amyloidosis is characterized by a slowly progressive peripheral sensorimotor neuropathy and autonomic neuropathy as well as non-neuropathic changes of cardiomyopathy, nephropathy, vitreous opacities, and CNS amyloidosis. The disease usually begins in the third to fifth decade in persons from Portugal and Japan, countries with large endemic foci; onset is later in persons from other areas. Typically, sensory neuropathy starts in the lower extremities with paresthesias and hypesthesias of the feet, followed within a few years by motor

neuropathy. In some persons autonomic neuropathy is the first manifestation of the disease; findings can include: orthostatic hypotension, constipation alternating with diarrhea, attacks of nausea and vomiting, delayed gastric emptying, sexual impotence, anhidrosis, and urinary retention or incontinence. Cardiac amyloidosis is mainly characterized by progressive cardiomyopathy. Individuals with leptomeningeal amyloidosis may have the following CNS findings: dementia, psychosis, visual impairment, headache, seizures, motor paresis, ataxia, myelopathy, hydrocephalus, or intracranial hemorrhage. Diagnosis/testing: In addition to clinical symptoms, proven amyloid deposition in biopsy specimens and identification of a disease-causing mutation in TTR are necessary to establish the diagnosis. TTR amyloid deposition in tissue is demonstrated using Congo red staining and, ideally, immunocytochemical study. Although mass spectrometry can demonstrate a mass difference between wild-type and TTR protein variants in serum, it does not specify the site and kind of amino acid substitution in a number of disease-related TTR gene mutations; thus, DNA sequencing is usually required. Sequence analysis of TTR, the only gene known to be associated with TTR amyloidosis, detects more than 99% of disease-causing mutations. Treatment of manifestations: Orthotopic liver transplantation (OTLX) halts the progression of peripheral and/or autonomic neuropathy; OTLX is recommended in individuals younger than age 60 years with: (1) disease duration less than five years, (2) polyneuropathy restricted to the lower extremities or with autonomic neuropathy alone, and (3) no significant cardiac or renal dysfunction. Surgery is indicated for carpal tunnel syndrome and vitrectomy for vitreous involvement. Surveillance: serial nerve conduction studies to monitor polyneuropathy; serial electrocardiogram and echocardiography to monitor cardiomyopathy. Testing of relatives at risk: If the family-specific mutation is known, molecular genetic testing ensures early diagnosis and treatment. If the disease-causing mutation is not known, clinical evaluations ensure early diagnosis and treatment. Familial TTR amyloidosis is inherited in an autosomal dominant manner. Each child of an affected individual (who is heterozygous for one TTR mutation) has a 50% risk of inheriting the TTR mutation. For affected individuals homozygous for TTR mutations, (1) each sib is at a 50% risk of inheriting one TTR mutation and a 25% risk of inheriting two TTR mutations; (2) all offspring will inherit a mutation. Prenatal testing for pregnancies at increased risk is possible if the disease-causing mutation has been identified in the family. Requests for prenatal testing for adult-onset conditions which (like familial TTR amyloidosis) do not affect intellect and have some treatment available are not common. **Hereditary cardiac amyloidosis associated with the transthyretin (TTR) type, with the Ile122 mutation of the TTR gene. Echocardiography was characteristic of cardiac amyloid deposition showing biventricular hypertrophy and a speckled myocardium characteristic of amyloid infiltration. [Speckled-appearing myocardium=cardiac amyloidosis] = The univariate analysis showed that low-voltage and pseudo-infarction patterns on the ECG and increased myocardial thickness and speckled-appearing myocardium on the echocardiogram were associated with biopsy-proven cardiac amyloidosis.**

64. Familial aminoglycoside ototoxicity = inherited susceptibility to sensory hearing loss upon administration of aminoglycoside antibiotics due to a mutation in the mitochondrial genome.
65. Familial aortic ectasia syndrome = the concurrence as an autosomal dominant trait of bicuspid aortic valve often with premature calcification, ectasia, and dissection of the aorta and, rarely, coarctation of the aorta. Superficially resembles the Marfan syndrome. Syn: familial aortic ectasia
66. Familial cancer= cancer aggregating among blood relatives; rarely the mode of inheritance is clearly mendelian, either dominant, as in retinoblastoma, basal cell nevus syndrome, neurofibromatosis, and intestinal polyposis, or recessive, as in xeroderma pigmentosum.
67. Familial chylomicronemia syndrome= an inherited disorder resulting in accumulation of chylomicrons as well as triacylglycerol.
68. Familial Emphysema = emphysema inherited in association with severe α-1 antitrypsin deficiency. It may occur as an isolated feature or with cutis laxa and hemolytic anemia.
69. Familial erythrophagocytic lymphohistiocytosis (FEL) = familial hemophagocytic lymphohistiocytosis (FMLH) = an extremely rare, usually fatal disease of childhood characterized by multiorgan infiltration with activated macrophages and lymphocytes. The disease is often familial and appears to be inherited as an autosomal recessive trait. Syn: familial erythrophagocytic lymphohistiocytosis.
70. Familial hemiplegic migraine (FHM) is an **autosomal dominant** classical migraine subtype that typically includes hemiparesis (weakness of half the body) during the **aura phase. Photophobia, visual aura, scintillating scotomas (bright light or flashing lights) or visual field cuts are some of the symptoms of migraine headache.** (1st aid CK, p 225). It can be accompanied by other symptoms, such as ataxia, coma and epileptic seizures. There is clinical overlap in some FHM patients with episodic ataxia type 2 and spinocerebellar ataxia type 6, benign familial infantile convulsions, and alternating hemiplegia of childhood. There are 3 known loci for FHM. FHM1, which accounts for approximately 50% of FHM patients, is caused by mutations in a gene coding for the P/Q-type calcium channel α subunit, CACNA1A. FHM1 is also associated with cerebellar degeneration. FHM2, which accounts for <25% of FHM cases, is caused by mutations in the Na+/K+-ATPase gene ATP1A2. FHM3 is a rare subtype of FHM and is caused by mutations in a sodium channel α-subunit coding gene, SCNA1. These three subtypes do not account for all cases of FHM, suggesting the existence of at least one other locus (FHM4). Many of the non-familial cases of hemiplegic migraine (sporadic hemiplegic migraine = SHM) are also caused by mutations at these loci. (Kaplan psych, p 92)
71. Familial hyperlipoproteinemia = a group of diseases characterized by changes in concentration of β-lipoproteins and pre-β-lipoproteins and the lipids associated with them. See: type I familial hyperlipoproteinemia, type II familial

hyperlipoproteinemia, type III familial hyperlipoproteinemia, type IV familial hyperlipoproteinemia, type V familial hyperlipoproteinemia.

72. Type IV familial hyperlipoproteinemia= carbohydrate-induced hyperlipemia = familial hyperprebetalipoproteinemia = familial hypertriglyceridemia(2) = plasma levels of VLDL, pre-β-lipoproteins and triglycerides are increased on a normal diet, but β-lipoproteins, cholesterol, and phospholipids are normal; hypertriglyceridemia is induced by a high carbohydrate diet; may be accompanied by abnormal glucose tolerance and susceptibility to ischemic heart disease; probably **autosomal dominant** inheritance but genetic heterogeneity is a possibility.
73. Familial high-density lipoprotein deficiency = Tangier disease = familial HDL deficiency = Analphalipoproteinemia= High-density lipoprotein deficiency= a heritable disorder of lipid metabolism characterized by alpha-lipoprotein deficiency leading to low level of HDL and almost complete absence from plasma of high density lipoproteins (HDL), and by storage of cholesterol esters in foam cells, tonsillar enlargement, **Orange-yellow tonsillar hyperplasia,** an orange or yellow-gray color of the pharyngeal and rectal mucosa, hepatosplenomegaly, lymph node enlargement (Lymphadenopathy), corneal opacity, Polyneuropathy and peripheral neuropathy; **autosomal recessive inheritance**. Syn: familial high-density lipoprotein (=HDL) deficiency.
74. Familial hypertrophic cardiomyopathy = familial occurrence of hypertrophic cardiomyopathy exhibiting an autosomal dominant pattern of inheritance. Familial cardiomyopathy of various kinds occurs with autosomal dominant inheritance. There is also an asymmetrical form affecting the ventricles and the interventricular septum. (**I think this the same as Hypertrophic Obstructive Cardiomyopathy (=HOCM) and due to chromosome 14**).
75. Familial hypobetalipoproteinemia = a disorder similar to abetalipoproteinemia; chylomicron formation still occurs, but LDL levels are typically low.
76. Familial Hypercalciuric Hypocalcemia = Hypercalciuric Hypocalcemia = A familial syndrome of hypocalcemia (= Decrease Calcium in blood) with hypercalciuria due to mutations in the calcium-sensing receptor. A rare familial condition involving low levels of parathyroid hormone, Low blood calcium level, High urine calcium level, High blood phosphate level, Paresthesia around mouth.
77. Familial lipoprotein lipase inhibitor = an inhibitor found in certain individuals that inhibits lipoprotein lipase resulting in accumulation of chylomicrons, VLDL, and triacylglycerol; similar in symptoms to familial lipoprotein lipase deficiency.
78. Familial microcytic anemia = a rare type of autosomal recessive hypochromic microcytic anemia associated with a defect of iron metabolism characterized by high serum iron, hepatic iron deposits, and absence of stainable bone marrow iron stores.

79. Familial Otosclerosis = hereditary **autosomal dominant** disease, hearing loss, Otosclerosis in young patient (20-40 years old) with bilateral progressive conductive hearing loss, symptoms characteristically worsen during pregnancy or with OCP (oral contraceptive pill) use. (Also see otosclerosis).
80. Familial partial lipodystrophy= characterized by symmetric lipoatrophy of the trunk and limbs but the face is spared; with full rounded face, xanthomata, acanthosis nigricans, and insulin-resistant hyperglycemia; there is accumulation of fat around the neck and shoulders and genitalia. Syn: Kobberling-Dunnigan syndrome.
81. Familial periodic paralysis = one of the inherited muscle disorders manifested as recurrent episodes of marked generalized weakness. See: hyperkalemic periodic paralysis, hypokalemic periodic paralysis, normokalemic periodic paralysis .
82. Familial pseudo-inflammatory macular degeneration= macular degeneration that occurs during the fifth decade of life, with sudden development of a central scotoma in one eye followed rapidly by a similar lesion in the opposite eye; autosomal dominant inheritance. Syn: Sorsby macular degeneration.
83. Familial pseudoinflammatory maculopathy = familial macular degeneration resembling inflammatory changes.
84. Familial pyridoxine-responsive anemia= a rare autosomal recessive hereditary hypochromic anemia; responsive to pyridoxine
85. Familial glycinuria = a metabolic disorder believed to be due to defective renal glycine reabsorption; it may or may not be accompanied by oxalate urolithiasis; may be the heterozygous state of iminoglycinuria; autosomal dominant inheritance.
86. Familial long QT syndromes = long QT syndrome (LQTS) =a group of congenital and acquired diseases in which the electrocardiographic QT interval is longer than established measurements for age and sex; the presence of long QT intervals presages arrhythmias and sudden death. (Kaplan IM, p 87). Torsades de pointes is a polymorphic ventricular tachycardia which occurs in the setting of a prolonged QT interval and si seen in patients with familial long QT syndrome (Kaplan IM, p 87).

The two most common types of LQTS are genetic and drug-induced. Genetic LQTS can arise from mutation to one of several genes. These mutations tend to prolong the duration of the ventricular action potential (APD), thus lengthening the QT interval. LQTS can be inherited in an autosomal dominant or an autosomal recessive fashion. The autosomal recessive forms of LQTS tend to have a more severe phenotype, with some variants having associated syndactyly (LQT8) or congenital neural deafness (LQT1). A number of specific genes loci have been identified that are associated with LQTS. Drug induced LQT is usually a result of treatment by anti-arrhythmic drugs such as amiodarone or a number of other drugs that have been reported to cause this problem (e.g. cisapride). Some anti-psychotic drugs, such as Haloperidol and Ziprasidone, have a prolonged QT interval as a rare side effect. Genetic mutations may make one more susceptible to drug induced LQT.

