# 22q11.2 deletion syndrome

## Genetics

-Deletion of **~3Mb on 22q11.2; NAHR**

-AD, 90-95% de novo

-males = females

-complete penetrance

## Clinical findings/Dysmorphic features

-Congenital heart disease (74% of individuals; particularly **conotruncal defects**, **TOF**)

-Palatal abnormalities (69%)

-Learning difficulties (70%-90%)

-**Thymus hypo/aplasia** --> Immune deficiency (77%)

-Parathyroid hypo/aplasia --> **Hypocalcemia**

-Facial: micrognathia, ear anomalies, cleft palate, short palpebral fissures, short upper lip

## Etiology

-Prevalence 1:3000

## Pathogenesis

-Deleted region is flanked by low copy number repeats (LCRs)

-Contains TBX1, responsible for phenotype

## Genetic testing/diagnosis

-**FISH, MLPA, CMA; 5% with normal test result on FISH**

## Others

-most common microdeletion syndrome

-22q11.2 duplication syndrome with same region: normal to intellectual disability/learning disability, delayed psychomotor development, growth retardation, and/or hypotonia

# Alagille syndrome

## Genetics

-JAG1 (20p12, 95% of cases) and NOTCH2 (1p13-p11)

-AD, 50-70% de novo

## Clinical findings/Dysmorphic features

-**Bile duct paucity** --> Cholestasis (stop of bile [Galle] flow)

-Cardiac defect (most commonly **stenosis of the peripheral pulmonary artery** and its branches)

-Skeletal abnormalities (most commonly butterfly); pulmonic stenosis

-Eye: **posterior embryotoxin** (thickened and centrally displaced anterior border ring of Schwalbe)

-**Butterfly vertebrae**

-Developmental delay, failure to thrive

-Facial: broad forehead, deep-set eyes, pointed chin, straight nose with bulbous tip

## Etiology

-1:70,000

## Pathogenesis

-Truncated JAG1 unable to bind to the cell membrane resulting in functional haploinsufficiency

## Genetic testing/diagnosis

-Sequencing of JAG1 (>89%), JAG1 20p12 del FISH (~7%), NOTCH2 sequencing (1-2%)

## Others

-Variable expressivity with clinical features ranging from subclinical to severe

-Clinical Tests: Bile duct paucity on liver biopsy

-NOTCH signalling

# Brugada Syndrome

## Genetics

-Most common **SCN5A** (3p21; 15-30%), also 22 other genes (<1%)

-AD, except **KCNE5 (XLR)**

## Clinical findings/Dysmorphic features

-**ST-segment abnormalities** in leads V1-V3 on electrocardiogram

-Syncope (temporary loss of consciousness)

-Nocturnal agonal respiration

-High risk of ventricular arrhythmias and sudden death

-Mainly during adulthood (2 days to 85 yrs), mean age of sudden death: 40 yrs

-May present as SIDS or sudden unexpected nocturnal death syndrome (SUNDS)

## Etiology

-Prevalence of the disease in **endemic areas is on the order of 1:2,000**

## Pathogenesis

-SCN5A encodes the α-subunit of the cardiac sodium channel and is responsible for phase 0 of the cardiac action potential

-Pathogenic variants in SCN5A result in a decrease in Na+ current --> lack of expression of the mutated channel or accelerated inactivation of the channel

## Genetic testing/diagnosis

-Serial single-gene testing or gene panel

## Others

-In countries in Southeast Asia in which SUNDS is endemic, it is the second cause (following accidents) of death of men < 40 years

# Cardio-facio-cutaneous Syndrome

## Genetics

-**BRAF (~75%)**, MAP2K1 (encodes MEK1) and MAP2K2 (encodes MEK2)(~25%), and KRAS (<2%)

-**AD**, mostly de novo

## Clinical findings/Dysmorphic features

-**Cardiac**: pulmonic stenosis, **septal defects**, **hypertrophic cardiomyopathy**, arrhythmia

-**Facial** findings: high forehead, relative macrocephaly, bitemporal narrowing, hypoplasia of the supraorbital ridges, depressed nasal bridge with anteverted nares, highly arched palate, more coarse features and **more dolichocephaly (long head) than Noonan syndrome**

-Cutaneous abnormalities: xerosis (dry skin), hyperkeratosis, ichthyosis, eczema, ulerythema ophryogenes (rare cutaneous atrophic disorder

-Epicanthal folds and ptosis, ocular hypertelorism, **telecanthus** (increased distance between the medial canthi), down-slanting palpebral fissures,

## Etiology

-Overall prevalence not known; in Japan 1: 810,000

## Pathogenesis

-BRAF (serine/threonine protein kinase) is direct downstream effector of Ras --> proliferation, differentiation, motility, apoptosis, senescence

-BRAF has two known downstream effectors: MEK1 and MEK2

-BRAF pathogenic variants in CFC syndrome similar to somatic variants found in cancers

-Elevated kinase activity induce higher levels of MEK and ERK phosphorylation

## Genetic testing/diagnosis

-Multigene panel for RASopathies/Noonan spectrum disorders that includes BRAF, MAP2K1, MAP2K2, KRAS

## Others

-Most common BRAF pathogenic variant in cancer, p.Val600Glu, has not been identified in CFC syndrome, but a germline p.Val600Gly pathogenic variant has recently been reported in CFC

# Costello Syndrome

## Genetics

-**HRAS**

-AD; p.Gly12Ser: 81.3%

-Complete penetrance

## Clinical findings:

-Feeding issues, DD, ID, short stature, loose and soft skin; **curly or sparse, fine hair**

-Cardiac (hypertrophic cardiomyopathy, valvar pulmonary stenosis, arrhythmia)

-Facial findings: coarse facial features, full cheeks, full lips, large mouth, full nasal tip, epicanthal folds, wide nasal bridge, short full nose, deep, **hoarse or whispery voice**

-**Papillomata** (small wart-like growth on the skin) of the face and perianal region

## Etiology

-Rare (300 individuals reported worldwide)

-Birth prevalence is estimated at 1:300,000 in the UK

## Pathogenesis

-Pathogenic missense variants result in constitutive activation of the abnormal protein product --> increased signaling through Ras-MAPK and PI3K-AKT pathways

## Genetic testing/diagnosis

-Sequence analysis of **HRAS (only gene currently known)** --> pathogenic missense variants in 80%-90% of individuals with the clinical diagnosis

-Targeted analysis for pathogenic variants: **> 95% affect amino acid p.Gly12 or p.Gly13**

## Others

-No other phenotype is known to be associated with germline mutation of HRAS

-Approx. 15% lifetime risk for malignant tumors (**rhabdomyosarcoma and neuroblastoma, transitional cell carcinoma of the bladder**)

# Hereditary hemorrhagic telangiectasia

## Genetics

-**ACVRL1** (25-57%), **ENG** (39-59%), GDF2, SMAD4 (1-2%)

-AD; mostly inherited

## Clinical findings:

-**Epistaxis** (nosebleeds), spontaneous and recurrent (95%)

-**Mucocutaneous telangiectasias** (small blanchable red spots at characteristic sites, including lips, oral cavity, fingers, and nose) (80%)

