Disorders in L18/20/21/22

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|  Dz or syndrome | Autosomal (A) / X linked (X)Dominant (D) / recessive (R) Number of ch | Notes  |
|  GAUCHER | **A/R** | most common of a genetic disorder/deficiency of an enzyme β-glucocerebrocidase/fat can not be broken down and is stored primarily in the liver and spleen.Other body organ, tissues and bones are also effected , in rare cases it may also accumulates in the brain/c/f:Bone pain and fractures ,Easy bruising ,Fatigue ,Seizures ,Liver and spleen enlargement |
| G6PD deficiency  | **X/R** | Favism 🡪 drug induced hemolysis/Males hemizygous so all RBC can be hemolyzed ,,But in females, bcz of X-inactivation, some RBCs from BM may be with erroneous normal allele inactivationSo hemolysis can be present in females carriers too, but less severe than males |
| Fragile X | **X/D****an expansion of the CGG triplet repeat within the Fragile X mental retardation 1 (FMR1) gene on**  |   |
| Hypophosphatemic rickets  | **X/D** | increased phosphate wasting at proximal tubule |
| Vit D resistant rickets  | **X/D** | * 😊 (edit: hypophosphatemic rickets = vitD resistant rickets)
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| Hemophilia  | **X / R** | oldest known bleeding dz(queen Victoria family)/-males mostly /type A clotting factor 8 /type B clotting factor 9/tx: clotting factor different doses(weight&severity)/ clotting factors synthesized by recombinant DNA/not human plasma clotting due to chance of contamination with viruses/current studies on TypeB gene transfer to treat but still will pass to children  |
| Duchenne muscular dystrophy (DMD)  | **X/R** | Cardiomyopathy which will lead to Ht.Failure /Weak Diaphragm will lead to respiratory failureLoss of muscle mass,inflamation and fibrosis which requires wheelchair//  gowers sign |
| APKD (adult polycystic kidney dz) | **A/D****ch16** | 90% due to MutatedAPKD1 on/Bilateral enlargement of kidney due to multiple cysts/C/F: b/l flank pain, hematuria, HTN,progressive renal failure/Usually ->adulthood /cysts in the liver ( 30% ) berry aneurysms of the circle of Willis ( 10-15%)  /mitral valve prolapse (MVP) Colonic diverticulosis |
| Familial Adenomatous Polyposis  | **A/D****Deletion on chromosome 5q21-22 (APC gene)** | Colon covered with polyps after puberty that progress to 100 % cancer if not resected around 30 years/c/f:anemia, melena, changes in bowel habits/ Screening, Definite -> Will need yearly colonoscopies beginning age of 12/Once you see polyps do colectomy /Also do upper GI endoscopy to rule out polyps  |
| Lynch Syndrome (HNPCC) | **A/D** **Due to defects in Mismatch Repair Genes** | Other Cancer like endometrial (2nd most common), ovarian and gastric cancers common /Three or more family members with colon cancers, one of whom is a first degree relative of the other two/ Two successive affected generations/Colon cancer in one family member under age 50 years 1.Will need yearly colonoscopies beginning age of 20 to 25 2.Endometrial sampling beginning at age of 30 3.Gastric and ovarian cancer screening at age of 30 |
| Neurofibromatosis 1 (NF1/von Recklinghausen’s dz) | **A/D****Ch****17q11** | This neurofibronin gene is a negative regulator of Ras oncogene (Increases incidence of cancers like Juvenile myelomonocytic leukemia and Malignant Nerve Sheet Tumor)/ c/f: café-au-lait spot, neural tumors, Lisch nodules (pigmented iris hamartomas)/Increased incidence of Optic Gliomas, pheochromocytomas, susceptibility to tumors, and skeletal disorders |
| Neurofibromatosis 2 (NF2)  | **A/D** ch 22q12Merlin gene \* as well as through random mutation |  Bilateral acoustic neuromas on CN8 is the diagnostic,Tumors may cause tinnitus, hearing loss, balance problems, vertigo, etc.,#Juvenile Subscapular Cataract,#Brain and other crainial nerve tumors: Schwanomas, meningiomas, astrocytomas ,#Spine; astrocytomas and ependymomas,if unilateral acoustic neuroma with meningioma, glioma , schwanoma, Cataract or First degree relative with NF II  |