Long QT syndrome 1 = **LQT1** = LQT1 is the most common type of long QT syndrome, making up about 40 to 55 percent of all cases. The LQT1 gene is KCNQ1 which has been isolated to chromosome 11p15.5. KCNQ1 codes for the voltage-gated potassium channel KvLQT1 that is highly expressed in the heart. It is believed that the product of the KCNQ1 gene produces an alpha subunit that interacts with other proteins (particularly the minK beta subunit) to create the IKs ion channel, which is responsible for the delayed potassium rectifier current of the cardiac action potential. Mutations to the KCNQ1 gene can be inherited in an autosomal dominant or an autosomal recessive pattern in the same family. In the autosomal recessive mutation of this gene, homozygous mutations in KVLQT1 leads to severe prolongation of the QT interval (due to near-complete loss of the IKs ion channel), and is associated with increased risk of ventricular arrhythmias and congenital deafness. This variant of LQT1 is known as the Jervell and Lange-Nielsen syndrome. Most individuals with LQT1 show paradoxical prolongation of the QT interval with infusion of epinephrine. This can also unmark latent carriers of the LQT1 gene. Many missense mutations of the LQT1 gene have been identified. These are often associated with a high frequency of syncopes but less sudden death than LQT2. = Jervell and Lange-Nielsen syndrome= Jervell - Lange-Nielsen syndrome =is a form of congenital long QT syndrome = a prolonged Q-T interval recorded in the electrocardiogram of certain congenitally deaf children subject to attacks of unconsciousness resulting from Adams-Stokes seizures and ventricular fibrillation; patient with this syndrome are predisposed to a particular type of ventricular tachycardia called torsades De pointes. Torsades De pointes causes syncopal episodes and sudden death. Jervell and Lange-Nielsen syndrome is **autosomal recessiv**e inheritance, caused by homozygosity for a mutation in the potassium channel gene (KVLQT1) on chromosome 11 or minimal potassium ion channel gene (KCNE1) on 21. Syn: surdocardiac syndrome.

Long QT syndrome 2 =**LQT2** = The LQT2 type is the second most common gene location that is affected in long QT syndrome, making up about 35 to 45 percent of all cases. This form of long QT syndrome most likely involves mutations of the human ether-a-go-go related gene (HERG) on chromosome 7. The HERG gene (also known as KCNH2) is part of the rapid component of the potassium rectifying current (IKr). (The IKr current is mainly responsible for the termination of the cardiac action potential, and therefore the length of the QT interval.) The normally functioning HERG gene allows protection against early after depolarizations (EADs). Most drugs that cause long QT syndrome do so by blocking the IKr current via the HERG gene. These include erythromycin, terfenadine, and ketoconazole. The HERG channel is very sensitive to unintended drug binding due to two aromatic amino acids, the tyrosine at position 652 and the phenylalanine at position 656. These amino acid residues are poised so a drug binding to them will block the channel from conducting current. Other potassium channels do not have these residues in these positions and are therefore not as prone to blockage.

Long QT syndrome 3 = **LQT3** = The LQT3 type of long QT syndrome involves mutation of the gene that encodes the alpha subunit of the Na+ ion channel. This gene is located on chromosome 3p21-24, and is known as SCN5A (also hH1 and NaV1.5). The mutations involved in LQT3 slow the inactivation of the Na+ channel, resulting in

prolongation of the Na+ influx during depolarization. Paradoxically, the mutant sodium channels inactivate more quickly, and may open repetitively during the action potential. A large number of mutations have been characterized as leading to or predisposing LQT3. Calcium has been suggested as a regulator of SCN5A, and the effects of calcium on SCN5A may begin to explain the mechanism by which some these mutations cause LQT3. Furthermore mutations in SCN5A can cause Brugada syndrome, Cardiac Conduction disease and dilated cardiomyopathy. Rarely some affected individuals can have combinations of these diseases.

Long QT syndrome 5 =**LQT5** = is an autosomal dominant relatively uncommon form of LQTS. It involves mutations in the gene KCNE1 which encodes for the potassium channel beta subunit MinK. In its rare homozygous forms it can lead to Jervell and Lange-Nielsen syndrome

Long QT syndrome 6 =**LQT6** = is an autosomal dominant relatively uncommon form of LQTS. It involves mutations in the gene KCNE2 which encodes for the potassium channel beta subunit MiRP1, constituting part of the IKr repolarizing K+ current.

Long QT syndrome 7 =**LQT7** = Andersen-Tawil syndrome is an autosomal dominant form of LQTS associated with skeletal deformities. It involves mutation in the gene KCNJ2 which encodes for the potassium channel protein Kir 2.1. The syndrome is characterized by Long QT syndrome with ventricular arrhythmias, periodic paralysis and skeletal developmental abnormalities as clinodactyly, low-set ears and micrognathia. The manifestations are highly variable.

Long QT syndrome 8 =**LQT8** = Timothy's syndrome is due to mutations in the calcium channel Cav1.2 encoded by the **gene CACNA1c**. Since the Calcium channel Cav1.2 is abundant in many tissues, patients with Timothy's syndrome have many clinical manifestations including congenital heart disease, autism, syndactyly and immune deficiency.

Long QT syndrome 9 =**LQT9** = This newly discovered variant is caused by mutations in the membrane structural protein, caveolin-3. Caveolins form specific membrane domains called caveolae in which among others the NaV1.5 voltage-gated sodium channel sits. Similar to LQT3, these particular mutations increase so-called 'late' sodium current, which impairs cellular repolarization.

Long QT syndrome 10 =**LQT10=** This novel susceptibility gene for LQT is the gene **SCN4B** encoding the protein NaVβ4, an auxiliary subunit to the pore-forming NaV1.5 (gene: **SCN5A**) subunit of the voltage-gated sodium channel of the heart. The mutation leads to a positive shift in inactivation of the sodium current, thus increasing sodium current. Only one mutation in one patient has so far been found.
Associated syndromes with long QT syndrome: A number of syndromes are associated with LQTS.

Jervell and Lange-Nielsen syndrome = The Jervell and Lange-Nielsen syndrome (JLNS) is an **autosomal recessive** form of LQTS with associated congenital deafness. It is caused specifically by mutation of the **KCNE1 and KCNQ1 genes**.
In untreated individuals with JLNS, about 50 percent die by the age of 15 years due to ventricular arrhythmias. Jervell and Lange-Nielsen syndrome= Jervell -

Lange-Nielsen syndrome =is a form of congenital long QT syndrome = a prolonged Q-T interval recorded in the electrocardiogram of certain congenitally deaf children subject to attacks of unconsciousness resulting from Adams-Stokes seizures and ventricular fibrillation; patient with this syndrome are predisposed to a particular type of ventricular tachycardia called torsades De pointes. Torsades De pointes causes syncopal episodes and sudden death. Jervell and Lange-Nielsen syndrome is **autosomal recessiv**e inheritance, caused by homozygosity for a mutation in the potassium channel gene (KVLQT1) on chromosome 11 or minimal potassium ion channel gene (KCNE1) on 21. Syn: surdocardiac syndrome.

Romano-Ward syndrome =Romano-Ward syndrome is an **autosomal dominant** form of LQTS that is not associated with deafness.

87. Familial short stature = Familial (or genetic) short stature: This is a condition in which shorter parents tend to have shorter children. This term applies to short children who don't have any symptoms of diseases that affect their growth. Children with familial short stature still have growth spurts and enter puberty at normal ages, but they usually will only reach a height similar to that of their parents. (Kaplan Peds, p 29)
88. Fanconi Anemia = Constitutional Fanconi Pancystopenia (Kaplan Peds, p 201) =an **autosomal recessive** disorder. Fanconi Anemia is associated with aplastic anemia and congenital musculoskeletal and cutaneous abnormalities(Kaplan Peds, p 201) . Approximately 80% of patients with Fanconi anemia can exhibit a variety of congenital anomalies. The characteristic aplastic anemia is usually not evident before the age of 5 years. Other key features which can help distinguish this disorder are: hyperpigmentation of skin, short stature, upper limb anomalies (which can include absent, hypoplastic, supernumerary or bifid thumbs and aplasia of the first metacarpal or the radius), hypogonadism, Microcephaly. The only potential cure for Fanconi anemia is bone marrow transplant and early diagnosis is a key element in prognosis. Fanconi anemia (FA) is a genetic disease that affects children and adults from all ethnic backgrounds. The disease is named after the Swiss pediatrician who originally described this disorder, Guido Fanconi. **It should not be confused with Fanconi syndrome, a kidney disorder also named after Fanconi.** FA is characterized by short stature, skeletal anomalies, increased incidence of solid tumors and leukemias, bone marrow failure (aplastic anemia), and cellular sensitivity to DNA damaging agents such as mitomycin C. FA is primarily an autosomal recessive genetic disorder. There are at least 13 genes of which **mutations are known to cause Fanconi Anemia (=FA): FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM and FANCN. FANCB is the one exception to FA being autosomal recessive, as this gene is on the X chromosome**. The carrier frequency in the Ashkenazi Jewish population is about 1/90. Bone marrow transplantation is the accepted treatment to repair the hematological problems associated with FA. However, even with a bone marrow transplant, patients face an increased risk of acquiring cancer and other serious health problems throughout their lifetime.
89. Fanconi Syndrome = a group of conditions with characteristic disorders of renal tubular function, which may be classified as: 1) cystinosis, an **autosomal**

recessive disease of early childhood; 2) adult Fanconi syndrome, a rare hereditary form, probably due to a recessive gene different from that found in **cystinosis**, characterized by the tubular malfunction seen in cystinosis and by osteomalacia, but without cystine deposit in tissues; 3) acquired Fanconi syndrome, which may be associated with **multiple myeloma** or may result from chemical poisoning, injury, or persisting damage of proximal tubular epithelium due to various causes, leading to multiple defects of tubular function. (Kaplan peds, p201). **Fanconi syndrome causes type 2 renal tubular acidosis (=RTA type 2 = proximal tubule dysfunction = inability to absorb bicarbonate, also get hypokalemia (IM, p 253). Fanconi syndrome produces a generalized dysfunction of proximal convoluted tubules (PCT) of the kidneys with glucosuria, generalized aminoaciduria and hypophosphatemia (with bony abnormalities) (Q book, p 428). Side effect of tetracyclines includes: Fanconi's syndrome, tooth discoloration, photosensitivity (=fixed drug eruption) (CK, p 465). Fanconi Anemia should not be confused with Fanconi syndrome, a kidney disorder also named after Fanconi.**

90. Farber Disease= Farber syndrome = Disseminated lipogranulomatosis = due to deficiency of lyosomal enzyme ceramidase and therefore accumulation of ceramide in the tissue = a form of mucolipidosis, developing soon after birth because of deficiency of ceramidase; characterized by swollen joints, subcutaneous nodules, lymphadenopathy, and accumulation in lysosomes of affected cells of PAS-positive lipid consisting of ceramide.
91. Favism= An acute condition seen chiefly in Italy, following the ingestion of certain species of beans, e.g., *Vicia faba*, or inhalation of the pollen of its flower; characterized by fever, headache, abdominal pain, severe anemia, prostration, and coma; it occurs in certain individuals with genetic erythrocytic deficiency of glucose 6-phosphate dehydrogenase. Chance exposure to the Vicia faba, by its impact on the phenotype of glucose-6-phosphate dehydrogenase, impinges on the expression or the gene, an example of incomplete penetrance. Syn: fabism.[origin: Ital. *favismo,* from *fava,* bean]
92. Fazio-Londe disease = a progressive bulbar palsy affecting the brainstem; due to motor neuron degeneration; a variant of spinal muscular atrophy (q.v.)
93. Fibrodysplasia Ossificans Progressiva (FOP) is an extremely rare genetic disease that causes muscle to be turned into bone. The condition was first reported in the 17th century by Patin, a French physician, who **described a woman who "turned into wood"**. The wood he described was actually the formation of new bone. FOP is an **autosomal dominant** condition, but most cases are sporadic. FOP patients have a genetic fault, which means that their bodies cannot switch off the mechanism that grows the skeleton in the womb. Any small injury to connective tissue (muscles, ligaments, and tendons) can result in the formation of hard bone around the damaged site. Children are born with a characteristic malformation of the great toes and begin to develop heterotopic (extra) bone formation during early childhood. Eventually, a second skeleton begins to form that severely restricts mobility. FOP affects 1 of 2 million people. Because of the very small numbers of patients, identifying the mutation(s) causing FOP is difficult. There are several

genes that have been implicated in the disease process. For example, when the Noggin gene (NOG) is deleted in mice, the mice are unable to stop the deposition of bone, causing an FOP-like disease. Another gene of interest is the Bone Morphogenic Protein gene (BMP), which Noggin regulates. Proteins encoded by BMP induce bone formation, and one of their roles is to stimulate the formation of the fetal skeleton. In FOP, lymphocytes deliver BMP4 to areas of damaged muscle, and so initiate bone growth rather than aid tissue repair.