-**Arteriovenous visceral malformation** (arteriovenous malformation lacks capillaries and consists of direct connections between arteries and veins)

-Hemorrhage is often the presenting symptom of cerebral AVM; exercise intolerance

## Etiology

-Overall incidence in North America is estimated at 1:10,000

-Elevated risk for DVT

## Pathogenesis

-Haploinsufficiency

## Genetic testing/diagnosis

-Diagnosis: >3 of the following clinical features: epistaxis (nose-bleeds), **mucocutaneous telangiectases**, visceral AVMs, and/or a family history of HHT

-Serial single-gene testing or gene panel

## Others

-Clinical: contrast echo for pulmonary AVM, head MRI for cerebral AVM, US for hepatic AVM

-Liver transplant if hepatic AVM is causing heart failure

# Holt-Oram Syndrome

## Genetics

-**TBX5**, **SALL4**

-AD, **85% de novo**

## Clinical findings

-**Malformation of the carpal bone(s) (100%)**

-Radial and/or thenar bones (left often more severe than right)

-**Thumb anomaly**

-Congenital heart malformation (75%): most often **atrial septal defect (ASD) and ventricular septal defect (VSD)**, cardiac conduction disease, arrhythmia (even if no CHD)

## Etiology

-**Most common heart-hand syndrome**; 0.7 and 1 per 100,000 births

## Pathogenesis

-TBX5 protein product is TF with important role in cardiogenesis and limb development

-Mutant TBX5 mRNAs degrades rapidly or transcripts with diminished DNA binding —> decreased gene dosage

## Genetic testing/diagnosis

-TBX5 sequencing (>70%), Del/Dupl analysis (<1%)

-More than 70% of ind. with clinical diagnosis have heterozygous pathogenic variant in TBX5

-Rarely: SALL4 mutations result in similar syndrome

## Others

-Variants at the 5' end of T-box (which binds the major groove of the target DNA sequence) with more serious cardiac defects vs. missense variants at 3' end of the T-box (which binds the minor groove of the target DNA) result in more pronounced limb defects

# Noonan syndrome with multiple lentigines (LEOPARD)

## Genetics

-**PTPN11**, **RAF1**, BRAF, MAP2K1

-AD

## Clinical findings/Dysmorphic features

-**Multiple lentigines**

-Cardiac abnormalities (particularly **hypertrophic cardiomyopathy**)

-Poor linear growth/short stature; pectus deformity; SNHL

-Variable degree of cognitive deficits

-**Café au lait macules (70%-80%)**

-Facial features: hypertelorism, down slanting palpebral fissures, low set ears

## Etiology

-Not known

## Pathogenesis

-**LoF mutations in PTPN11** ( **vs. Noonan: GoF**)

## Genetic testing/diagnosis

-**PTPN11 sequencing (90%), RAF1 (<5%)**, others rare

# Noonan Syndrome

## Genetics

-**PTPN11 (50%, pathogenic missense variant), SOS1 (13%),** KRAS (<5%), RAF1 (5%), NRAS, CBL, SHOC2, BRAF, RIT1 (5%), SOS2, MAP2K1

-AD, **affected parent in 30-70%**

## Clinical findings/Dysmorphic features

-Short stature

-Congenital heart defect (**50-80%; pulmonary valve stenosis**, **hypertrophic cardiomyopathy**)

-Ocular abnormalities (95%; strabismus, refractive errors, amblyopia, nystagmus)

-**Broad or webbed neck; f**eeding problems; unusual chest shape (superior pectus carinatum and inferior pectus excavatum); renal malformation

-Lymphedema, bleeding disorders, myeloproliferative disorder (**risk of leukemia**)

-DD of variable degree

## Etiology

-**1:1000 to 1:2500**

## Pathogenesis

-GoF mutations --> constitutive activation of the Ras MAP Kinase pathway

## Genetic testing/diagnosis

-Multigene panel is test of choice for an individual suspected of having Noonan syndrome

-Significant phenotypic overlap with cardio-facio-cutaneous syndrome and Costello syndrome

## Others

-Early term "Male Turner syndrome" incorrectly implied that condition is not found in females

-**Pulmonary valve stenosis + increased nuclear translucency == Noonan**

# Williams Syndrome

## Genetics

-Contiguous gene deletion syndrome, **ELN in the critical region, 1.5Mb, ~28 genes**, **7q11.23**

-**AD, majority of cases de novo**

## Clinical findings/Dysmorphic features

-Cardiovascular disease (elastin arteriopathy, **peripheral pulmonary stenosis**, **supravalvar aortic stenosis**, hypertension)

-Connective tissue abnormalities (hoarse voice, hernia, rectal prolapse, joint limitation or laxity)

-ID (usually mild) and unique personality characteristics

-Growth abnormalities; endocrine abnormalities (**hypercalcemia, hypercalciuria, hypothyroidism**, early puberty)

-Facial features: broad brow, bitemporal narrowness, **periorbital fullness**, lacy iris pattern, strabismus, short nose, **full nasal tip**, malar hypoplasia, **long philtrum, full lips**, wide mouth, small jaw, and prominent earlobes

## Etiology

-Prevalence of **1:7500**

## Pathogenesis

-ELN deletion causes the CV and CT problems, LIMK1 has been linked to the visuospatial construction cognitive deficit

## Genetic testing/diagnosis

-Detection of recurrent 7q11.23 contiguous gene deletion of the Williams-Beuren syndrome critical region (WBSCR) --> encompasses ELN

-Can be detected using **FISH or In/Del or microarray (~99%)**

## Others

-**Overfriendliness**, empathy, generalized anxiety, specific phobias, attention deficit disorder

# Ataxia-telangiectasia

## Genetics

-**ATM** on 11q22.3

-AR (**carriers with 4x increased risk for cancer and coronary artery disease**)

-**Amish founder mutation: c.1564\_1565delAG**

## Clinical findings/Dysmorphic features

-**Progressive gait and truncal ataxia** with onset between 1-4yo and progressively slurred speech

-**Oculomotor apraxia** (inability to follow an object across visual fields)

-**Choreoathetosis** (occurrence of involuntary movements, combination of chorea and athetosis)

-**Telangiectasias of the conjunctivae** (tissue that lines inside of eyelids and covers the sclera)

-**Immunodeficiency** and increased risk for malignancy (particularly leukemia and lymphoma)

## Etiology

-Prevalence in the US: 1:40,000-1:100,000 live births

## Pathogenesis

-ATM is activated by double-stranded DNA breaks --> coordinates cell-cycle checkpoints prior to repair, attaches near damage sites, recruits other repair proteins to damaged sites

-Most mutations LOF

## Genetic testing/diagnosis

-Sequence analysis of ATM first, followed by gene-targeted deletion/duplication analysis if only one variant is found --> 90% sequence analysis, 1-2% deletion/duplication

-Targeted analysis for ATM pathogenic variants in specific populations, i.e. Amish

## Others

-Most common cause of progressive cerebellar ataxia in childhood in most countries with low coefficients of inbreeding

-Individuals with **AT are sensitive to ionizing radiation**!