| Tuberous Sclerosis | **A/D****mutation of either of two genes, TSC1 and TSC2** | code for the proteins hamartin(1) and tuberin(2), respectively-> These proteins act as tumor growth suppressors, agents that regulate cell proliferation and differentiation->benign HAMARTOMAS to in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin./Most common cause of Morbidity ->Sclerosis is Seizures->Mostly patient present with a type of seizures called as infantile spasm/hypsarrythmia can be seen on EEG/Rx with ACTH therapy to reduce CRH levels->*CRH* is known to have excitatory physiological actions on neurons and can induce seizures/ facial angiofibromas in characteristic butterfly pattern |
| Huntington’s dz | **A/D** **Ch4** | TN of (CAG)n -> normal (9-35) dz->(36-121)/affects folding of Huntington protein ->clumps->kill neurons producing GABA n Ach/\*\*sym.: uncontrolled movements (chora)/ loss of intellectual functions(continues to decline )/Emotional Disturbance/Mood Swings/ irritability/depression/loss of memory /progresses to walking and speech difficulties\*\* /appears at 30-40 yo/death within 5-10years/no tx/there’s a test. |
| Marfan’s synd.This syndrome and the next one affects structural proteins | **A/D** **Ch15** | Affects fibrillin of elastin/\*\*(affects:eyes/slkeleton/CS/)\*\*/\*\*symp.:( tall stature, long fingers, pigeon breast deformity, hyper-extensible joints, high arched palate, subluxation of lens, floppy Mitral valve, Aortic aneurysm , defects in skin, lungs, long fingers, pigeon breast deformity, hyper-extensible joints, high arched palate, subluxation of lens, floppy Mitral valve, Aortic aneurysm , defects in skin, lungs.// Marfanoid Habitus:  group of symptoms resemble marfans syndrome, arm span that exceeds the height of the individual, and a crowded oral maxilla, and hyperlaxity.)=marafantall stature \*\* |
| Ehler-Danlos Syndrome(Cutis Hyperelastica) | **A/D** | defects in collagen synthesis/fragile, hyper-extensible skin, hyper-mobile joints, rupture of internal organs like the colon, cornea and large arteries, poor wound healing |
| Familial hypercholestremiaThis one and the next 2 ->metabolic proteins | **A/D** | Common(on of the most)/LDL receptor gene mutation/higher risk of CAD and atherosclerosis/ xanthomas (high cholesterol)< only familial hypercholesteraemia related to metabolic proteins>HLP type 2A: Xanthelasma palpebrarum /tendon xanthomas (classically on the Achilles tendon) severe atherosclerotic dz / MI may develop early  |
| Albinism | **A/R** | are unable to produce skin or eye pigments, and thus are light-sensitive |
| Glycogen storageIMPORTANT | **A/R** |

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| **Category** | **Disease** | **Enzyme** |
| **Hepatic Type.** | **Von Gierke’s Disease type 1.** | **Glucose-6-phosphotase.** |
| **Myopathic Type.** | **McArdle Syndrome.** | **Muscle Phosphorylase.** |
| **Miscellaneous Type.** | **Pompe’s Disease type II** | **Lysosomal Glucosidase.** |

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| Achondroplasia | **A/D** | affects the growth of bones and causes dwarfism |
| Polydactyly | **A/D** | extra number of fingers and toes |
| ACHONDROPLASIA=Dwarfism  | A/D | Defect in Fibroblast Growth Factor receptor 3 gene/ abnormal cartilage development/Phenotypic : short limbs, head and neck normall size/Associated with advance paternal age/one parent affected then 50% of children affected /In about 80% of cases this occurs as a new mutation during early development/Homozygotes die either before or shortly after birth/Those affected have an average adult height of 131 centimetres for males and 123 centimetres for females/Other features include an enlarged head and prominent forehead, Intelligence is generally normal. |