94. Flecked retina syndrome= hereditary retinal disorder with abnormal transmission of fluorescence through the retinal pigment epithelium on angiography
95. Generalized Recessive Dystrophic Epidermolysis Bullosa (Eb)= Absence Of Type VII Collagen
96. G syndrome= a syndrome of characteristic facies associated with hypospadias, ventral curvature of the penis, and dysphagia. Apparently the same as the BBB syndrome of Opritz et al. **Autosomal dominant inheritance**. Origin=[first letter of surname of affected person reported]
97. Gilbert Syndrome = familial nonhemolytic jaundice= Gilbert disease= constitutional hepatic dysfunction=benign familial icterus mild jaundice due to increased amounts of **unconjugated bilirubin (=indirect bilirubin, insoluble in water, bound to albumin in blood)** in the plasma without evidence of liver damage, biliary obstruction, or hemolysis; thought to be due to an inborn error of metabolism in which the excretion of bilirubin by the liver is defective, ascribed to decreased conjugation of bilirubin as a glucuronide or impaired uptake of hepatic bilirubin; **autosomal dominant inheritance** (caused by mild **deficiency in glucuronosyltransferase enzyme**) **. Get unconjugated hyperbilirubinemia (= increase indirect bilirubin in blood) with Gilbert Syndrome and with Crigler-Najjar Syndrome.**
98. Glycogenosis= Any of the glycogen deposition diseases characterized by accumulation of glycogen of normal or abnormal chemical structure in tissue; there may be enlargement of the liver, heart, or striated muscle, including the tongue, with progressive muscular weakness. Seven types (Cori classification) are recognized, depending on the enzyme deficiency involved, all of autosomal recessive inheritance, but with a different gene for each enzyme deficiency (type 1 to type 7 glycogenosis). Syn: dextrinosis, glycogen-storage disease.
99. G_{M1} gangliosidosis = Generalized Gangliosidosis = one of the **hereditary** metabolic disorders , three forms exist: infantile (= type1 GM1), generalized (= generalized GM1); juvenile; and adult; gangliosidosis characterized by accumulation of a specific mono-sialo-ganglioside, G_{M1}; due to deficiency of G_{M1}-β-galactosidase.
100. Type 1 GM1 gangliosidosis = infantile generalized GM1 gangliosidosis = familial neurovisceral lipidosis = pseudo-Hurler disease= Type 1 GM1 gangliosidosis= familial neurovisceral lipidosis = infantile, generalized GM1 gangliosidosis,

infantile= One of the **hereditary** metabolic diseases of infancy; resembles Tay-Sachs disease, except other organ systems (bone, liver, kidney) are affected.

101. G_{M2} gangliosidosis = one of the **hereditary** metabolic disorders; several forms exist, including Tay-Sachs disease, Sandhoff disease, AV variant and adult onset; characterized by accumulation of a specific metabolite, G_{M2} ganglioside, due to deficiency of hexosaminidase A or B, or G_{M2} activator factor.

102. Goldenhar syndrome = Oculo-Auriculo-Vertebral/OAV syndrome= is a congenital defect characterized by incomplete development of the ear, nose, soft palate, lip, and mandible. It is associated with anomalous development of the first branchial arch and second branchial arch. The term is sometimes used interchangeably with Hemifacial Microsomia, although this definition is usually reserved for cases without internal organ/verterbrae disruption. Causes of Goldenhar Syndrome are unknown, and is thought in most cases to be multifactorial, **there have been recent accounts of familiar patterns (Is this a Genetic Disease??)**. It has been suggested that there is a brachial arch development issue late in the first trimester, also there is anecdotal evidence linking it to exposure to certain toxins (e.g. dioxin) before or during pregnancy. There is circumstantial evidence suggesting the incidence of GS is higher in children of Gulf War veterans (see Gulf War Syndrome), though the small numbers involved make interpretation of the data difficult. **Goldenhar syndrome = (Malar/Maxillary hypoplasia, Microtia, Hemivertebrae)** (Kaplan Peds, p 72). **Goldenhar syndrome produces an asymmetric face, malformed ears, small eyes, hearing loss, a large mouth, a small mandible and vertebral anomalies** (Q book, p 434).

103. Graves Disease = Genetic analysis has shown that polymorphisms in the cytotoxic T-lymphocyte antigen 4 (CTLA-4) gene are associated with Graves' disease. CTLA-4 is a receptor expressed on activated T cells that inhibits T cell proliferation by binding to the costimulatory B7 molecule and preventing further activation. The polymorphisms linked to Graves' disease may correspond with lessened effectiveness of this inhibitory receptor . CTLA-4 has also been linked to other organ-specific autoimmune diseases, indicating that it may play a general role in autoimmunity. Another gene that have linked to Graves' disease is the vitamin D-binding protein (DBP) gene. Graves' disease patients have much less vitamin D in their bloodstream than healthy individuals. A polymorphism of the DBP gene was associated with susceptibility to Graves' disease but not Hashimoto's thyroiditis, a hypothyroid illness. The mechanism whereby DBP could affect autoimmunity is unknown, but such a relationship indicates that vitamin D regulation might be important in Graves' disease. Graves Disease is associated with HLA-B8, HLA-DR3 (Kaplan Peds, p 195)

104. Hemoglobin F (hereditary persistence of)=a condition due to an allele that depresses synthesis of β and δ chains (as in thalassemia), but this is fully compensated by increased γ chain synthesis and there is no anemia; there are 3 types: 1) African type, no (*= beta) or (, = gamma) chain synthesis by the chromosome with the abnormal gene, heterozygotes have 20–30% Hb F and Hb A_2 slightly decreased, homozygotes form no Hb A or Hb A_2; 2) Greek type, reduced β

and δ chain synthesis, heterozygotes have 10–20% Hb F and normal Hb A_2; 3) Swiss type, heterozygotes have only 1 to 3% Hb F and normal Hb A_2.

105. Hemoglobin H =a homotetramer of Hb (all four polypeptides identical) of molecular formula β_4, found only when α chain synthesis is depressed and not effective in oxygen transport. Hb H disease (α-thalassemia intermedia) is a thalassemia-like syndrome in individuals heterozygous for both severe and mild genes for α-thalassemia; moderate anemia and red cell abnormalities with 25–35% Hb Bart at birth, but with Hb Bart later replaced by Hb H and with Hb A_2 decreased. Hb H shows no cooperativity with O_2 binding and does not exhibit a Bohr effect.

106. Hemoglobin I= an abnormal Hb with a single α chain substitution, molecular formula $\alpha_2{}^{16Lys\rightarrow Glu}\beta_2{}^{A}$; a thalassemia-like syndrome has been found in persons heterozygous for both Hb I and)-thalassemia genes, with formation of about 70% Hb I.

107. Hemoglobin Lepore= a group of abnormal Hb's with normal α chains, but the non-α chains consist of the N-terminal portion of the δ chain joined to the C-terminal portion of the β chain, apparently as the result of nonhomologous pairing and crossing over between the genes for β and δ chains. The major types are Hb $Lepore_{Boston}$ (identical to Hb $Lepore_{Washington}$), Hb $Lepore_{Hollandia}$, and Hb $Lepore_{Baltimore}$, which differ in the region of crossing over (δ87–β116, δ22–β50, and δ50–β86, respectively). Heterozygotes form about 10% Hb Lepore, normal amounts of Hb A_2, and moderately increased amounts of Hb F and usually have mild anemia, microcytosis, and hypochromia; homozygotes form only Hb Lepore and Hb F and have severe anemia. *Cf.* hemoglobin anti-Lepore

108. Hemoglobin M= a group of abnormal Hb's in which a single amino acid substitution favors the formation of methemoglobin in spite of normal quantities of methemoglobin reductase. Strictly speaking, Hb's M are hemoglobins with mutations at the proximal or distal histidyl residues. Other Hb's M tend to favor the Fe(III) state. Heterozygotes have congenital methemoglobinemia; the homozygous state of these genes is unknown and is presumably lethal. Specific types include: Hb M_{Iwate}, $\alpha^{87His\rightarrow Tyr}$ (α chain, position 87, histidine replaced by tyrosine); Hb $M_{Hyde\ Park}$, $\beta^{92His\rightarrow Tyr}$; Hb M_{Boston}, $\alpha^{58His\rightarrow Tyr}$; Hb $M_{Saskatoon}$, $\beta^{63His\rightarrow Tyr}$; Hb $M_{Milwaukee\text{-}1}$, $\beta^{67Val\rightarrow Glu}$.

109. Hemophilia C= hemophilia due to deficiency of factor XI; clinically resembles hemophilia A and B but is transmitted as an **autosomal dominant** inheritance; occurs primarily in persons of Jewish ancestry.

110. HEMPAS = hereditary erythroblastic multinuclearity associated with positive acidified serum. HEMPAS cells = the abnormal erythrocytes of type II congenital dyserythropoietic anemia.

111. Hereditary angioedema = an inherited, autosomal dominant disease characterized by episodic appearance of brawny nonpitting edema, most often affecting the extremities but can involve any part of the body, including mucosal surfaces such as those of the intestine (causing abdominal pain) or respiratory tract

(causing asphyxia, which can require intubation to avoid fatal outcome). Associated with deficiency of inhibitor of first component of complement pathway (C1). Emergency treatment with epinephrine, long-term treatment with a variety of agents is effective.

112. Hereditary benign telangiectasia = an autosomal dominant disorder in which the face, upper trunk, and arms develop telangiectasias.

113. Hereditary cerebellar ataxia = a disease of later childhood and early adult life, marked by ataxic gait, hesitating and explosive speech, nystagmus, and sometimes optic neuritis. It probably comprises several distinct conditions with diverse patterns of inheritance.

114. Hereditary clubbing = acropachy = simple hereditary clubbing of the digits without associated pulmonary or other progressive disease, often more severe in males; most common in black patients; autosomal dominant inheritance. Syn: acropachy

115. Hereditary coproporphyria = an inherited (autosomal dominant) disorder of a deficiency of coproporphyrinogen oxidase, resulting in overproduction of porphyrin precursors leading to neurological disturbances and photosensitivity.

116. Hereditary folate malabsorption = an inherited disorder in which there is defective transport of folates in intestine and choroid plexus, results in megaloblastic anemia and neurologic abnormalities.

117. Hereditary hearing impairment = hearing impairment occurring in syndromic forms (in which there are other anomalies in addition to the hearing impairment) and nonsyndromic forms (in which hearing impairment is the only unusual finding) with autosomal dominant and recessive, X-linked, and mitochondrial modes of transmission; may be congenital, of early onset in childhood, or late onset in mid-life and advanced age.

118. Hereditary hypersegmentation of neutrophils = an autosomal dominant condition characterized by neutrophil hypersegmentation; affected persons are asymptomatic.

119. Hereditary hyperthyroidism = a rare inherited (autosomal dominant) disorder with constitutive stimulation of the thyrocytes

120. Hereditary hypophosphatemic rickets = with hypercalciuria, an inherited disorder in which there is a defect in renal tubular reabsorption.

121. Hereditary myokymia = a syndrome consisting of muscle contractions and night cramps; autosomal dominant inheritance.

122. Hereditary nephritis = familial renal disease occurring in adulthood characterized by proteinuria, hematuria, and hypertension progressing to chronic renal failure. There is no ocular defect or deafness; autosomal dominant inheritance. See Also: Alport syndrome

123. Hereditary nonpolyposis colorectal cancer = HNPCC = an autosomal dominant predisposition to cancer of the colon and rectum.

124. Hereditary photomyoclonus = photomyoclonus associated with diabetes mellitus, deafness, nephropathy, and cerebral dysfunction; autosomal dominant inheritance.
125. Hereditary pyropoikilocytosis = pyropoikilocytosis= A rare **recessive** disorder manifested by severe hemolysis, marked poikilocytosis, and a characteristic sensitivity of the red cells to heat-induced fragmentation in vitro; apparently due to a defect in spectrin self-association.
126. Hereditary renal hypouricuria = an autosomal recessive disorder caused by defective reabsorption of urate in the renal proximal tubule.
127. Hereditary sensory radicular neuropathy = polyneuropathy characterized by the occurrence of severe, relapsing foot ulcerations of neuropathic origin, destruction of terminal digits of feet and hands, and a loss of sensation; autosomal dominant inheritance is associated with onset in the second decade or later.
128. Hereditary spherocytosis= spherocytic anemia= chronic familial icterus= congenital hemolytic icterus= chronic acholuric jaundice= chronic familial jaundice=congenital hemolytic jaundice = a congenital defect of spectrin, the main component of the erythrocyte cell membrane, which becomes abnormally permeable to sodium, resulting in thickened and almost spherical erythrocytes that are fragile and susceptible to spontaneous hemolysis, with decreased survival in the circulation; results in chronic anemia with reticulocytosis, episodes of mild jaundice due to hemolysis, and acute crises with gallstones, fever, and abdominal pain; symptomatology is highly variable; autosomal dominant inheritance, caused by mutation in the ankyrin gene (ANK1) on 8p. However, as with elliptocytosis, there is an autosomal recessive form, caused by mutation in the alpha-spectrin 1 gene (SPTA1) on chromosome 1q.
129. Heredofamilial tremor = Benign Essential Tremor= familial tremor = a benign tremor inherited as a **dominant** character; it may be a rapid oscillation resembling that seen in thyrotoxicosis, a coarse tremor during rest and inhibited by a voluntary effort, or one which appears only upon movement; of **autosomal dominant inheritance**. Benign Essential tremor is autosomal dominant, get tremor when try to reach an object. Tx: propranolol.
130. Harlequin Ichthyosis= a fetal form of ichthyosis thought to be distinct from lamellar ichthyosis, with plaques having a diamondlike shape resembling the suit of a harlequin clown; the keratinocytes contain increased amounts of tonofibrils, which are fibrillar structural proteins; autosomal **recessive inheritance**.
131. Hers disease = type 6 glycogenosis = Type 6 glycogen storage disease = glycogenosis due to **hepatic glycogen phosphorylase deficiency**, resulting in accumulation of **glycogen of normal chemical structure** in **liver and leukocytes**. Syn: hepatophosphorylase deficiency glycogenosis.
132. Hirata's disease = is an autoimmune disease. Hirata's disease (HLA-DRB1*0406+ drug induction) = Insulin autoantibodies, hypoglycemia. For example, administration of a sulfhydryl-containing drug such as methimazole may

be stopped when it is the cause of Hirata's disease (insulin-autoimmune syndrome with insulin autoantibody– induced hypoglycemia).