-Elevated AFP in blood

# Bloom’s syndrome

## Genetics

-BLM (15q26.1)

-AR

## Clinical findings/Dysmorphic features

-Severe pre- and postnatal growth deficiency; short stature throughout postnatal life

-**Sparseness of subcutaneous fat tissue** throughout infancy and early childhood

-Erythematous and sun-sensitive skin lesion of the face (**Butterfly rash**)

-Women may be fertile, but menopause occurs unusually early; **men are infertile**

-Immunodeficiency; increased risk of cancer (wide distribution of type and site (colon most common), often multiple primary tumors)

## Etiology

-**1/100 carrier frequency in AJ**

## Pathogenesis

-Abnormal DNA replication and repair leading to genomic instability --> **chromosome breakage**

## Genetic testing/diagnosis

-Identification of biallelic pathogenic variants in BLM

-**c.2207\_2212delinsTAGTTC in AJ (97%),** no del/dup reported

-If genetic testing is inconclusive --> increased frequency of sister-chromatid exchanges on specialized cytogenetic studies

## Others

-Normal intelligence

-Chromatid/chromosome breaks; **triradial and quadriradial figures**

-**Harlequin Chromosomes**

# Fanconi anemia

## Genetics

-FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, **BRCA2**, BRIP1

-**AR,** **AD (RAD51), XLR (FANCB)**

## Clinical findings/Dysmorphic features

-**Physical abnormalities (75%)**: short stature, abnormal skin pigmentation (40%), skeletal malformations of **upper and lower limbs (35%)**, microcephaly, ophthalmic and GI anomalies

-Progressive bone marrow failure: **pancytopenia** (typically in the 1st decade, 6-8 years)

-Incidence of **acute myeloid leukemia is 13%** by age 50 years (500-fold increase)

-Solid tumors (head, neck, skin, gastrointestinal tract, and genitourinary tract) more common

## Etiology

-Most common genetic cause of aplastic anemia and one of the most common genetic causes of hematologic malignancy

-Carrier frequency of **1:180 in North Americans**

## Pathogenesis

-Proteins encoded by the FA-related genes work together in pathway called "**the FA pathway**”

-Regulates cellular **resistance to DNA cross-linking agents**

## Genetic testing/diagnosis

-Increased chr breakage and radial forms of lymphocytes with **diepoxybutane and mitomycin C**

-Biallelic pathogenic variants in one of 18 genes, known to cause AR FA

-Heterozygous pathogenic variant in RAD51, known to cause AD FA

-Hemizygous pathogenic variant in FANCB, known to cause XLR FA

## Others

-**More common in females (1.2:1)**

-Biallelic path variants in BRCA2 associated with early-onset acute leukemia and solid tumors

# Congenital contractural arachnodactly (Beals syndrome)

## Genetics

-**FBN2** (Fibrillin 2) is only gene known

-AD; mostly inherited; some de novo

## Clinical findings/Dysmorphic features

-Marfanoid appearance; long slender fingers/toes; **crumpled ears**; **contractures of major joints** (knees and ankles) at birth; muscle hypoplasia; kyphosis/scoliosis; **severe/lethal: aortic dilation**

## Etiology

-Prevalence lower than Marfan syndrome

## Pathogenesis

-Fibrillin 2 is a glycoprotein of the extracellular matrix microfibrils --> co-distributed with fibrillin 1 in many tissues; precise function is not known

## Genetic testing/diagnosis

-FBN2 sequencing (75%)

# Ehlers-Danlos syndrome classic type (types I and II)

## Genetics

-**COL5A1 (75%-78%), COL5A2 (14%), COL1A1 (<1%)**

-**AD; 50% inherited, 50% de novo**

## Clinical findings/Dysmorphic features

-**Skin hyperextensibility; atrophic scarring;** generalized **joint hypermobility;** hypotonia; chronic pain; easy bruising; hernia (part of an internal organ bulges through a weak area of muscle)

-Aortic root dilation (more common in young individuals and rarely progressive)

## Etiology

-1:20,000

## Pathogenesis

-40%-50% of COL5A1 are **haploinsufficiency** --> half amount of normal type V collagen

-Small proportion COL5A1 variants affect the structural integrity of type V collagen --> production of functionally defective type V collagen (**dominant-negative variant**)

## Genetic testing/diagnosis

-Diagnosis of cEDS is established in a proband with the minimal clinical diagnostic criteria:

--> skin hyperextensibility and atrophic scarring and either GJH or ≥3 minor clinical criteria and

--> identification of a heterozygous pathogenic variant in COL5A1, COL5A2, or COL1A1

-COL5A1 null allele test on cDNA from a skin biopsy

## Others

-Beighton Criteria for GJH

-No genotype/phenotype correlations known

# Ehlers-Danlos syndrome hypermobility (type III)

## Genetics

-**Genes unknown**

-AD

## Clinical findings/Dysmorphic features

-Joint hypermobility; recurrent joint dislocation/subluxation; chronic joint or limb pain

-Soft or velvety skin with normal/slightly increased elasticity --> **Absence of skin or soft tissue fragility (vs. cEDS)**

-Easy bruising, high narrow palate, dental crowding, and low bone density

## Etiology

-Prevalence estimates ranging between 1:5,000 and 1:20,000

## Pathogenesis

-Abnormal dermal elastic fibers

## Genetic testing/diagnosis

-No biochemical or genetic tests clinically available

## Others

-**Least severe type of EDS**

# Ehlers-Danlos syndrome vascular (type IV)

## Genetics

-**COL3A1** (2q31)

-AD; **penetrance ~100%**

## Clinical findings

-**Usually no soft, doughy, stretchy skin/abnormal scars/large-joint hypermobility (vs. cEDS)**

-Major criteria: **arterial rupture, intestinal rupture, uterine rupture during pregnancy**

-Minor criteria: **thin, translucent skin**, easy bruising, thin lips and philtrum, small chin, thin nose, large eyes, aged appearance of hands, **small joint hypermobility**

## Etiology

-1:200,000

## Pathogenesis

-**COL3A1 encodes the proα1(III) chain of type III procollagen --> major structural component of skin, blood vessels, hollow organs**

-**Majority of identified pathogenic variants result in single amino-acid substitutions for glycine** in the Gly-X-Y repeat of the triple helical region of the type III procollagen molecule

-Pathogenic variants in COL3A1 --> structural alteration of type III collagen --> intracellular storage/impaired secretion of collagen chains

## Genetic testing/diagnosis

-Sequence analysis of COL3A1 (95%), then gene-targeted deletion/duplication analysis (~1%)

-Abnormalities in synthesis and mobility of type III collagen chains on biochemical analysis of type III procollagen from cultured fibroblasts when vEDS is suspected

-Individuals with COL3A1 null variants have 15y delay in onset of complications and improved life expectancy

# Ehlers-Danlos syndrome kyphoscoliotic (type VI)

## Genetics

-**PLOD1** (Procollagen-lysine,2-oxoglutarate 5-dioxygenase 1)

-**AR**; **penetrance 100%**

## Clinical findings/Dysmorphic features

-Major criteria: **congenital muscular hypotonia** (--> **progressive or non-progressive congenital or early-onset kyphoscoliosis**), GJH with dislocations/subluxations (shoulders, hips, knees)