| a1-antitrypsin deficiency | **A/R****ch** **14q32.1** | A1AT is Serine protease inhibitor produced by the liver and protects the lungs from Neutrophil Elastase  Less A1AT in blood ->The elastase dissolves alveolar septae resulting in COPD <> Important when presented with pt who has COPD and has only smoked for a few years /Mutant A1AT protein is not secreted into the blood stream.->It accumulates in the liver cells , resulting in cirrhosis in early adulthood<>High risk of hepatocellular carcinoma several forms and degrees of deficiency; the form and degree depend on whether the sufferer has one or two copies of a defective [allele](https://en.wikipedia.org/wiki/Allele). In the literature it has been described as either a [recessive](https://en.wikipedia.org/wiki/Recessive) or [co-dominant trait](https://en.wikipedia.org/wiki/Dominance_%28genetics%29) as there is some evidence that smoking heterozygotes are affected |
| Sickle cell anemia | **A/R****GAG(glu)->****GTG(val)** | RBCs(10-20days)/heterozygotes usually silent..requires > 90% HbS to sickle in systemic vasculature exception is in the renal papilla where oxygen tension is low enough to induce sickling but sometimes renal papillary necrosis /point mutation in beta-globin chain/allele for the disease is codominant with the normal allele/\*\*(homozygotes -> vaso-occlusive crises : Chest pain , bone pain/Fever, stroke/Abdominal pain ->Gallstones /Dactylitis ->painful swelling of the hands and feet)\*\* \*\*NOTE:THERE’S MORE DETAILS IN THE SLIDES ABOUT THE PATHOGENISIS OF THIS DZ I skipped them (L20S9-16)\*\*/\*\*TX: Antibiotics /Pain-relieving Medications/Supplemental Oxygen/Blood Transfusions/Health maintenance starts with early diagnosis.\*\*  |
| Thalasemia | **A/R****Ch16->alpha****Ch11-> beta** | absence or errors in genes responsible for production of hemoglobin/Reduce fertility or even infertility, jaundice, paleness, poor appetite/Thalassemia Major; Bone Changes& protuberant spleen..benefits by transfusions /without BT-> survival until 7-8 yo,with>25 yo/ \*\*IRON CHELATION because Iron accumulates in the liver *(> liver failure)*/ in the endocrine glands (*hypogonadism, hypoparathyroidism, diabetes, other hormonal deficiencies)*/ in the heart *(heart failure; the* *major cause of death)\*\** |
| CFThis one is important  | **A/R****Ch7 (7q31.2)** | CFTR closed/more than 900mutations/affects sodium channels -> respiratory and digestive problems &Defective Cl channel / respiratory symp. More in adulthood -> abnl thick mucus into lungs,Pulm infections (P. *aeruginosa* and S. *aureus*)Chronic bronchitis, bronchiectasis, chronic sinusitis,chronic& productive cough,dyspnea on exertion,hemoptysisGI symp. More in infancy ->chronic, frequent diarrhea ,greasy stool with flatulence from malabsorption secondary to pancreatic insufficiency,can lead to rectal prolapsed ,meconium ileus( It is extremely sticky and causes the bowel to be blocked at birth) in infants (15%) , pancreatitis(thick mucus in the ducts) .others\*\*thick mucus in the liver also ,pancreatic insufficiency, male infertility (absence of vas deferens),calcium oxalate kidney stones secondary to fat malabosorption-> advise decreased Calcium in DietSome difficulty breathing ,Tiredness, lethargy or an impaired exercise ability ,Frequent visits to the toilet ,Salt loss in hot weather which may produce muscle cramps or weakness ,Poor appetite \*\*/\*\*Diagnosis: 1.Increased concentration of Cl in sweat test ( 1st test to be done )2.Genetic Testing is not sensitive (more than 900 mutation in CFTR gene)3.Nasal Potential Test is confirmatory\*\*/There is no cure for Cystic Fibrosis and treatment can slow progression of the disease /One in 25 people carry the gene ->with no symptoms/usually diagnosed at birth /not contagious /occurs in males and femalesTx: Chest physiotherapy /Antibiotics /Inhalations via a compressed air pump and nebuliser /Enzyme replacement capsules with meals and snacks /N-acetylcysteine to loosen mucus plugs/A well balanced diet high in protein, fat and calories/Supplementary vitamins/Salt supplements/Regular exerciseIf presented with . . . THINK CF!(Newborn with meconium ileus (90% will have CF)or failure to thrive/Fat soluble vitamin deficiency/Pancreatic insufficiency) |