133. Homosexuality = Freud believe it was an arrest of psychosexual development. Recent studies indicate it may be due to **genetic** and biologic causes (Kaplan psych, p 83)

134. Hurler-Scheie syndrome= type I H/S mucopolysaccharidosis = a phenotypic intermediate between Hurler syndrome and Scheie syndrome; a deficiency of α-L-iduronidase.

135. Hypergonadotropic hypogonadism = Hypergonadotropic hypogonadism= 1) hypergonadotropic = get high level of gonadotropins (= get increase in LH and increase FSH), 2) hypogonadism= lack of development of secondary sexual characteristics such as amenorrhea. In Hypergonadotropic hypogonadism pt gets primary amenorrhea with absent secondary sexual characteristic and increase FSH level. A differential diagnosis for hypergonadotropic hypogonadism include: turner syndrome (45, XO), savage syndrome, ovarian resistance syndrome (46,XX) , male gonadal agenesis (46, XY) and defect in testosterone production such as deficiency of 17-alpha –hydroxylase and 17,20 desmolase (46, XY) → do karyotyping first to identify the cause of Hypergonadotropic hypogonadism (Kaplan OB, p 154). Males with congenital adrenal hyperplasia (17 hydroxylase deficiency and 17 and 20 desmolase deficiencies) have testes but lack the enzyme to synthesize sex steroids and may appear to be phenotypic females.

136. Hyperimmunoglobulin E syndrome= Job syndrome = (decrease activation of macrophages) (1st aid p190) = an immunodeficiency disorder characterized by high levels of plasma IgE concentrations, a leukocyte chemotactic defect, and recurrent staphylococcal infections of the skin, upper respiratory tract, and other sites.

137. Hyperostosis corticalis deformans = marked irregular thickening of the skull and bone cortex, with thickening and widening of the shafts of long bones and high serum alkaline phosphatase; **autosomal recessive** inheritance.

138. Hyperostosis frontalis interna = abnormal deposition of bone on the inner aspect of the os frontale, visible by x-ray; may be a part of Morgagni syndrome (is sometimes familial). **See Morgagni Syndrome**.

139. Ichthyosis Vulgaris = Autosomal dominant defect in profilaggrin. Most common form of inherited ichthyosis, characterized by generalized fine white scale on the **extensor surface of the extremities, spring the flexures**.

140. Infantile Hypertrophic Pyloric Stenosis (IHPS) = Congenital Pyloric Stenosis = muscular hypertrophy of the pyloric sphincter, associated with projectile vomiting appearing in the first few weeks of life, more commonly seen in males. Pyloric stenosis is **multifactorial inherence or polygenic in origin**. Pyloric stenosis is more common in male. (Kaplan OB, p 7 and 8). Pyloric Stenosis causes **projectile vomiting** and excessive "**vomiting"** causes **"Hypochloremic Hypokalemic Metabolic Alkalosis"** . (Kaplan IM, p 254), (Kaplan Surgery, p 45).

141. Intelligence quotient (IQ) is genetic. But IQ is genetically linked to what chromosome???
142. Intermittent Explosive Disorder = Affects men more than women, especially men in prisons and women in psychiatric facilities. **May have genetic linkage** because it is seen frequently among first-degree relatives (Kaplan Psych, p 63).
143. Jansen disease = Jansen's Metaphyseal Chondrodysplasia =JMC= Jansen disease is another **inherited disorder** of hypercalcemia. It is due to excessive activity of the PTH receptor in target tissue. Serum PTH levels will be very low. Patients typically have extensive bone disorders such as short-limbed dwarfism and cystic bone disease. A disease that results from ligand-independent activation of the type 1 of the parathyroid hormone receptor (PTHR1), due to one of three reported mutations (activating mutation). JMC is extremely rare and as of 2007 there are less than 20 reported cases worldwide. Jansen disease is a skeletal abnormality in which the epiphyses are normal, but the metaphyseal tissues are replaced by masses of cartilage, producing interference with endochondral bone formation, expansion and thinning of the metaphyseal cortices. It is also known as Jansen metaphyseal dysostosis. Murk Jansen Type Metaphyseal chondrodysplasia, JMC
144. Johanson-Blizzard syndrome = a clinical syndrome manifested by pancreatic insufficiency, scalp defects, aplasia of the alae nasi, deafness, low birthweight, microcephaly, psychomotor delay, hypothyroidism, dwarfism, and missing permanent teeth. (Is this due to a genetic mutation?)
145. Kasabach-Merritt syndrome= in which platelets become trapped; associated with thrombocytopenic purpura.(Kaplan peds, p 202), (is this a genetic disorder? Or acquired?)
146. Kenny-Caffey syndrome= a disorder characterized by intermittent hypocalcemia (associated with abnormalities in parathyroid hormone secretion) and bone and eye abnormalities; autosomal dominant and autosomal recessive forms exist.
147. Klippel-Trenaunay-Weber syndrome = an anomaly of the extremity in which there is a combination of angiomatosis (cutaneous capillary hemangioma) and anomalous development of the underlying bone and muscle (bone and soft tissue hypertrophy), venosus varicosities, sometimes associated with localized gigantism; if a leg is extensively involved, it may longer than the other leg; probably **autosomal dominant inheritance**, with most cases sporadic. Syn: congenital dysplastic angiectasia, hemangiectatic hypertrophy, angioosteohypertrophy syndrome= CVLM= **C**ongenital (slow flow) **V**ascular **L**ymphatic **M**alformation= Klippel-Trenaunay-Weber syndrome is a sporadic genetic syndrome characterized by localized hemangiomas, venous varicosities, and asymmetric osseous hypertrophy of the ipsilateral extremities. Most commonly seen in association with hemangiomas, **Kasabach-Merritt syndrome** is defined by the presence of thrombocytopenia and a consumptive coagulopathy.

148. Laurence-Moon syndrome= disorder characterized by mental retardation, pigmentary retinopathy, hypogenitalism, and spastic paraplegia; **autosomal recessive inheritance**. This syndrome is to be distinguished from Bardet-Biedl: in the past, the two syndromes have been lumped together under the designation of **Laurence-Moon-Bardet-Biedl syndrome.**

149. Learning Disability = a disorder in one or more of the basic cognitive and psychological processes involved in understanding or using written or spoken language; may be manifested in age-related impairment in the ability to read, write, spell, speak, or perform mathematical calculations. Learning disabilities occurs ore frequently in males and in those of low socioeconomic status (SES) often has a **familial pattern**. (1st aid CK, p 334)

150. Leukocyte Adhesion Deficiency (LAD)= an inherited disorder (autosomal recessive) in which there is a defective CD18 adherence complex that disturbs chemotaxis (= phagocytic immunodeficiency disease) . It is characterized by recurrent bacterial pyogenic infections and impaired wound healing. To test, do chemotactic assay (peds p 118).

151. Left-handedness and inheritance =Dr. Sue Forrest at Murdoch Institute in Victoria, Australia has been involved in a full genome search for left-handedness. **About 10% of the population prefers to use the left hand** for the majority of tasks, the number being slightly more common in males. **The majority of University Professors, in one survey in the 1970's were shown to be left-handed**. This is supported by evidence to show that **most "Gifted and Talented students" are left-handed**. Bach, Beethoven and Paul McCartney are well known left-handers. For some reason, left -handers are more proficient at Gregg's shorthand rather than Pittman's.

152. Limb-girdle muscular dystrophy= a group of muscular dystrophies, probably heterogeneous in nature. Onset usually in childhood or early adulthood and both sexes affected. Characterized by weakness and wasting, usually symmetrical, of the pelvic girdle muscles, the shoulder girdle muscles, or both, but not the facial muscles. Muscle pseudohypertrophy, heart involvement, and mental retardation are absent. Autosomal dominant and recessive inheritance have been described. Syn: Leyden-Möbius muscular dystrophy, pelvofemoral muscular dystrophy, scapulohumeral muscular dystrophy.

153. Malignant hyperthermia = fulminant hyperpyrexia = is a rare complication associated with succinylcholine administration. Malignant hyperthermia is an **autosomal dominant hypermetabolic disorder of skeletal muscle**. (BRS surgery, p 10). There is **family history** may exists with malignant hyperthermia (Kaplan Surgery, p22). Malignant hyperthermia is a mutation of the ryanodine receptor in skeletal muscle resulting in increase calcium efflux from the sarcoplasmic reticulum and increase intracellular calcium. This results in tetany, increased skeletal muscle metabolism and hyperthermia. Tx is with dantrolene with blocks calcium efflux from endoplasmic reticulum → dantrolene is a muscle relaxant. = malignant hyperthermia = rapid onset of extremely high fever with muscle rigidity, precipitated by exogenous agents in genetically susceptible persons, especially by halothane or succinylcholine. *Cf.* futile cycle.

154. Marinesco-Sjögren Syndrome = Marinesco-Garland Syndrome= Marinesco Sjögren syndrome is a rare neurologic disorder characterized by cerebellar ataxia, congenital cataracts, and growth and mental retardation; **autosomal recessive** inheritance. Syn: cataract-oligophrenia syndrome, Torsten Sjögren syndrome.

155. McArdle disease = type 5 glycogenosis = type 5 glycogen storage disease = glycogenosis due to **muscle glycogen phosphorylase deficiency**, resulting in **accumulation of glycogen of normal chemical** structure in **muscle**. Syn: McArdle-Schmid-Pearson disease, myophosphorylase deficiency glycogenosis, McArdle syndrome.

156. Medullary cystic kidney disease = Medullary cystic disease = autosomal dominant.

157. Meesman dystrophy = epithelial dystrophy characterized by progressive cysts and opacities of the corneal epithelium, with onset in infancy; autosomal dominant inheritance with incomplete penetrance. Syn: hereditary epithelial dystrophy.

158. Monilethrix = beaded hair = moniliform hair = An **autosomal dominant** trichodystrophy in which brittle hairs show a series of constrictions, usually without a medulla. Origin [L. *monile,* necklace, + G. *thrix,* hair]

159. Morgagni syndrome= hyperostosis frontalis interna in elderly women, with obesity and neuropsychiatric disorders of uncertain cause; at least sometimes familial. Syn: metabolic craniopathy, Stewart-Morel syndrome.

160. Mucolipidosis II = I-cell disease= Inclusion-cell disease = Inclusion cell disease = a metabolic disorder with onset in early childhood characterized by clinical and radiographic findings similar to those in Hurler syndrome including gum hypertrophy, gingival hyperplasia, thoracic dysplasia, **congenital hip dislocation**, growth retardation, coarse facial features, macroglossia, big tongue, craniofacial abnormalities, joint immobility, club foot, claw hand, scoliosis, presence of lyosomal enzyme in blood. (Biochem, p59) and mental retardation; vacuolated lymphocytes and unusual inclusion bodies in cultured fibroblasts (I-cells) are found; lysosomal enzymes are increased in serum, spinal fluid, and urine; urinary mucopolysaccharides are normal; associated with a deficiency of N-acetylglucosaminyl-1-phosphotransferase; **autosomal recessive** inheritance.