-Minor criteria: skin hyperextensibility, skin fragility (easy bruising, friable skin, poor wound healing, widened atrophic scarring), **rupture/aneurysm of a medium-sized arteries**, osteopenia/osteoporosis, blue sclerae, scleral/ocular fragility/rupture, pectus deformity, marfanoid habitus

-Life span may be normal, but risk for rupture of medium-sized arteries

## Etiology

-Disease incidence of approximately 1:100,000 live births

## Pathogenesis

-Enzyme deficiency leads to **deficiency in hydroxylysine-based pyridinoline** **crosslinks in types I and III collagen**

## Genetic testing/diagnosis

-Sequencing of PLOD1 (67%), PLOD1 deletion/duplication analysis (33%)

# Loeys-Dietz Syndrome (LDS)

## Genetics

-**TGFBR2 (55-60%), TGFBR1 (20-25%)**, TGFB2 (5-10%), **SMAD3** (5-10%), **SMAD2** (1-5%), TGFB3 (1-5%), deletions and duplications are rare

-AD

## Clinical findings/Dysmorphic features

-Vascular findings: **cerebral, thoracic, abdominal arterial aneurysms and/or dissections**

-Skeletal manifestations: pectus excavatum or pectus carinatum, scoliosis, joint laxity, arachnodactyly, **talipes equinovarus** (clubfoot)

-75% have **LDS type I** with **craniofacial** manifestations (ocular **hypertelorism**, **bifid uvula**/cleft palate, **craniosynostosis**)

-25% have **LDS type II** with **cutaneous** manifestations (velvety and translucent skin; easy bruising; widened, atrophic scars)

## Etiology

-Not known

## Pathogenesis

-**Increased TGFβ signaling** in the vasculature of persons with LDS

-SMAD3, TGFB2, TGFB3 --> predicted loss of function variants somehow still increase TGFβ-signaling in aortic walls of affected individuals

## Genetic testing/diagnosis

-Gene Panel

# Marfan Syndrome

## Genetics

-**FBN1**

-AD; **75% inherited, 25% de novo**

## Clinical findings/Dysmorphic features

-CV: **dilation or dissection of the ascending aorta**

-Skeletal: pectus carinatum or excavatum; **reduced upper to lower segment or arm span to height**; scoliosis; **pes planus**; high palate; reduced elbow extension

-Eye: **ectopia lentis** (retinal detachment; in 60-70%); glaucoma; early cataracts (60%)

-**Lumbosacral dural ectasia** (widening/**ballooning of the dural sac** surrounding the spinal cord)

-Family history: pathogenic FBN1 variant or 1st degree relative with Marfan syndrome

-Major morbidity and early mortality because of cardiovascular system and dilatation of the aorta at the level of the sinuses of Valsalva

## Etiology

-**1:5,000-1:10,000**

## Pathogenesis

-Abnormal fibrillin-1 is believed to have **dominant-negative** activity

-Severe reduction of microfibrils in explanted tissues and in matrix deposited by cultured dermal fibroblasts

## Genetic testing/diagnosis

-Major involvement of two body systems and minor involvement of a 3rd

-Sequencing of FBN1 (90-93%), Deletion/Duplication (~5%)

-No family history:

--> Aortic root enlargement (Z-score≥2) + ectopia lentis/pathogenic variant/systemic score ≥7

--> Ectopia lentis + pathogenic FBN1 variant previously associated with aortic enlargement

-Family history:

--> Ectopia lentis or systemic score ≥7 or aortic root enlargement (Z-score≥2 in those ≥20yo or Z-score≥3 in those ≤20yo)

## Others

-Beta blockers/Losartan for aortic root dilation; bracing/surgery for scoliosis; annual dilated eye exam and echocardiography

-Surgical repair of the aorta is indicated once:

--> the **maximal measurement approaches 5.0 cm** in adults or older children

--> the **rate of increase of the aortic root diameter approaches 1.0 cm per year**

# Hypohidrotic ectodermal dysplasia

## Genetics

-**EDA** (Ectodysplasin A), **EDAR**, EDARADD

-Mostly **XLR** (**EDA:95%**), AD or AR (5%)

## Clinical findings/Dysmorphic features

-Peeling skin and perioral hyperpigmentation at birth

-**Hypotrichosis** (sparseness of scalp and body hair)

-**Hypohidrosis** (reduced ability to sweat)

-**Hypodontia** (congenital absence of teeth)

## Etiology

-**1 in 5,000 – 1 in 10,000**

## Pathogenesis

-**Defective ectodysplasin A** cannot be activated to mediate the cell-to-cell signaling that regulates **morphogenesis of ectoderm**

## Genetic testing/diagnosis

-Diagnosed after infancy on the basis of physical features in most affected individuals

-Hemizygous EDA pathogenic variant in an affected male

-Biallelic EDAR, EDARADD, or WNT10A pathogenic variants in affected male or female

-EDA sequencing (~95% XL HED), EDAR and EDARADD sequencing

## Others

-**Wigs and saliva substitutes**

# Hidrotic ectodermal dysplasia 2

## Genetics

-**GJB6** (13q12) only known gene

-AD

## Clinical findings/Dysmorphic features

-Malformed, thickened, small nails

-**Hypotrichosis** (partial or total alopecia)

-**Palmoplantar hyperkeratosis**

-**Normal sweating and normal teeth**

## Etiology

-Common in the **French-Canadian** population of southwest **Quebec**

## Pathogenesis

-Helps to form a gap junction channel which mediates **ion diffusion**

-Mutations affect trafficking of the protein and thus the formation of the gap junction

## Genetic testing/diagnosis

-Targeted analysis for the four known pathogenic variants in GJB6 (**p.Gly11Arg, p.Val37Glu, p.Asp50Asn, p.Ala88Val**); account for 100%

# Incontinentia pigmenti

## Genetics

-**IKBKG (aka NEMO)**

-**XLD (most male fetuses miscarry); 65% de novo**

## Clinical findings/Dysmorphic features

-Major: **Four stages of skin changes**: **1) erythema, 2) blister, 3) hyperpigmented streaks, 4) atrophic skin patches**

-Minor: **small or malformed teeth**, **alopecia**, woolly hair, nail ridging or pitting, **retinal neovascularization** causing retinal detachment

-Neurologic findings can including seizures, ID, DD

## Etiology

-0.6–0.7/1,000,000; at birth of 1.2/100,000 in the EU; **female:male ratio is 20:1**

## Pathogenesis

-**Lack of NF-kappa beta activation --> cells are sensitive to proapoptotic signals --> apoptosis**

## Genetic testing/diagnosis

-Most efficacious molecular genetic testing approach is single-gene testing --> **common 11.7-kb IKBKG deletion** first --> sequence analysis of IKBKG --> gene-targeted deletion/duplication

-Long-range PCR, southern blot

## Others

-Clinical test: **free melanin granules if hyperpigmented streak biopsied**

-**Males with IP have had either a 47,XXY karyotype or somatic mosaicism**

-Normal life expectancy for females

# Oculocutaneous albinism

## Genetics

-**TYR (null variants cause OCA1A, pathogenic variants cause OCA1B)**

-OCA2 (only gene known to cause OCA2, AR; in PWS/AS region)