| PKU | **A/R****Ch12** **rare** | Defect in phenylalanine hydroxylase which converts Phenylalanine to Tyrosine/Excess phenylalanine in the body will result in mass production of phenylpyruvic acid->cannot be absorbed by the kidney and enters cerebrospinal fluid and then the brain causing severe mental retardation/phe is essential AA and is found in nearly all foods which contain protein, dairy products, nuts, beans, tofu… etc/patients cannot consume any product that contains aspartame/The mother's body is able to break down phenylalanine during pregnancy->infants are normal at birth, Mental retardation & seizures, Albinism,“musty and mousy odor” to urine and sweat,Increased muscle tone,Fair skin ,Vomiting, Active muscle tendon reflexes, If Untreated in Infants:Severe brain damage/Epilepsy/Behavioral Problems/Stunted growth /Very treatable diet low in Phe and high in Tyr(low protei)/Newborn screening is Mandatory! |
| TAY SACHS dz | **A/R****CH15** | Fatal/harmful quantities of a fatty substance called Ganglioside GM2 accumulate in the nerve cells in the brain/is caused by a decrease in the functioning of Hexosaminidase A enzyme(mutated gene) /c/f paralysis, dementia, blindness and even death |
| PARKINSON’S DISEASE | **A/R** | neurological condition that has a genetic component next to Alzheimer’s/ as age increases->higher chance for developing the dz/DOPAMINE chemical produced in the middle part of the brain that is responsible for organizing coordinated movements and to send this signal to the control centers of the brain -> In Parkinson's chemical production less and functioning starts to shut down slowly and patient begins to lose control over vital voluntary movement/Symptoms; Memory loss, blurriness and lack of postural stabilityVERY IMPORTANT NOTE FROM THE DOCTOR ; WE GIVE THE PATIENT DOPA NOT DOPAMINE . |
| ALZHEIMER’S |  | form of dementia that causes changes in the brain/ Also affects a person’s memory, mood and behavior/ over 65/There is no specific -> physician are able to look at a person medical history and give a physiological and memory tests to see how efficient the brain is/Symptoms; Memory loss etc IMPOTRTANT : abnormal tau accumulates in specific brain regions involved in memory->Beta-amyloid clumps into plaques between neurons |
| Down Syndrome | **Trisomy** **Ch21****Most common chromosomal disorder and cause of congenital mental retardation** | 1.95% of cases due to meiotic nondisjunction of homologous -> Associated with advanced maternal age (1:1500 at maternal age 20-24##1: 210 at maternal age 35-39##1: 25 at maternal age >45)..2. 4% of cases due to Robertsonian translocation (Long arm of chrom 21 is attached to another chromosome and is kept diploid during gametogenesis)3. 1% of cases due to Down mosaicism /(cells within the same person have a different genetic makeup-> affect any type of cell, including:Blood cells,Egg and sperm cells (gametes),Skin cells)/Diagnosis :triple screen1.decr a-fetoprotein, decr estriol, incr. b-hCG 2.Quad screen is (.1) plus inhibin A (incr is +)3.U/S shows increased nuchal translucency/ c/f: Mental retardation, flat facies, prominent epicanthal folds, simian crease, duodenal atresia, congenital heart dz (septum primum type ASD), hypotoniashort stature, heart defects, and mental disability, increased risk of infection /increased risk of ALL and Alzheimer's dz /1 in 800 children born in the U.S/There is no single, standard treatment for Down syndrome. Treatments are based on each individual's physical and intellectual needs as well as his or her personal strengths and limitations.1.Physical therapy ->exercises that help build motor skills, increase muscle strength, and improve posture and balance2.Speech-language therapy improve their communication skills and use language more effectively.3.Occupational therapy -> adjust everyday tasks and conditions to match a person's needs and abilities.4.Emotional and behavioral therapies work to find useful responses to both desirable and undesirable behaviors |