161. Multifactorial inheritance = polygenic in origin = characteristic mendelian patterns are not found , but there is an increase frequency of the disorder or phenotype in families. The overall recurrence rate is 2-3%. Example of multifactorial inheritacne includes **neural tube defects (NTDs), Congenital heart disease (CHD), cleft lip (=harelip) and cleft palate (=palatoschisis=palatum fissum), and pyloric stenosis**. (Kaplan OB, p 7 and 8)

162. Multiple lentigines syndrome = LEOPARD syndrome = syndrome consisting of *l*entigines (multiple, Lentigines are benign, dark brown macules, which can be mistaken for nevi), *e*lectrocardiographic abnormalities (such as prolonged P-R interval, abnormal QRS, abnormal P wave), *o*cular hypertelorism,

*p*ulmonary stenosis, *a*bnormalities of genitalia, *r*etardation of growth, and *d*eafness (sensorineural). An **autosomal Dominant** hereditary disorder. (Kaplan peds, p 251)

163. MULTIPLE PTERYGIUM SYNDROME, ESCOBAR VARIANT = Multiple pterygium syndromes comprise a group of multiple congenital anomaly disorders characterized by webbing (pterygia) of the neck, elbows, and/or knees and joint contractures (arthrogryposis). The multiple pterygium syndromes are phenotypically and genetically heterogeneous but are traditionally divided into prenatally lethal and nonlethal (Escobar) types. **MOLECULAR GENETICS** = Hoffmann et al. (2006) and Morgan et al. (2006) demonstrated that both the lethal and the nonlethal (Escobar) variants of multiple pterygium syndrome can be caused by mutations in the gamma, or fetal, subunit of the nicotinergic acetylcholine receptor (CHRNG; 100730). Hoffmann et al. (2006) found 8 mutations in 7 families with Escobar syndrome. Morgan et al. (2006) found 6 homozygous mutations in 6 families with lethal or Escobar variants. In 1 family both variants were present. Hoffmann et al. (2006) noted that the congenital contractures characteristic of Escobar syndrome may be caused by reduced fetal movements at sensitive times of development. Possible causes of decreased fetal mobility include space constraints such as oligohydramnios, drugs, metabolic conditions, or neuromuscular disorders including myasthenia gravis. Myasthenia is characterized by intermittent muscle weakness, most commonly caused by autoantibodies binding to nicotinergic acetylcholine receptor (AChR). During pregnancy, autoantibodies may cross the placenta and cause transient muscle weakness or, more seriously, an arthrogryposis-like syndrome. Mutations causing congenital myasthenic syndrome (e.g., 608931) have been identified in subunits of the AChR (e.g., CHRNA1, 100690). The CHRNG gene encodes the gamma subunit of the AChR and is expressed before the 33rd week of gestation in humans but is replaced by the epsilon subunit (100725) in the late fetal and perinatal period, thereby forming the adult AChR. The demonstration that Escobar syndrome and the lethal form of multiple pterygium syndrome can be caused by mutations in CHRNG by Hoffmann et al. (2006) and Morgan et al. (2006) showed that these are examples of dysmorphology caused by the transient inactivation of the neuromuscular end plate. Because CHRNG gene expression is restricted to early development, patients have no myasthenic symptoms later in life. This is the major difference from mutations in the other AChR subunits and the striking parallel to the symptoms found in neonates with arthrogryposis when maternal AChR autoantibodies cross the placenta and cause the transient inactivation of the AChR pathway.

164. Myasthenia Gravis = a disorder of neuromuscular transmission marked by fluctuating weakness and fatigue of certain voluntary muscles, including those innervated by brainstem motor nuclei; caused by a marked reduction in the number of acetylcholine receptors in the **postsynaptic** membrane of the neuromuscular junction (NMJ) resulting from an **autoimmune** mechanism → get antibodies to Ach receptors. Syn: Goldflam disease. If give Acetylcholinesterase inhibitors such as Tensilon for TX of myasthenia gravis, the resulting increasing acetylcholine should result in an increase in muscle strengths (usually measure as grip strength) in cases of true myasthenia. The "**Congenital Myasthenia Gravis**" might have a **genetic** etiology (Kaplan Peds, p 229).

165. Naegeli syndrome= Franceschetti-Jadassohn syndrome = reticular skin pigmentation, diminished sweating, hypodontia, hyperkeratosis of the palms and soles, and blistering; may be confused with incontinentia pigmenti but is as common in males as in females; **autosomal dominant inheritance**.

166. Nephronophthisis= juvenile form, **autosomal recessive**. Nephronophthisis is a genetic disorder of the kidneys, which affects children. It is classified as a medullary cystic kidney disease. The disorder is inherited in an autosomal recessive fashion and, although rare, is the most common genetic cause of childhood kidney failure. 8 different genes in which mutations can cause the disease. These genes are called NPHP1, NPHP2, NPHP3, NPHP4, NPHP5, NPHP6, NPHP7, and NPHP8, and the proteins for which they encode are known as the nephrocystins.

167. Netherton syndrome is a severe, autosomal recessive form of ichthyosis associated with SPINK5.It is named for E.W. Netherton. Netherton syndrome is a severe, autosomal recessive form of ichthyosis associated with SPINK5. **SPINK5 gene = Serine protease inhibitor Kazal-type 5** is an enzyme that in humans is encoded by the SPINK5 gene. This gene encodes a multidomain serine protease inhibitor that contains 15 potential inhibitory domains. The inhibitor may play a role in skin and hair morphogenesis and anti-inflammatory and/or antimicrobial protection of mucous epithelia. Mutations may result in **Netherton syndrome**, a disorder characterized by ichthyosis, defective cornification, and atopy. SPINK5 is a serine protease inhibitor of Kazal type responsible for the genetic defect that results in Netherton syndrome, a rare **autosomal recessive** genodermatosis of cause **characterized by erythroderma, trichorrhexis invaginata (bamboo hair), ichthyosis linearis circumflexa, ichthyosiform dermatitis, atopic diathesis, and failure to thrive**.

168. Type II diabetes Mellitus = non-insulin-dependent diabetes mellitus (NIDDM) = there is a suggestion that is transmitted as an **autosomal dominant** trait. (Kaplan IM, p 46).

169. Nezelof syndrome = Cellular immunodeficiency with abnormal immunoglobulin synthesis = an ill-defined group of sporadic disorders of unknown cause, occurring in both males and females and associated with recurrent bacterial, fungal, protozoal, and viral infections; there is **thymic hypoplasia** with depressed cellular (T-lymphocyte) immunity (= **cellular immunodeficiency**) combined with defective humoral (B-lymphocyte) (= **humoral immunodeficiency**) immunity, although **immunoglobulin levels may be normal**. (Compare with ataxia telangiectasia).

170. Nezelof syndrome ?? = Immune Defect due to absence of Thymus = T-Lymphocyte Deficiency = Thymic Aplasia = Nezelof syndrome (a form of thymic dysplasia) is an **autosomal recessive congenital immunodeficiency** condition due to underdevelopment of the thymus. It considered a form of combined immunodeficiency in ICD-10 but a deficiency of cell-mediated immunity in ICD-9. It causes severe infections and malignancies. Treatment includes antimicrobial therapy, IV immunoglobulin, bone marrow transplantation,

thymus transplantation and thymus factors. Nezelof Syndrome is characterized by elevated immunoglobulin that function poorly.

171. Nezelof type of thymic alymphoplasia = cellular immunodeficiency with failure of development of T cells and T-cell function.

172. Ocular albinism 2= type of ocular albinism characterized by hypoplasia of the fovea, marked impairment of vision, nystagmus, myopia, astigmatism, and protanomalous color blindness, in addition to albinism of the fundus. Syn: **Aland Island albinism, Forsius-Eriksson albinism.**

173. Ocular hypertelorism = increased width between the eyes due to an arrest in development of the greater wings of the sphenoid, thus fixing the orbits in the widely separated fetal position; **autosomal dominant inheritance**. Ocular hypertelorism is a feature of many syndromes. A distinct form shows other congenital defects such as hypospadias and esophageal anomalies. See Also: faciodigitogenital dysplasia. Syn: Greig syndrome, Opitz BBB syndrome, Opitz G syndrome. Please note: [**telecanthus= canthal hypertelorism=** Increased distance between the medial canthi of the eyelids.]

174. Oculoauriculovertebral dysplasia = OAV dysplasia = a syndrome characterized by epibulbar dermoids, preauricular appendages, micrognathia, and vertebral and other anomalies (scoliosis) (peds p 72). Syn: Goldenhar syndrome, OAV syndrome.

175. Olivopontocerebellar atrophy= a group of genetically distinct, mostly autosomal dominant progressive neurologic diseases characterized by loss of neurons in the cerebellar cortex, basis pontis, and inferior olivary nuclei; results in ataxia, tremor, involuntary movement, and dysarthria; five clinical types (four with dominant, one with recessive inheritance) have been described, each type characterized by additional findings, such as sensory loss, retinal degeneration, ophthalmoplegia, and extrapyramidal signs. Several loci are involved, autosomal dominant and recessive. See Also: spinocerebellar ataxia. Syn: olivopontocerebellar degeneration.

176. Ortner's Syndrome = Ortner's syndrome is a rare cardiovocal syndrome and refers to recurrent laryngeal nerve palsy from cardiovascular disease. It was first described by N. Ortner, an Austrian physician, in 1897. The most common historical cause is a dilated left atrium due to mitral stenosis, but other causes, including pulmonary hypertension, thoracic aortic aneurysms and aberrant subclavian artery syndrome have been reported. Dysphagia caused by a similar mechanism is referred to as dysphagia aortica, or, in the case of subclavian artery aberrancy, as dysphagia lusoria. A second Ortner's syndrome, Ortner's syndrome II, refers to abdominal angina. **(Is this a genetic disease????)**

177. Osteopetrosis = Excessive formation of dense trabecular bone and calcified cartilage, especially in long bones, leading to obliteration of marrow spaces and to anemia with myeloid metaplasia and hepatosplenomegaly beginning in infancy, to bone fragility, and to progressive deafness and blindness; autosomal dominant inheritance. There are also autosomal recessive forms, which may be mild, severe, or lethal, and sometimes involve a renal tubular defect. A milder, autosomal

dominant form has onset in childhood and no neurologic sequelae. Syn: marble bones, Albers-Schönberg disease, marble bone disease.

178. Osteopoikilosis = Mottled or spotted bones caused by widespread small foci of compact bone in the substantia spongiosa; autosomal dominant inheritance, Syn: osteopathia condensans.

179. Otitis media = inflammation of the middle ear, or tympanum. There is significant evidence from epidemiologic, anatomic, physiologic, and immunologic studies that susceptibility to recurrent episodes of acute otitis media (OM) and persistent OM with effusion is largely genetically determined. The genetics of OM are most likely complex, i.e., many genes are probably contributing to the overall phenotype. The knowledge of a hereditary component has important implications because closer surveillance of children at risk for OM could result in earlier detection and treatment. Further, once OM susceptibility genes have been identified it may be possible to develop molecular diagnostic assays that could enable the clinician to identify the child at high risk for OM and to develop more focused treatments in the future.

180. Otosclerosis = **autosomal dominant inheritance** (positive family history) with variable penetrance, otosclerosis is one of the cause of conductive hearing loss, normally pt present in their mid thirties. A disease of the otic capsule (bony labyrinth) characterized by formation of soft, vascular bone and resulting in progressive conductive hearing loss because of fixation of the stapes and sensory hearing loss because of involvement of the cochlear duct. (Also see familial otosclerosis).

181. Pachydermoperiostosis = A syndrome of clubbing of the digits, periosteal new bone formation, especially over the distal ends of the long bones (idiopathic hypertrophic osteoarthropathy), and coarsening of the facial features with thickening, furrowing, and oiliness of the skin of the face and forehead (cutis verticis gyrata); there is seborrheic hyperplasia with open sebaceous pores filled with plugs of sebum; often of **autosomal dominant** inheritance, usually more severe in males. Syn: acropachyderma

182. Pernicious Anemia = At least two **autosomal recessive** forms are known. In one there is a defect of intrinsic factor and in the other a defective absorption of vitamin B12 from the intestine. **Syn: Biermer anemia, addisonian anemia, macrocytic achylic anemia, Biermer disease, malignant anemia, Addison anemia, Addison-Biermer disease**. Pernicious anemia a chronic progressive anemia of older adults (occurring more frequently during the fifth and later decades, rarely prior to 30 years of age), due to failure of absorption of vitamin B_{12}, usually resulting from a defect of the stomach accompanied by mucosal atrophy and associated with lack of secretion of "**intrinsic" factor**; characterized by numbness and tingling, weakness, and a sore smooth tongue, as well as dyspnea after slight exertion, faintness, pallor of the skin and mucous membranes, anorexia, diarrhea, loss of weight, and fever; laboratory studies usually reveal greatly decreased red blood cell counts, low levels of hemoglobin, numerous characteristically oval shaped macrocytic erythrocytes (color index greater than normal, but not truly

hyperchromic), and hypo- or achlorhydria, in association with a predominant number of megaloblasts and relatively few normoblasts in the bone marrow; the leukocyte count in peripheral blood may be less than normal, with relative lymphocytosis and hypersegmented neutrophils; a low level of vitamin B_{12} is found in peripheral red blood cells; administration of vitamin B_{12} results in a characteristic reticulocyte response, relief from symptoms, and an increase in erythrocytes, provided that pernicious anemia is not complicated by another disease; the condition is not actually "pernicious," as it was prior to the availability of therapy with vitamin B_{12}. in pernicious anemia get **antibody to parietal cell (Anti-parietal antibody and Anti- Intrinsic factor Antibody) and Schilling test** can be performed to diagnose the disease. Pernicious Anemia may be associated with other autoimmune endocrinopathies, including Hashimoto's thyroiditis, Type 1 Diabetes Mellitus, Addison's Disease (= primary adrenal insufficiency), gonadal failure, primary hypoparathyroidism, Grave's disease, Vitiligo, Myasthenia Gravis and Eaton-Lambert Syndrome (Lambert-Eaton syndrome (LES) a generalized disorder of neuromuscular transmission caused by a defect in the release of acetylcholine quanta from the **presynaptic** nerve terminals = Lambert-Eaton syndrome results for autoimmune attack against voltage gated calcium channels on the presynaptic motor nerve).