-TYRP1 (causes OCA3, AR)

-SLC45A2 (only gene to cause OCA4, AR)

-GPR143 (causes X-linked ocular albinism)

## Clinical findings/Dysmorphic features

-**OCA1A** (**no melanin synthesis**): nystagmus, reduced iris pigment, foveal hypoplasia, reduced visual acuity, strabismus, white hair and skin, translucent iris

-**OCA1B** (some melanin synthesis): **milder** eye and skin manifestation than OCA1

-**OCA2:** ocular problems same as OCA1 but **better vision**, range of skin and eye pigmentation from minimal to near normal

-**OCA3**: gene product necessary to synthesize black/brown eumelanin but not reddish pheomelanin --> phenotype for OCA3 is a milder OCA, **reddish pigment** in hair and skin

-**OCA4**: very similar to OCA2

-X-linked OCA: minor skin manifestations; congenital and persistent visual impairment in affected males

## Etiology

-OCA1: 1:40,000

-**Carrier frequency for OCA1 is approximately 1 in 100**

## Pathogenesis

-**Tyrosinase** is the key enzyme, catalyzing several steps in **melanin synthesis**, including the essential first and second steps: the **hydroxylation of tyrosine to L-DOPA** and the oxidation of L-DOPA to DOPA quinone

-Most variants of TYR are missense variants that produce enzyme with no catalytic activity

## Genetic testing/diagnosis

-Sequencing of TYR for OCA1A and OCA1B, Deletion/Duplication analysis (<1%)

# X-linked adrenal hypoplasia congenita

## Genetics

-**NR0B1** (Xp21.3-Xp21.2)

-XLR

-**X-linked AHC** vs. **Xp21 deletion** (includes deletion of **NR0B1** (causing X-linked AHC) and **GK** (causing glycerol kinase deficiency), in some cases deletion of **DMD**)

-**1/3 contiguous gene deletion with GK, DMD; 2/3 isolated AHC (50% de novo)**

## Clinical findings/Dysmorphic features

-Acute onset of **adrenal insufficiency** (**Nebenniere**): **hyperkalemia** (high K+ in blood), **acidosis**, **hypoglycemia** (low blood sugar), shock

-Adrenal insufficiency is infantile onset (~ 3 wks) in ~60%; childhood onset (~1-9 years) in ~40%

-Cryptorchidism, delayed puberty

-Xp21 deletion might cause DD

## Etiology

-Current estimates are fewer than 1:70,000 males

## Pathogenesis

-OB1 is a neg. regulator of nuclear receptor pathways; defective nuclear localization of protein

## Genetic testing/diagnosis

-Diagnosis is established by detection of either a hemizygous pathogenic variant in NR0B1 or a non-recurrent Xp21 deletion that includes NR0B1

-Sequencing: 75%, deletion/duplication analysis: 25%

## Others

-**Glycerol kinase deficiency**: elevated serum concentrations of glycerol (**hyperglycerolemia**) and triglycerides (**pseudohypertriglyceridemia**)

# 21-Hydroxylase-Deficient Congenital Adrenal Hyperplasia

## Genetics

-**CYP21A2** (6p21.3)

-AR

## Clinical findings/Dysmorphic features

-**Adrenal glands produce excess androgens** (male sex hormones) --> **virialized female** **or** **childhood virilization in males**; precocious puberty or adrenarche (early); ambiguous genitalia

-Infant with **Na+ losing crisis at birth**, life-threatening (adrenal glands make too little aldosterone --> body unable to retain enough Na+ --> lost in urine)

-Non-classic form: moderate enzyme deficiency with variable postnatal virilization, **no salt wasting**, but rare cortisol deficiency

## Etiology

-Overall incidence of 1:15,000 live births for the classic form of 21-OHD

-Non-classic 21-OHD CAH: 1:100

## Pathogenesis

-Deficient function of **21-hydroxylating cytochrome 450** --> cortisol production pathway is blocked --> accumulation of 17-hydroxyprogesterone (17-OHP) --> 17-OHP is shunted into the intact androgen pathway --> 17,20-lyase enzyme converts the 17-OHP to Δ4-androstenedione --> converted to androgens

## Genetic testing/diagnosis

## -Classic 21-OHD CAH: clinical features + elevated serum 17-OHP + elevated adrenal androgens

## -Non-classic 21-OHD CAH: comparison of baseline serum 17-OHP and ACTH-stimulated serum 17-OHP or early morning elevated 17-OHP

-Sequencing: ~70-80%, Deletion/Duplication: ~20-30%

## Others:

-Newborn screening for 21-OHD CAH serves two purposes:

--> identify infants with classic form of 21-OHD CAH --> risk for life-threatening salt-wasting

--> expedite diagnosis of females with ambiguous genitalia

-NBS rarely detects individuals with non-classic form of 21-OHD CAH

# Androgen insensitivity syndrome (Testicular feminization)

## Genetics

-AR (Androgen receptor; Xq11-q12)

-XLR

## Clinical findings/Dysmorphic features

-Evidence of **feminization (i.e. undermasculinization) of ext. genitalia;** abnormal secondary sexual development; infertility in those with 46, XY karyotype

-**Spectrum**: complete androgen insensitivity syndrome (**CAIS**), with typical female genitalia --> partial androgen insensitivity syndrome (**PAIS**) with predominantly female/predominantly male/ambiguous genitalia --> mild androgen insensitivity syndrome (**MAIS**) with normal male genitalia

## Etiology

-2:100,000 to 5:100,000 for CAIS

## Pathogenesis

-Nearly all missense variants in the **androgen-binding domain impair androgen binding** and impair transactivation by the AR --> male sex hormone androgen cannot bind/activate

-Missense variants in the zinc fingers or α-helical portions of the DNA-binding domain impair binding to a sequence of regulatory nucleotides known as an androgen response element

## Genetic testing/diagnosis

-No formal diagnostic criteria for identifying AIS have as yet been published

-Single gene sequencing of AR: 97%, Deletion/Duplication analysis: 3%

# Isolated Gonadotropin-Releasing Hormone Deficiency (Kallman syndrome)

## Genetics

-More than 25 genes; **KAL1 (ANOS1)**, FGFR1 (AD), CHD7

-X-linked, AD, AR

## Clinical findings/Dysmorphic features

-**Low** serum concentrations of the **gonadotropins** **LH** (luteinizing hormone) and **FSH** (follicle-stimulating hormone) in the presence of low circulating concentrations of sex steroids

-**Typical IGD (40%): normal sense of smell vs. Kallman syndrome (60%): impaired sense of smell/anosmia**

-Absent or partial puberty at presentation in adolescents

-Low serum testosterone or estradiol on biochemical testing

-Type 1 can also include mirror hand movements, ataxia, GU anomaly, high palate, pes cavus

## Etiology

-Incidence of KS of 1:30,000 in males and 1:125,000 in females

-Males predominate with a **male-to-female ratio of nearly 4:1**

## Pathogenesis

-Impaired function of **anosmin** results in a migratory defect of the olfactory and GnRH neurons from the olfactory placode during development