| Turner's syndrome | **XO (1 X FM)** | short height, webbed/Bull neck, lack of underarm and pubic hair, and underdeveloped ovaries , and broad chest, Individuals are sterile, and lack expected secondary sexual characteristics, Mental retardation typically not evident |
| Kleinfelter’s syndrome | **XXY** | Male/ tall height, low IQ scores, speech and language difficulty,development of breast tissue normally seen in females,Little body hair is present, have small testes, Infertility results from absent sperm,Evidence of mental retardation may or may not be present /Disorder occurring due to nondisjunction of the X chromosome(The Sperm containing both X and Y combines with an egg containing the X, results in a male child,The egg may contribute the extra X chromosome) |
| Patau syndrome | **trisomy** **ch 13** | Heart defects, abnormalities of the eyes, ears, brain and spinal cord, cleft palate and/or lip, small head, low IQ scores, additional fingers and toes, 95% mortality in the first year of life, children rarely live past a few months |
| Edward’s Syndrome | **trisomy** **ch18** | Slow growth before birth, low birth weight, abnormal organ growth, heart defects, small head, 90-95% mortality rate during the first year->1 in 12 babies will survive beyond one year & they will live with severe physical & mental disabilities |
| SEVERE COMBINE IMMUNODEFICIENCY(SCID) | **Half liked to X (passed by mother)** **All forms are inherited**  | ALYMPHOCYTOSIS,GLANZMANN–RINIKER SYNDROME,SEVERE MIXED IMMUNODEFICIENCY SYNDROME,THYMIC ALYMPHOPLASIA /group of rare, sometimes fatal, congenital disorders characterized by little or no immune respons due to defect in the specialized white blood cells (B- and T-lymphocytes->>recurrent infections such as pneumonia, meningitis and chicken pox, and can die before the first year of life/ invasive, new treatments such as bone marrow and stem-cell transplantation save as many as 80% of SCID patients /commonly known as "bubble boy" cause famous boy David Vetter, lived in a sterial bubble and diest at 12 from unscreened EBV right after his newly transplanted bone marrow from his sister, an unmatched bone marrow donor / (TYPES : X-linked severe combined immunodeficiency/Adenosine deaminase deficiency/Purine nucleoside phosphorylase deficiency/Reticular dysgenesis /Omenn syndrome/Bare lymphocyte syndrome/JAK3{Janus Kinase-3}.) |
| AUTISM | \***Complex,****polygenic** **and multifactoral** #**Highly heritable**#**Gene-environment interaction**\*Vaccines | Severe ->from an array of the Autism Spectrum Disorders (ASD),another common form of ASD is Asperger Syndrome/Developmental disorder affects parts of brain, notably the amygdala {are almond-shaped groups of nuclei located deep and medially within the temporal lobes of the brain}, hippocampus{plays important roles in the consolidation of information from short-term memory to long-term memory},and cerebellum, immune system, and gastrointestinal tract/1 out of 150 /males>females/ c/f : difficulties with social interaction, problems with verbal and nonverbal communication, repetitive behaviors or narrow, obsessive interests, behaviors can range in impact from mild to disabling.  |
| Prader-Willi | Deletion of normally active PATERNAL allele15q(11-13) | Mental retardation/Obesity/Hypogonadism /Hypotonia /At birth usually demonstrates "floppy baby" with "undescended testicles"  |
| Angelman’s syndrome “Happy Puppet Syndrome” | Deletion of normally active MATERNAL allele15q(11-13) | Mental retardation/ seizures/ataxia/innapropriate laughter .. AS is named after a British [pediatrician](https://en.wikipedia.org/wiki/Pediatrician), [Harry Angelman](https://en.wikipedia.org/wiki/Harry_Angelman), 1965   |

Ch16 : APKD/thalasemia

Note: Cri du chat, and VHL dz are not included in this sum
Also colour blindness-> X/R / patients can't see red or green coloured things

Ch15 : marfan’s /taysach/prader willi/AS
TNR : huntigton’s / fragile X s / Myotonic dystrophy