183. Pierre Robin Sequence = Robin syndrome = micrognathia and U-shaped cleft palate (remember would get T-shape uterus with diethylstilbestrol ,DES use during pregnancy), glossoptosis (= protruding tongue), often associated with upper airway obstruction and feeding difficulties; weak evidence of **autosomal recessive inheritance** (peds p 249).

184. PHACE Syndrome = Children with this syndrome also get Dandy-Walker malformation syndrome= (P =Posterior Fossa brain malformations/ Cerebral cortico-vascular dysplasia. This can cause problems with coordination and/or balance, H= Hemangioma. The hemangioma grows for approximately six months ex: **facial hemangioma associated with CNS defects**, A = Arterial anomalies/defect, **coarctation of the aorta**, C = Cardiac defects, E= Eye abnormalities). (Is this a genetic disease or acquired? Mutation of what gene??) .

185. Pheochromocytoma = A functional chromaffinoma, usually benign, derived from adrenal medullary tissue cells and characterized by the secretion of catecholamines, resulting in hypertension, which may be paroxysmal and associated with attacks of palpitation, headache, nausea, dyspnea, anxiety, pallor, and profuse sweating. Pheochromocytoma is often hereditary, not only in phacomas such as Hippel-Lindau disease, neurofibromatosis, and familial endocrine neoplasia, but also as an **isolated defect as an autosomal dominant** trait = Familial Pheochromocytoma occurs in 5% of cases and is transmitted as an **autosomal dominant trait** (Kaplan IM, p 56). Secretion of dopamine occurs more in familial syndromes and is NOT associated with hypertension (Kaplan IM, p 57).

186. pisciform cataract = a hereditary cataract with bilateral fish-shaped opacities in the axial region of the fetal nucleus.
187. POEMS syndrome (plasmacytoma) = Polyneuropathy, organomegaly, endocrinopathy, serum M protein, skin changes.
188. Poland Syndrome = an anomaly consisting of absence of the pectoralis major and minor muscles, ipsilateral breast hypoplasia, and absence of two to four rib segments, amastia, pectoralis muscle aplasia, rib deformities, webbed finger, radial nerve aplasia (peds p 4) ← is this genetic or congenital condition? Probably congenital anomalies.
189. Pompe Disease = generalized glycogenosis = type 2 glycogenosis = Type 2 glycogen storage disease = glycogenosis due to lysosomal α-1,4-glucosidase deficiency (**=acid maltase deficiency**) , Resulting in **accumulation of** excessive amounts of **glycogen** of **normal chemical structure in heart, muscle, liver, and nervous system**. Accumulation of glycogen in heart produces both restrictive cardiomyopathy and dilated cardiomyopathy (IM, p 150, 154). Adult acid maltase deficiency is most likely to present as **recurrent respiratory paralysis**. The adult variant of acid maltase deficiency has prominent diaphragm involvement. Treatment is supportive during the acute episode. **Exo-1,4-α-D-glucosidase= γ-amylase= amyloglucosidase= glucoamylase= acid maltase** = A hydrolase removing terminal α-1,4-linked D-glucose residues from nonreducing ends of chains, with release of β-D-glucose. (Is this a genetic disease or acquired? Mutation of what gene??).
190. Pseudoxanthoma Elasticum (PXE) = ABNORMAL ELASTIC FIBERS
191. ORGAN SYSTEMS INVOLVED = An inherited disorder of connective tissue characterized by slightly elevated yellowish plaques on the neck, axillae, abdomen, and thighs, developing in the second or third decade, associated with angioid streaks of the retina and similar elastic tissue degeneration and calcification in arteries; autosomal dominant and autosomal recessive types have been described, with much milder systemic complications in the latter.
192. Progeria (Greek, "old age") refers specifically to Hutchinson-Gilford Progeria syndrome. Hutchinson-Gilford Progeria syndrome is an extremely rare condition in which physical aspects of aging are greatly accelerated, and few affected children live past age 13. About 1 in 8 million babies are born with this condition. **It is a genetic condition** but occurs sporadically and is usually not inherited in families. Hutchinson-Gilford Progeria Syndrome (HGPS) is a childhood disorder caused by mutations in one of the major architectural proteins of the cell nucleus. Unlike most other "accelerated aging diseases" (such as Werner's syndrome, Cockayne's syndrome or xeroderma pigmentosum), progeria is not caused by defective DNA repair. Because the "accelerated aging" diseases display different aspects of aging, but never every aspect, they are often called "segmental progerias.
193. Activated Protein C resistance = APC resistant = Activated protein C resistance is a hemostatic disorder characterized by a **poor anticoagulant response to activated protein C (APC)**. This results in **hypercoagulable state**

with an **increased risk of venous thrombosis (DVT)**, which can cause heart attacks, strokes, and other problems with circulation. The disorder can be acquired or inherited, the hereditary form having an **autosomal dominant inheritance** pattern.

194. Protein C Deficiency = **(protein S and protein C = Stop clotting = bleeding → if deficiency of protein C and protein S, clot won't stop → keeps clotting → protein C deficiency, Protein S deficiency, factor V Leiden all causes hypercoagulable states.)**. Protein C Deficiency is a rare **genetic trait** that predisposes to thrombotic disease. The main function of **protein C is its anticoagulant property as an inhibitor of coagulation factors V and VIII**. There are two main types of protein C mutations that lead to protein C deficiency: 1) Type I: Quantitative defects of protein C (low production or short protein half life). 2) Type II: Qualitative defects, in which interaction with other molecules is abnormal. Defects in interaction with thrombomodulin, phospholipids, factors V/VIII and others have been described. **The majority of people with protein C deficiency lack only one of the functioning genes, and are therefore heterozygous**. Before 1999, only sixteen cases of homozygous protein C deficiency had been described (two abnormal copies of the gene, leading to absence of functioning protein C in the bloodstream). This may manifest itself as **purpura fulminans** in the newborn.

195. Protein S deficiency= is a disorder associated with increased risk of venous thrombosis. Protein S, a vitamin K-dependent physiological anticoagulant, acts as a nonenzymatic cofactor to activated protein C in the proteolytic degradation of factor Va and factor VIIIa. Decreased (antigen) levels or impaired function (activity) of protein S, leads to decreased degradation of factor Va and factor VIIIa and an increased propensity to venous thrombosis. There are three types of hereditary protein S deficiency: 1) Type I - decreased protein S activity: decreased total protein S (=both bound and free protein S) levels AND decreased free protein S levels (quantitative defect). 2) Type II - decreased protein S activity: normal free protein S levels AND decreased total protein S levels (qualitative defect) 3) Type III - decreased protein S activity: decreased free protein S levels AND normal total protein S levels (quantitative defect) . Protein S deficiency can also be acquired due to vitamin K deficiency or treatment with warfarin, systemic sex hormone therapy and pregnancy, liver disease, and certain chronic infections (for example HIV). Vitamin K deficiency or treatment with warfarin generally also impairs the coagulation system itself (factors II, VII, IX and X), and therefore predisposes to bleeding rather than thrombosis. Protein S deficiency is the underlying cause of a small proportion of cases of disseminated intravascular coagulation (DIC), deep venous thrombosis (DVT) and pulmonary embolism (PE). Hereditary PSD is an **autosomal dominant condition**, resulting in a 50 percent chance of passing the disease to offspring. Less than half of those diagnosed with PSD will experience thrombosis, and those who do usually are affected only from the age of the late teens onwards.

196. Proximal myotonic myopathy (PROMM)= an autosomal dominant, multisystem disorder, with onset in young adult life, characterized by proximal myotonia and weakness, muscle pain, baldness, cataracts, cardiac conduction disturbances, and testicular atrophy. In contrast to myotonic dystrophy, features of

this disorder do not include facial weakness and ptosis, distal limb weakness and wasting, and trinucleotide repeat expansion at the gene loci for myotonic dystrophy.

197. Prune Belly Syndrome = Eagle-Barrett Syndrome = a syndrome of deficient abdominal muscle, undescended testes (=cryptorchidism), large hypotonic bladder and dilated, tortuous ureters. Prune belly syndrome results from a congenital absence of the anterior abdominal wall muscle. It consists of the triad of urinary anomalies (hypoplastic kidneys, hydronephrosis, hydroureter), deficiency of abdominal wall muscles and undescended tested. Intestinal malrotation is common. Ninety-five percent of patients are males. One third are stillborn or die early because of pulmonary complication. (Kaplan peds, p 253).

198. Psoriasis = A common **multifactorial inherited** condition characterized by the eruption of circumscribed, discrete and confluent, reddish, silvery-scaled maculopapule; the lesions occur predominantly on the elbows, knees, scalp, and trunk, and microscopically show characteristic parakeratosis and elongation of rete ridges with shortening of epidermal keratinocyte transit time due to decreased cyclic guanosine monophosphate. Origin: [G. *psōriasis,* fr. *psōra,* the itch]

199. Pyknodysostosis= A condition characterized by short stature, delayed closure of the fontanels, and hypoplasia of the terminal phalanges. Autosomal recessive inheritance. Syn: osteopetrosis acro-osteolyt

200. Pyrin= An abnormal neutrophil protein encoded by the MEFV gene in familial Mediterranean fever. Syn: marenostrin.

201. Renal Tubular Acidosis (RTA) = The primary or hereditary form of distal renal tubular acidosis (dRTA), although rare. Inherited defects in two of the key acid/base transporters involved in distal acidification, as well as mutations in the cytosolic carbonic anhydrase gene, can cause dRTA. The syndrome is inherited in both **autosomal dominant and autosomal recessive** patterns; patients with recessive dRTA present with either acute illness or growth failure at a young age, sometimes accompanied by deafness, whereas dominant dRTA is usually a milder disease and involves no hearing loss. The *AE1* gene encodes two Cl¡/HCO3 ¡ exchangers that are expressed in the erythrocyte and in the acid-secreting intercalated cells of the kidney. *AE1* contributes to urinary acidification by providing the major exit route for HCO3 ¡ across the basolateral membrane. Several mutations in the *AE1* gene cosegregate with dominant dRTA. Other *AE1* mutations have been linked to a recessive syndrome of dRTA and hemolytic anemia in which hypofunction can be discerned by in vitro studies **Several mutations in the carbonic anhydrase II gene are associated with the autosomal recessive syndrome of osteopetrosis, renal tubular acidosis, and cerebral calcification. Some of these individuals present with deafness of the conductive type (conductive hearing loss).** By contrast, more recent studies have shown that mutations in *ATP6B1*, encoding the B-subtype unit of the apical HC ATPase, are responsible for a group of patients with autosomal recessive dRTA associated with sensorineural deafness. Thus, the presence of deafness and the type provide an important clue to the genetic lesion underlying hereditary dRTA. Type 1 (distal) and type 2 (proximal) renal tubular acidosis (RTA) will cause "**hyperchloremic-Hypokalemic non-anion gap metabolic acidosis"** whereas type 4 (distal) tubular

acidosis (RTA) will cause "**hyperchloremic-Hyperkalemic non-anion gap metabolic acidosis"** (1st aid CK, p 370), (Kaplan IM, p 253,255).

202. Richards-Rundle syndrome = a neurologic disorder beginning in early childhood with severe, progressive sensorineural hearing loss, ataxia, muscle wasting nystagmus, absent deep tendon reflexes, mental retardation, failure to develop secondary sexual characteristics, and ketoaciduria; **autosomal recessive inheritance**.

203. Rieger Syndrome= iridocorneal mesenchymal dysgenesis combined with hypodontia or anodontia and maxillary hypoplasia; **autosomal dominant**; there is a **delayed sexual development and hypothyroidism**.

204. Rhesus isoimmunization= Rhesus (Rh) factor is an antigenic protein located on RBCs in Rh-positive individuals. Transmission is **autosomal dominant**. (First aid CK, p 254). A blood incompatibility disorder where the mother's blood type is not compatible with the fetus. This incompatibility results in antibodies from the mother's blood destroying the baby's red blood cells when they come into contact during pregnancy and after birth. Without treatment the condition can cause serious complications and even death. The two different blood types involved are Rh-negative or Rh-positive. The mother does not develop the antibodies to the baby's blood until after delivery so the first baby is not affected but any subsequent babies can be affected during the pregnancy or after the birth. Also known as Rh isoimmunization. Rhesus disease = sensitization of the mother during pregnancy to Rh factor in fetal blood, leading to **erythroblastosis fetalis**.

205. Robinow syndrome= a skeletal dysplasia characterized by bulging forehead, hypertelorism, depressed nasal bridge (so-called fetal face), wide mouth, acromesomelic shortening of limbs, hemivertebrae, and hypoplastic genitalia; there is also an autosomal recessive form. See Also: fetal face syndrome. Syn: Robinow dwarfism.