-Abnormal FGFR1 gene products result in impaired receptor signaling

## Genetic testing/diagnosis

-X-linked: Sequencing of ANOS1 (KAL1) is the highest-yield molecular test

-Sequencing ANOS1 (KAL1) (5-10%), FGFR1 (8-16%)

## Others

-Treatment: Normalize gonadal steroid levels

# Klinefelter syndrome

## Genetics

-**47,XXY** and its variants 48,XXXY, 49,XXXXY, and 46XY/47,XXY mosaicism in male patients

-Klinefelter syndrome is **not inherited**

## Clinical findings/Dysmorphic features

-Hypotonia; tall stature; slightly delayed motor and language skills; learning difficulties (better receptive language skills than expressive); reduced testosterone (plateaus age 14); small **fibrosed testes**; **azoospermia and infertility; g**ynecomastia (enlarged breast tissue) increased cholesterol; higher risk of autoimmune disorders and mediastinal germ cell tumors (1% risk); increased risk of male breast cancer and type 2 diabetes

## Etiology

-**1 in 500 to 1,000 newborn boys**

## Genetic testing/diagnosis

-In some cases, features are so mild that it is not diagnosed until puberty or adulthood

-Karyotype/FISH

## Other

-**Maternal and paternal meiotic non-disjunction equally distributed in KS (nearly 50 % each)**

-**Additional maternal X chromosome: non-disjunction in either the first or second meiotic division** is most likely to have occurred

-**Additional paternal X: can only derive from a non-disjunction in the first meiotic division**, since meiosis II error will result in either XX or YY gametes and therefore XXX or XYY zygotes

# Fibrous Dysplasia (McCune-Albright Syndrome)

## Genetics

-**GNAS** (**Guanine nucleotide-binding protein G**(s), alpha subunit; 20q13.2)

-Early embryonic postzygotic **somatic activating pathogenic variants**

## Clinical findings/Dysmorphic features

-**Abnormal scar-like (fibrous)** tissue in the bones (polyostotic fibrous dysplasia)

-Involvement of skin, skeleton, certain endocrine organs

-**Polyostotic fibrous dysplasia** --> high risk of fractures, deformity, functional impairment, pain

-Large irregular **café au lait (**“**coast of Maine”)**

-**Cranial foramina thickening** (may cause deafness and blindness)

-Gonadotropin-independent precocious puberty (early)

-Thyroid lesions with characteristic ultrasonographic features (+/- non-autoimmune hyperthyroidism)

## Etiology

-1:100,000 to 1:1,000,000

## Pathogenesis

-GNAS variants at residues p.Arg201 and p.Gln227 disrupt the activity of intrinsic GTPase, causing **constitutive activity and inappropriately increased cAMP signaling**

## Genetic testing/diagnosis

-**Targeted analysis of codons p.Arg201 and p.Gln227**

-Somatic mosaicism for pathogenic missense variants at p.Arg201 has been identified in more than 95% of all published reports of FD/MAS

-Sample of affected tissue --> ~80% (yield) vs. ~20%-30% in peripheral blood lymphocytes

## Others

-Not inherited (somatic mutations)

-Spectrum of FD/MAS: asymptomatic incidental findings to neonatal lethality

# 6q24-related transient neonatal diabetes mellitus

## Genetics

-Genetic aberrations of the **imprinted locus at 6q24**

## Clinical findings/Dysmorphic features

-Severe intrauterine growth retardation; shortage of the hormone insulin; **hyperglycemia** in the neonatal period in a term infant, resolves by age 18 months; d**ehydration; absence** **of ketoacidosis; macroglossia** and umbilical hernia may be present

-Hypotonia, congenital heart disease, deafness, neurologic features (epilepsy), renal malformations

## Etiology

-1:400,000

## Pathogenesis

-Overexpression of imprinted, paternally expressed genes PLAGL1 and HYMAI

-Three different genetic mechanisms --> twice the normal dosage of PLAGL1 and HYMAI:

(1) **paternal uniparental disomy of chromosome 6**

(2) **duplication of 6q24 on the paternal allele**

(3) **hypomethylation of the maternal PLAGL1 TSS**

## Genetic testing/diagnosis

-6q24-TNDM is caused by overexpression of the imprinted genes at 6q24 (PLAGL1 and HYMAI)

-DMR (i.e., PLAGL1 TSS alt-DMR) is present within the shared promoter of these genes

-Normally: expression of PLAGL1 and HYMAI is silenced on maternal allele and only paternal alleles of PLAGL1 and HYMAI are expressed

## Others

-**Biallelic ZFP57** pathogenic variants account 50% of TNDM associated with a **multilocus imprinting disturbance (MLID)**

**-**ZFP57 variants result in inactivation of ZFP57 --> important in maintaining genomic imprinting at the DMR of PLAGL1 and HYMAI

# Turner syndrome

## Genetics

-**SHOX haploinsufficiency** because of numeric or structural aberration of the sex chromosome

-**SHOX (Xpter-p22.32)**

## Clinical findings/Dysmorphic features

-Short stature; gonadal dysgenesis; webbed neck; low posterior hairline; broad chest; widely spaced nipples; renal anomalies; cardiovascular anomalies (dilated aortic root, **coarctation of the aorta**, **bicuspid aortic valve** [30%]); hypertelorism and low set ears; **lymphedema; l**ack of secondary sex characteristics; amenorrhea; usually normal intelligence; SNHL; Crohn’s disease; renal malformation; osteoporosis

## Etiology

-TS occurs in **1:2,500 to 1:3,000 live female births**

-**99% of 45,X pregnancies lead to spontaneous abortions (Trisomy 21, only 80%)**

## Genetic testing/diagnosis

-**45,X (50%), 46,X,i(Xq) (15%), 45,X/46,XX mosaic (15%)**, **45,X/46,X,i(Xq) mosaic (5%)**

-Karyotype

## Others

-Lifelong cardiac follow-up, at risk for aortic dilation and dissection with bicuspid aortic valve

-Cystic hygroma on

# Blepharophimosis, ptosis, and epicanthus inversus (BPES)

## Genetics

-**FOXL2** (3q23) is only gene associated with BPES

-AD; 50% de novo

## Clinical findings/Dysmorphic features

-Complex eyelid malformation invariably characterized by four major features:

1) **Blepharophimosis** (horizontally narrow palpebral fissure, from canthi to canthi),

2) **Ptosis** (drooping of the upper eyelid)

3) **Epicanthus inversus** (fold over canthi comes from below)

4) **Telecanthus** (increased distance between the medial canthi of the eyes with normal inter-pupillary distance)

-BPES type I: + premature ovarian failure (POF), BPES type II: only the four major features

## Etiology

-unknown

## Pathogenesis

-FOXL2 protein belongs to the large family of winged-helix/forkhead transcription factors

-**Haploinsufficiency** of FOXL2 (82% of pathogenic variants are LoF)

-FOXL2 is a transcriptional repressor of granulosa cell differentiation

-Mutations cause **accelerated differentiation of granulosa cells** and secondary depletion of the primordial follicle pool

## Genetic testing/diagnosis

-FOXL2 sequencing: 75%, Deletion/Duplication: 10-15%, Regulatory region: 5%

# Congenital hearing loss - Connexin 26 and 30

## Genetics

-**GJB2/DFNB1** (Connexin 26), **GJB6/DFNA3** (Connexin 30); **13q11-12**

-AR

## Clinical findings/Dysmorphic features

-Congenital mild to profound sensorineural hearing loss (cause lies in the inner ear or sensory organ (cochlea and associated structures) or the vestibulocochlear nerve (cranial nerve VIII))

## Etiology

-DFNB1: ~50% of congenital severe-to-profound AR nonsyndromic hearing loss in the US

-14:100,000

## Pathogenesis

-**Homozygous or compound heterozygous for GJB2 pathogenic variants (99%)**

-Compound heterozygous for one GJB2 pathogenic variant and one of three large deletions that includes sequences upstream of GJB2 and a portion of GJB6 (<1%)

## Genetic testing/diagnosis

-NBS

-Sequencing of GJB2: >99%, Deletion/Duplication: <1%

-Common GJB2 pathogenic variants: **35delG Caucasians; 235delC Asians; 167delT, del35G and Cx30 gene deletion in AJ**; Val37Ile in Thailand

## Others

-Rare patients can have AD Cx26 hearing loss which can include skin findings: palmar-planter keratoderma, **KID syndrome** (keratitis-ichthyosis-deafness)

# Hermansky-Pudlak Syndrome

## Genetics

-**AP3B1** (HPS2), AP3D1, BLOC1S3, BLOC1S6, DTNBP1, HPS1, HPS3, HPS4, HPS5, HPS6

-AR

-Proteins associate into four HPS protein complexes --> involved in intracellular vesicle formation and trafficking

## Clinical findings/Dysmorphic features

-**Oculocutaneous albinism**, **bleeding diathesis, granulomatous colitis (colon inflammation)**

-**Eye**: reduced iris pigment with iris transillumination, reduced retinal pigment, foveal hypoplasia with significant reduction in visual acuity, nystagmus (wandering eye movements), increased crossing of the optic nerve fibers

-**Pulmonary fibrosis** (early 30s; can progress to death within a decade) --> **HPS1, HPS2, HPS4**

-Neutropenia and/or immune defects primarily in ind. with variants in AP3B1 and AP3D1

## Etiology

-1-9 per 1,000,000

-Prevalence of **HPS1-related HPS in northwestern Puerto Rico is 1:1800**

## Pathogenesis

-Mechanism of pulmonary fibrosis, colitis, cardiomyopathy, renal failure unknown

-Likely associated with aberrant biogenesis of lysosome-related organelles in specialized cells

## Genetic testing/diagnosis

-Diagnosis: oculocutaneous albinism + **absence of platelet delta granules (dense bodies)**

-Multigene panel; biallelic pathogenic variants in AP3B1 (10%), AP3D1, BLOC1S3, BLOC1S6, DTNBP1, HPS1 (37%), HPS3 (12%), HPS4 (12%), HPS5 (10%), or HPS6 (17%) confirms the diagnosis if clinical features are inconclusive

-**HPS1**: **c.1470\_1486dup16 or HPS3 3.9kb deletion** in ind. from northwestern **Puerto Rican**

-**HPS3** splice site variant **c.1163+1G>A** can be performed first in individuals **AJ**

## Others

-Annual ophthalmologic examination; annual examination of the skin for solar keratoses (premalignant lesions), **basal cell carcinoma, squamous cell carcinoma**

-Annual pulmonary function testing in those older than age 20 years

# Jervell and Lange-Nielsen Syndrome

## Genetics

-**KCNQ1** (K+ channel protein; 11p15.5) and **KCNE1** (K+ voltage-gated channel; 21q22.1)

-AR (Heterozygotes at risk **for AD long QT a.k.a. Romano Ward syndrome**)

## Clinical findings/Dysmorphic features

-**Congenital severe-profound bilateral SNHL**

-**Prolonged QT interval** --> at risk for arrhythmia, syncope, and sudden death

## Etiology

-high (1:200,000) in North Europe --> founder variants

## Pathogenesis

-In cardiac cells: abnormal repolarization of the ventricular action potential

-In cochlear cells: abnormal depolarization of the auditory nerve

## Genetic testing/diagnosis

-LoF variants in: **KCNQ1** sequencing (90%), **KCNE1** (10%)

## Others

-Cochlear implants for HL, beta blockers, cardiac pacemakers, and/or implantable defibrillators

-Avoid QT prolonging drugs

# Leber Hereditary Optic Neuropathy

## Genetics

-**MTND1, MTND4, MTND6 (complex I subunits** of the mitochondrial respiratory chain)

-Mitochondrial inheritance

## Clinical findings/Dysmorphic features

-**Develops during young adult life -->** visual blurring in central visual field in one eye

-Similar symptoms appear in **the other eye an average of two to three months later**

-Visual acuity is severely reduced

-Visual field testing shows an enlarging dense central or centrocecal scotoma

-After the acute phase, the optic discs become atrophic

## Etiology

-In Northern Europe: 1:10,000 – 1:50,000

## Pathogenesis

-Focal degeneration of the retinal ganglion cell layer and optic nerve

## Genetic testing/diagnosis

-Bilateral, painless, subacute visual failure that develops during young adult life

-Common variants: **m.3460G>A in MT-ND1, m.11778G>A in MT-ND4, m.14484T>C in MT-ND6**

## Others

-**Males 4x more likely affected**

# Pendred syndrome

## Genetics

-**SLC26A4** (PDS) most common; FOX11, KCNJ10 in rare cases

-**AR**

## Clinical findings/Dysmorphic features

-SNHL that is **usually congenital** and often severe to profound

-**Vestibular dysfunction**, and temporal bone abnormalities (**bilateral enlarged vestibular aqueduct** with or without cochlear hypoplasia**; Mondini malformation**)

-**Goiter in 75%** though only 10% have abnormal thyroid function

## Etiology

-not known

## Pathogenesis

-**SLC26A4 is a chloride/iodide exchanger in the inner ear and thyroid** --> mutation leads to inner ear malformation and abnormal iodide processing in the thyroid

## Genetic testing/diagnosis

-Biallelic pathogenic variants in SLC26A4 or **double heterozygosity** for one pathogenic variant in SLC26A4 and one pathogenic variant in either FOXI1 or KCNJ10

-p.Leu236Pro (26%), p.Thr416Pro (15%), c.1001+1G>A (14%) --> 50% of variants in SLC26A4

## Others

-Pathogenic variants in SLC26A4 are the third most frequent cause of hearing loss

# Usher syndrome

## Genetics

-Multiple genes, majority of cases due to **MYO7A (Type 1) and USH2A (Type 2)**

-**AR**

## Clinical findings/Dysmorphic features

-Type I: congenital profound HL, balance problems, retinitis pigmentosa (RP) onset pre-puberty

-Type II: congenital mild-severe HL, normal balance, RP onset in teens-20’s

-Type III: progressive later onset HL, progressive balance problems, variable onset RP