206. Rokitansky-Küster-Hauser syndrome = Mayer-Rokitansky-Küster-Hauser syndrome= Mullerian Agenesis = primary amenorrhea due to müllerian duct agenesis, resulting in absence of the vagina, or presence of a short vaginal pouch, and absence of the uterus with **normal karyotype** and ovaries. Syn: müllerian agenesis, Rokitansky-Küster-Hauser syndrome. **(Is this a genetic disease?)** (Kaplan OB, p 154)

207. **Rotor syndrome** = Autosomal recessive disorder of bilirubin storage. Hereditary disease, jaundice appearing in childhood due to impaired biliary excretion; most of the plasma bilirubin is conjugated (= get conjugated hyperbilirubinemia), liver function tests are usually normal, and there is **no hepatic pigmentation.** (Pathology, p187) (Peds, p 14) (Get dark hepatic pigmentation with Dubin-Johnson syndrome). (Rotor Syndrome can be distinguished by an elevation in urinary coproporphyrins?? ← an answer in Kaplan Q bank). **(Conjugated bilirubin is insoluble in water and is bound to albumin and can NOT be filtered by the glomerulus and there for is not excreted in the urine. Unconjugated bilirubin is water soluble and in case of unconjugated hyperbilirubinemia can be excreted from the body in the urine through kidneys).**

208. **Sacral agenesis (or hypoplasia of the sacrum) (also more commonly called caudal regression syndrome) = Sacral agenesis Syndrome** = is a little known and rather infrequent congenital condition of spinal deformity affecting the sacrum - the caudal partition of the spine. It occurs at a rate of approximately 1 per 25,000 live births. The condition arises from some factor or set of factors present during approximately the 3rd week to 7th week of fetal development. Formation of the sacrum/lower back and corresponding nervous system is usually nearing completion by the 4th week of development. While the exact etiology is unknown, it has been speculated that the condition may be associated with certain dietary deficiencies including a lack or insufficient amounts of folic acid or other developmental aids. **The condition may also be associated with or resultant from maternal** diabetes Mellitus. However, it's important to note that the correlation between onset of sacral agenesis and the above-mentioned possible causes is weak. The d**ominant inherited sacral agenesis (also referred to as Currarino syndrome) is very often correlated with a mutation in the Hb9** (also called HlxB9) gene. There are four levels (or "types") of malformation. The least severe indicates partial formation (unilateral) of the sacrum. The second level indicates a bilateral (uniform) deformation. And the most severe types involve a total absence of the sacrum. Depending on the type of sacral agenesis - bowel or urinary bladder deficiencies may be present. A permanent colostomy may be necessary in the case of imperforate anus. Incontinence may also require some type of continence control system (e.g. self-catheterization) be utilized. Occasionally if deformities of the knees, legs or feet would prove unresponsive to corrective action - amputation at the knee may be proposed. Before more comprehensive medical treatment was available, full amputation of the legs at the hip was often performed (God forbid).

209. Segawa Disease = hereditary progressive dystonia with "---" = Segawa syndrome, autosomal recessive and autosomal dominant (Both were listed online): A very rare birth disorder characterized mainly by involuntary jerky movements that start during infancy. The disorder is caused by a genetic defect resulting in a deficiency of an enzyme called tyrosine hydroxylase. The disorder is usually treatable by administering low doses of L-DOPA medication. Symptoms, of Segawa syndrome are: Involuntary jerky movements, Rigidity, Lack of spontaneous movement, Expressionless face, Droopy eyelids. TX is with "L-Dopa"

210. Segawa's Syndrome = Autosomal Dominant Dopa-responsive Dystonia = autosomal dominant dopa-responsive dystonia caused by GTP cyclohydrolase deficiency, or Segawa's disease. Identification and treatment of this disorder can be extremely rewarding because patients often benefit greatly with directed treatment of the associated dopamine deficiency state. Patients with a classic presentation of exercise-induced dystonia are not difficult to recognize. This diagnosis should also be considered in patients with spastic diplegia, especially when significant fluctuation in gait or worsening gait at the end of the day is noted, and in patients with more atypical presentations, including writer's cramp, asymmetric limb dystonia, tremor, or restless leg type symptoms. In patients with a classic presentation, many clinicians can make the diagnosis on a presumptive basis,

after observing remission of symptoms with a trial of L-dopa/carbidopa. Inheritance is autosomal dominant, penetrance is incomplete, and variable expressivity among family members with the same mutation are well-documented. For instance, one might see spastic diplegia, writer's cramp, restless leg syndrome, and more typical exercise-induced dystonia phenotypes among different members of the same family. The female-to-male ratio in sporadic cases is 4:1, and investigators have confirmed increased penetrance of GTPCH I mutations in females.

211. Sandifer syndrome= torticollis (q.v.) in infants, associated with gastroesophageal reflux; may be a mechanism to protect the airway or reduce acid reflux–associated pain. People with Sandifer syndrome present with gastroesophageal reflux (GER) and opisthotonus, presumable to avoid aspiration or decrease pain.(Kaplan peds, p 173). [It may be linked to a mutation in the CACNA1A gene (145), which is associated with familial hémiplégie migraine. Sandifer Syndrome] (is this a genetic disease??)

212. Savage syndrome= obsolete term for resistant ovary syndrome [Savage is from surname of first reported patient]= Resistant ovary syndrome= amenorrhea associated with hypogonadotropism and usually normal ovarian follicles; may be **autosomal dominant** in inheritance. Savage syndrome is a condition in which although follicles are seen in the ovary by sonogram, they (= follicles) do not respond to gonodotropins. (Kaplan OB, p 156)

213. Schizophrenia = A term coined by Bleuler, synonymous with and replacing *dementia praecox;* a common type of psychosis, characterized by abnormalities in perception, content of thought, and thought processes (hallucinations and delusions) and by extensive withdrawal of interest from other people and the outside world, with excessive focusing on one's own mental life; The lifetime incidence risk is about 1%. Onset is typically gradual, without an obvious precipitating cause. Early symptoms include shortened attention span, memory deficits, and diminished ability to make decisions. Most patients become ill before age 40. Psychotic symptoms persist for months or years, and there is a lifelong risk of relapse. Cognitive malfunctions are typically accompanied by reduced energy level, flat or depressed affect, anhedonia, and abulia. Virtually all patients display impoverished thought content, social withdrawal, and impairment of occupational functioning, and even with intensive psychotherapy and drug treatment about 25% require custodial or institutional care. Although some persons with schizophrenia become assassins or mass murderers, the vast majority pose no threat to society; about 10% commit suicide. Neurophysiologic studies have shown generalized limbic lobe and prefrontal cortical abnormalities, abnormal smallness of the thalamus, and changes in signal intensity in adjacent white matter. Brain imaging inconsistently demonstrates structural or physiologic abnormalities in the prefrontal cortex, cingulate cortex, temporal cortex, and hippocampal formation. The amelioration or exacerbation of schizophrenia by certain pharmacologic agents seems to indicate that it represents a malfunction of neuronal systems using dopamine, serotonin, glutamate, and γ-aminobutyric acid (GABA) as transmitters or modulators. **Genetic studies suggest that susceptibility to schizophrenia is inherited as a complex of variations affecting several genes**. According to the neurodevelopmental

hypothesis, a brain lesion is present or acquired early in life but does not fully manifest itself until late adolescence or early adulthood, when it triggers abnormalities of neuronal proliferation, axonal outgrowth, cell migration, cell survival, synaptic regression, or myelination. Psychotherapy and behavioral therapy are inconsistently effective in the treatment of schizophrenia. Neuroleptic drugs shorten episodes of acute psychosis, limit the need for institutional care, and reduce the risk of relapse, but their long-term use is associated with serious side effects, particularly tardive dyskinesia. Newer agents such as clozapine, olanzapine, quetiapine, and risperidone are more effective in improving cognitive function and less likely to induce extrapyramidal side effects. Persons with schizophrenia frequently stop taking their medicine, and it is estimated that at any given time only one-half of them are receiving medical treatment or supervision. Origin[schizo- + G. *phrēn,* mind]

214. Shwachman syndrome= Shwachman-Diamond syndrome = an autosomal recessive disorder characterized by sinusitis, bronchiectasis, pancreatic insufficiency resulting in malabsorption, neutropenia with defect in neutrophile chemotaxis, short stature, and skeletal changes with radiographic findings of metaphyseal flaring of long bones.

215. Sickle cell-thalassemia disease= anemia clinically resembling sickle cell anemia, in which individuals are compound heterozygous for the sickle cell gene and a thalassemia gene; about 60–80% of hemoglobin is Hb S, up to 20% Hb F, and the remainder Hb A. Syn: microdrepanocytic anemia.

216. Sideroblastic anemia, sideroachrestic anemia= refractory anemia characterized by the presence of sideroblasts in the bone marrow. There are both **hereditary** as well as acquired forms of sideroblastic anemia. The **hereditary form** is from either a **defect in aminolevulinic acid synthase (= ALA synthetase)** or an abnormality in vitamin B6 metabolism (vitamin B6 = pyridoxine and related compounds pyridoxal; pyridoxamine). Acquired forms are from drugs such as chloramphenicol, isoniazid (INH), or alcohol, Pyrazinamide, cycloserine. All these drugs have anti-vitamin B6 Properties. Lead poisoning can also cause sideroblastic anemia. There is an association with myelodysplastic syndromes (MDS) and refractory anemia. These can progress to acute myelogenous leukemia (AML) in a small percentage of patients. (Kaplan IM, p 174). Sideroblastic Anemia is characterized by a reduced RBC count because of ineffective erythropoiesis. Sideroblastic anemias are a group of disorders in which relative iron overload and ineffective heme synthesis are found in the mitochondria where the final steps in heme synthesis occur. The bone marrow, when stained with Prussian blue, shows RBC precursors with pigmented rings around the cell nucleus (the ringed sideroblast). These rings are formed by iron-overloaded mitochondria in the RBC precursor.

217. Somatization disorder= a mental disorder characterized by presentation of a complicated medical history and of physical symptoms referring to a variety of organ systems, but without a detectable or known organic basis. See: conversion, hysteria, Briquet syndrome. Data suggest that there maybe a **genetic linkage** to the disorder (Kaplan psych, p 37). Within families, male relative tend to have antisocial

personality disorder, whereas female relatives tend to have histrionic personality disorder. Somatization disorder affects women more than men and is usually inversely related to SES (= Socioeconomic Status) (Kaplan psych, p 37). A researcher investigated the contribution of **hereditary factors** in somatoform disorders. Fourteen monozygotic and 21 dizygotic index twins and their co-twins were personally interviewed. The results showed a concordance of 29% in monozygotic and 10% in dizygotic pairs. However, similarity in childhood experience seemed to influence the concordance rates. Thus, even if **somatoform disorders appear familial, the transmission may be environmental**. Furthermore, the study showed a high frequency of anxiety disorders, especially generalized anxiety disorders, in the co-twins of somatoform-disordered twins.

218. Sotos syndrome = Cerebral Gigantism = cerebral gigantism and generalized large muscles in childhood, with mental retardation and defective coordination; of **unknown etiology**. Most cases have been sporadic, perhaps **new dominant mutations** with low fitness, but there is one set of concordant identical twins on record. Cerebral gigantism= a syndrome characterized by increased birth weight and length (above 90th percentile), **large for gestational age (LGA)**, accelerated growth rate for the first 4 or 5 years without elevation of serum growth hormone levels, and then reversion to normal growth rate; characteristic facies include prognathism, hypertelorism, antimongoloid slant, and dolichocephalic skull; moderate **mental retardation, mild hydrocephalus** and impaired coordination are also associated. (Kaplan peds, p30)
219. SPEECH1=Gene that when mutated is responsible for motor dyspraxia.
220. Spinobulbar muscular dystrophy = triplet repeat expansion (p58)
221. Spinocerebellar ataxia= the most common hereditary ataxia, with onset in middle to late childhood, manifested as limb ataxia, nystagmus, kyphoscoliosis, and pes cavus; the major pathologic changes are found in the posterior columns of the spinal cord; most often autosomal recessive inheritance.
222. Sturge-Weber syndrome (SWS) = in its complete form, a triad of unilateral occurrence of 1) congenital capillary malformation (flame nevus) in the distribution of the trigeminal nerve (=**port wine stain of the face**= hemangioma of the face). Facial nevus is most of the time unilateral and always includes the upper face and eyelids (in V1 distribution area = first branch of trigeminal nerve ophthalmic nerve) ; 2) leptomeningeal vascular malformations (= leptomeningeal angioma) with intracranial calcification and neurologic signs; and 3) vascular malformation of the choroid, often with secondary glaucoma. Patient present with mental retardation, seizure, congenital unilateral cavernous hemangioma, hemianopia, hemiparesis, hemi-sensory disturbance, ipsilateral glaucoma. **Inheritance is unclear** with most cases sporadic. (Kaplan peds, p 232) (CK p 83, 208). See Also: encephalotrigeminal vascular syndrome. Syn: cephalotrigeminal angiomatosis, encephalotrigeminal angiomatosis, Sturge-Weber disease, Sturge-Kalischer-Weber syndrome.
223. Tapetoretinal degeneration= a hereditary disorder of the retina mainly affecting photoreceptors and retinal pigment epithelium; this may be a manifestation

of Friedreich ataxia, Refsum disease, and abetalipoproteinemia. Syn: primary pigmentary degeneration of retina.

224. Tietz syndrome= autosomal dominant inheritance of albinism and deafness caused at least in some subsets of families by a mutation of the microphthalmia transcription factor gene.

225. α Thalassemia= thalassemia due to one of two or more genes that depress (severely or moderately) synthesis of α-globin chains by the chromosome with the abnormal gene. Heterozygous state: severe type, thalassemia minor with 5–15% of Hb Barts at birth, only traces of Hb Barts in adult; mild type, 1–2% of Hb Barts at birth, not detectable in adult. Homozygous state: severe type, erythroblastosis fetalis and fetal death, only Hb Barts and Hb H present; mild type not clinically defined. See Also: hemoglobin H.

226. β Thalassemia= thalassemia due to one of two or more genes that depress (partially or completely) synthesis of β-globin chains by the chromosome bearing the abnormal gene. Heterozygous state (A_2 t.): thalassemia minor with Hb A_2 increased, Hb F normal or variably increased, Hb A normal or slightly reduced. Homozygous state: thalassemia major with Hb A reduced to very low but variable levels, Hb F very high level.

227. β-δ Thalassemia= thalassemia due to a gene that depresses synthesis of both β- and δ-globin chains by the chromosome bearing the abnormal gene. Heterozygous state: thalassemia minor with Hb F comprising 5–30% of total hemoglobin but distributed unevenly among cells, Hb A_2 reduced or normal. Homozygous state: moderate anemia with only Hb F present, no Hb A or Hb A_2. Syn: F thalassemia.

228. Thalassemia major (Cooley, homozygous B) = is a blood disorder resulting from an imbalance of alpha and beta globin chains. There is a surplus of alpha globulin chains, causing ineffective erythropoiesis and hemolysis. (Kaplan peds, p200)

229. Thrombocytopenia-absent radius syndrome, TAR syndrome= congenital absence of the radius associated with thrombocytopenia that is symptomatic in infancy but later improves; congenital heart disease and renal anomalies occur in some cases; **autosomal recessive inheritance**. (Kaplan peds, p 203).

230. Thrombotic thrombocytopenic purpura (TTP)= a rapidly fatal or occasionally protracted disease with varied symptoms in addition to purpura, including signs of central nervous system involvement, due to formation of fibrin or platelet thrombi in arterioles and capillaries in many organs. **The etiology of TTP is most of the time idiopathic**. Deficiency of the ADAM-TS protein is associated with the Thrombotic Thrombocytopenic Purpura (=TTP). Cellular disintegrin and metalloproteinase (ADAMs) are a family of genes with a sequence similar to those of snake venom metalloproteinase and disintegrins. The ADAMTS-1 gene encodes a new type of ADAM protein with respect to possessing the thrombospondin (TSP) type I motifs. Expression of the gene is induced in kidney and heart by in vivo

administration of lipopolysaccharide, suggesting a possible role in the inflammatory reaction.

231. Tourette syndrome = Tic = a tic disorder appearing in childhood, characterized by multiple motor tics and vocal tics present for more than 1 year. Obsessive-compulsive behavior (OCD), attention-deficit disorder (ADHD), learning disorder and other psychiatric disorders may be associated; coprolalia (coprolalia = repetitive speaking of obscene words) and echolalia (Echolalia= exact repetition of words) rarely occur; **autosomal dominant inheritance**. Genetic factors: 50% concordance rate in monozygotic versus 8% in dizygotic twins. There are associations between attention deficit hyperactivity disorder (ADHD) (50%) and obsessive-compulsive disorder (OCD) (40%) and Tourette disorder. Abnormalities in the dopaminergic and adrenergic system have been implicated. Tourette disorder is twice as frequent in males compare to females. (Kaplan psych, p 16). Syn: Gilles de la Tourette disease, Tourette disease, Gilles de la Tourette syndrome. (Kaplan psych, p 16). PANDAS, is an abbreviation for Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal Infections. The term is used to describe a subset of children who have **Obsessive Compulsive Disorder (OCD)** and/or **tic disorders** such as Tourette's Syndrome, and in whom symptoms worsen following Streptococcus infections such as "Strep throat" and Scarlet Fever. The children usually have dramatic, "overnight" onset of symptoms, including motor or vocal tics, obsessions, and/or compulsions. In addition to these symptoms, children may also become moody, irritable or show concerns about separating from parents or loved ones. This abrupt onset is generally preceded by a Streptococcus throat infection. Coprolalia = Involuntary utterances of vulgar or obscene words; seen in Gilles de la Tourette syndrome. Syn: coprophrasia. Origin: [copro- + G. *lalia*, talk]

232. Torre syndrome= Muir-Torre syndrome = genetic disease, **autosomal dominant**, associated with breast cancer (1st aid surgery, p 143), = multiple sebaceous gland adenomas associated with multiple visceral malignancies, often colorectal carcinoma.

233. Trichoepithelioma = Multiple small benign nodules, occurring mostly on the skin of the face, derived from basal cells of hair follicles enclosing small keratin cysts; **autosomal dominant** inheritance. Syn: epithelioma adenoides cysticum, hereditary multiple trichoepithelioma, Brooke tumor.

234. Triple A syndrome = AAA syndrome = **autosomal recessive** syndrome associated with Achalasia of the cardia, and Alacrima; associated problems include abnormalities of the nervous system such as mental retardation and autonomic dysfunction. Syn: Allgrove syndrome.

235. Triple repeat disorders= Disorders of Trinucleotide Repeat = a group of hereditary disorders in which a gene mutation on a specific chromosome produces an abnormal form of protein terminated by a long chain of amino acid glutamate repeats; includes **Huntington disease** (CAG repeat), **Kennedy disease (CAG) , Machado-Joseph disease (CAG), myotonic dystrophy (CTG) , fragile X syndrome (CGG repeat =** (cytosine- Guanine- Guanine repeat**)**, Spinocerebellar

Ataxia-I **(CAG repeat),** and some **spinal cerebellar disorders, Spinobulbar muscular dystrophy** (Nucleotides triplet repeat expansion)**, Friedreich ataxia** (GAA repeat). Anticipation = An increase in the severity of a phenotype in successive generations of a family, often associated with an increase in the number of trinucleotide repeats in a causative gene (e.g., fragile X syndrome, myotonic dystrophy, Huntington disease).

236. Trisomy C syndrome = trisomy for any chromosome of group C, numbers 6–12, most often number 8.
237. Type IA achondrogenesis = Houston-Harris syndrome = achondrogenesis with hypervascular cartilage and hypercellular bone; uncertain inheritance pattern.
238. Type III Osteogenesis Imperfecta = a progressive deforming form with severe **bone fragility, easy fractures, triangular facies** with relative **macrocephaly, skeletal deformities** with **scoliosis**, pectus and **bowing of limbs**, **dwarfism**, and radiographic findings of metaphyseal flaring of long bones with sutural bone formation. Most cases are **autosomal dominant** disorders, but autosomal recessive inheritance has also been described.
239. Type 7 glycogenosis = Type 7 glycogen storage disease = **phosphofructokinase deficiency of muscle** resulting in **muscle cramps** and myoglobinuria on extreme exertion. The clinical picture resembles type 5 glycogenosis.
240. Type 8 glycogenosis = Type 8 glycogen storage disease = due to **deficiency of enzyme phosphorylase –beta kinase of the liver**. Get **hepatomegaly** and hypoglycemia.
241. Urticaria pigmentosa = (is this a genetic/hereditary/familial disease or acquired/sporadic mutation??) is the most common form of cutaneous mastocytosis. It is a rare disease caused by excessive amounts of mast cells in the skin that produce hives or lesions on the skin when irritated. The majority of urticaria pigmentosa cases are caused by a **point mutation** at amino acid 816 of the proto-oncogene c-kit. c-kit is a transmembrane protein which, when bound to Mast Cell Growth Factor (MCGF), signals the cell to divide. Mutations in position 816 of c-kit can result in a constant division signal being sent to the mast cells, resulting in abnormal proliferation. Different mutations have been linked to different onset times of the disease. For example, the Asp816Phe and Asp816Val mutations (the aspartate normally at position 816 in the c-kit protein has been replaced with phenylalanine or valine respectively) have been associated with early manifestation of the disease (mean age of onset: 1.3 and 5.9 months respectively). **c-kit mutations are associated with mast cell tumors , such as urticaria pigmentosa and piebaldism.**
242. Usher syndrome= autosomal recessive inheritance with genetic heterogeneity; the three forms are distinguishable by linkage data: type 1 causes sensorineural hearing loss, loss of vestibular function, and retinitis pigmentosa; types 2 and 3 are characterized by hearing loss and retinitis pigmentosa.

243. Von Gierke Disease = Type 1 glycogenosis = type 1 glycogen storage disease = Gierke disease= glucose-6-phosphatase hepatorenal glycogenosis= glucose-6-phosphatase deficiency = glycogenosis due to **glucose 6-phosphatase deficiency**, resulting in accumulation of excessive amounts of **glycogen of normal chemical structure**, particularly in **liver and kidney**. Patient presents with hypoglycemia and hypoglycemic seizure, lactic acidosis, hyperuricemia, hyperlipidemia, **doll-like face (= fat cheeks)**, short stature (dwarfism), protuberant abdomen (due to enlarged liver and kidney = hepatomegaly, nephromegaly). Hepatic adenoma can be due to type 1 (=Von Gierke Disease) and type 3 glycogen storage disease.

244. Vogt Cephalodactyly= Type II acrocephalosyndactyly.

245. Vogt-Koyanagi syndrome = Vogt-Koyanagi-Harada syndrome = bilateral uveitis with iritis and glaucoma, premature graying of the hair, and alopecia, vitiligo, and dysacusia (=dysacousia) ; related to Harada syndrome and sympathetic ophthalmia. Syn: oculocutaneous syndrome, uveocutaneous syndrome.

246. Vitiligo, pl. Vitiligines = ares of depigmentation of skin. These depigmented areas completely lack melanocyte. The actual cause is NOT completely understood, but **genetic factors seem to play a role**. The pathogenesis is believed to involve an autoimmune process directed against melanocytes, and this theory is supported by the **concomitant occurrence of other autoimmune disease with vitiligo (vitiligo can be a part of polyglandular autoimmune syndrome = PAS). Some of these autoimmune conditions associated with vitiligo are pernicious anemia, autoimmune thyroid disease (usually Grave's disease or chronic autoimmune thyroiditis), type 1 diabetes mellitus, primary adrenal insufficiency (Addison's disease), hypopituitarism and alopecia areata).** (Kaplan IM, p 330) and (First aid CK p73) Vitiligo = The appearance on otherwise normal skin of nonpigmented white patches of varied sizes, often symmetrically distributed and usually bordered by hyperpigmented areas; hair in the affected areas is usually white. Epidermal melanocytes are completely lost in depigmented areas by an autoimmune process. Syn: acquired leukoderma. **(Dose this have to do with HLA and MHC in chromosome 6??)** .

247. Watson's Syndrome = A rare syndrome originally described as comprising **pulmonary valvular stenosis (= Pulmonary Stenosis), café-au-lait spots (=Café-Au-Lait Macules), dull intelligence**, and short stature. Later the phenotype has been expanded to include macrocephaly and Lisch' nodules in the majority of cases, and neurofibromatosis in one-third of the affected persons. Later studies indicate that the characteristics of this condition overlap those of neurofibromatosis and the Noonan syndrome (the neurofibromatosis-Noonan syndrome) (Q book3, p 202). Inheritance is autosomal dominant. Watson syndrome is an autosomal recessive condition characterized by Lisch nodules, axillary/inguinal freckling, and neurofibromas.

248. West Syndrome = Infantile Spasms = an encephalopathy in infancy characterized by infantile spasms, arrest of psychomotor development, and hypsarrhythmia. More common in male than females, associated with a positive

family history (familial?). (1st aid CK, p 228). Infantile spasm is associated with tuberous sclerosis.

249. Z gene= the structural gene for β-galactosidase.

250. Zimmerlin atrophy = a variety of **hereditary** progressive **muscular atrophy** in which the atrophy begins in the **upper half of the body**. **NOTE: Do NOT mix Zimmerlin atrophy** with **Vulpian atrophy**, which is a "spinal" muscular atrophy. (Vulpian atrophy = scapulohumeral atrophy = progressive **spinal muscular atrophy (SMA)** beginning in the **shoulder**).

251. Zunich-Kay Syndrome is considered to have an **autosomal recessive** inheritance pattern. Zunich-Kaye syndrome, also known as **Zunich neuroectodermal syndrome**, is a rare **congenital ichthyosis** first described in 1983. It is also referred to as CHIME syndrome, after its main symptoms (Colobomas, Heart defects, Ichthyosiform dermatosis, Mental retardation, and either Ear defects or Epilepsy). It is a congenital syndrome with only a few cases studied and published. Associated symptoms range from things such as colobomas of the eyes, heart defects, ichthyosiform dermatosis, mental retardation (MR), and ear abnormalities. Further symptoms that may be suggested include characteristic facies, hearing loss, and cleft palate.