## Etiology

-Prevalence may be as high **as 1 in 6,000**

## Pathogenesis

-Proteins part of “**Usher interactome**" --> localizing and organizing the assembly of larger protein complexes at the plasma membrane --> signal transduction, cell adhesion, subcellular transport --> one missing --> sensorineural degeneration occurs in the inner ear and the retina

-**MYO7A** is myosin --> migration of retinal pigment epithelial (RPE) melanosomes and phagosomes/differentiation, morphogenesis and organization of cochlear hair cell bundles

-RP is caused by **degeneration of rod and cone functions** of the retina

-For at least some genes: **inner hair cell function and structure** are affected in the ear

## Genetic testing/diagnosis

-Diagnosis of Usher syndrome type I: electrophysiologic and subjective tests of hearing and retinal function --> identification of biallelic pathogenic variants in one of six genes **(MYO7A (40-50%)**, USH1C, CDH23, PCDH15, USH1G, and CIB2) establishes diagnosis

-Type II: **USH2A sequencing (65%)**

## Others

-Digenic or oligogenic inheritance described

-MYO7A mutation can lead to AD deafness, AR deafness, or Usher syndrome

# Waardenburg syndrome

## Genetics

-**PAX3 (WS1/WS3)/** **MITF, SOX10, SNAI2** **(WS2)/** **EDNRB, EDN3, SOX10** **(WS4)**

-AD

## Clinical findings/Dysmorphic features

-Four types:

-**WS1**: **SNHL** (~60%), **heterochromic irides** (~30%), **white forelock** (~50%), early graying (~40%), **leukoderma** (also known as **Vitiligo**: loss of skin pigmentation; (~30%)), **dystrophia canthorum** (lateral displacement of the inner canthi), neural tube defect

-**WS2: like WS1 without dystrophia canthorum**

-**WS3**: like WS1 + limb hypoplasia or contracture, **carpal bone fusion** (middle hand), syndactyly

-WS4: Pigmentary abnormalities, hearing loss, Hirschsprung disease

## Etiology

- 1:20,000 to 1:40,000

-Approximately 3% of congenitally deaf children

## Pathogenesis

-Haploinsufficiency --> PAX3 is a homeobox TF involved in melanocyte development

## Genetic testing/diagnosis

-WS1: PAX3 sequencing --> 90%; Del/Dup --> 6%

## Others

-Hearing aids or cochlear implants

-Folic acid supplementation of pregnancies at risk for WS1 related neural tube defect

# Acute intermittent porphyria (AIP)

## Genetics

-**HMBS (11q23.3)**

-AD; only 1% de novo; low penetrance

## Clinical findings/Dysmorphic features

-Onset after puberty

**-Life-threatening acute neurovisceral** (neuronal system connected to internal organs) attacks

-Abdominal pain, muscle weakness, neuropathy, hysteria, anxiety, hepatocellular carcinoma

-No cutaneous findings

-More likely to present in women

## Etiology

-5 in 10,000 (but **penetrance is only ~1%)**

## Pathogenesis

-Partial deficiency of porphobilinogen deaminase (PBGD, encoded by HMBS): 3rd enzyme in **heme biosynthetic pathway**

-**Toxic delta-aminolevulinic acid (ALA) and PBG accumulation**

-Induction of hepatic ALA synthase activity

## Genetic testing/diagnosis

-Increased urine ALA and porphobilinogen (PBG) during acute attack

-HMBS gene sequencing (>98%)

## Others

-**Urine may be reddish-brown or red**; color is enhanced by exposure to air and light

-Mechanism of acute attacks not clear --> **PBG buildup may have toxic effects on neurons**

# Alpha thalassemia

## Genetics

-**HBA1** (**Hemoglobin subunit alpha** 1); **HBA2** (Hemoglobin subunit alpha 2); **16p13.3**

-AR

## Clinical findings/Dysmorphic features

-Alpha thalassemia results from deletions involving HBA1 and HBA2 --> both of these genes provide instructions for making a protein called **alpha-globin** (**subunit of hemoglobin A**)

1) **Hemoglobin Bart** hydrops fetalis (**Hb Bart**) syndrome: deletion of all **four** α-globin genes; **hydrops fetalis**, severe **hypochromic anemia**, **death in neonatal period**

2) **Hemoglobin H (HbH)** disease: deletion of **three** α-globin genes; **splenomegaly**, **mild jaundice**, sometimes **thalassemia-like bone changes**

**-α-thalassemia trait** --> loss of 2 α-globin genes either in cis (**--/αα**, α0 carrier) or in trans (**-α/-α**)

**-α-thalassemia silent carrier** --> Loss of 1 α-globin gene (**-α/αα**, α+ carrier)

## Etiology

-**Mediterranean**: alpha-thalassemia trait **-α3.7/-α3.7** is common (highest AF in Sardinia (0.18))

-**Southeast Asia**: alpha0-thalassemia alleles (--/αα) and α+-thalassemia alleles (-α/ αα) common

--> incidence of Hb Bart expected: 0.5 - 5 per 1000 births

--> incidence of HbH disease 4 and 20 per 1000 births

## Pathogenesis

**-Inability to form normal Hb A** (normally composed of two alpha and two beta chains)

## Genetic testing/diagnosis

-Hb Bart: characteristic radiographic and laboratory features

-HbH: characteristic laboratory and clinical features

-**Targeted deletion analysis for common deletions** of HBA1and HBA2 can be performed first:

1) Common 2 α-globin gene deletions (α0): Southeast Asian, Filipino, Mediterranean; common single α-globin gene deletions (α+): 3.7-kb deletion, 4.2-kb deletion --> **85%**

2) Sequence analysis of HBA1 and HBA2 if no common deletion was identified --> **15%**

3) Deletion analysis of HBA1, HBA2 and **HS-40** (regulatory region located 40 kb upstream from the α-globin cluster) can then be performed --> **5%**

## Others

-One parent has α-thal trait in cis (--/αα) and other parent is α-thal silent carrier (-α/αα):

--> 25% chance of having HbH disease (-α/--); --> 25% chance of having α-thalassemia trait (--/αα); --> 25% chance of being an α-thalassemia silent carrier (-α/αα); --> 25% chance of being unaffected and not a carrier (αα/αα)

# Beta-thalassemia

## Genetics

-**HBB (11p15.4)**

-AR

## Clinical findings/Dysmorphic features

-Reduced synthesis of the **hemoglobin subunit beta** --> **microcytic hypochromic anemia:**

1) **Major**: **Severe anemia and hepatosplenomegaly**; medical attention within the first two years of life; w/o treatment: affected children have severe FTT and shortened life expectancy

2) **Intermedia**: present later, mild anemia

## Etiology

-The highest incidences are reported in **Cyprus** (14%), **Sardinia** (12%), and Southeast Asia

## Pathogenesis

-Absence of globin beta chains --> **reduced amounts of hemoglobin A (2xalpha + 2xbeta)**

-**Non-assembled globin alpha chains that result from unbalanced globin alpha chain/non-globin alpha chain synthesis precipitate in the form of inclusions** --> damage the erythroid precursors in the bone marrow and spleen, causing ineffective erythropoiesis

## Genetic testing/diagnosis

-Diagnosis of β-thalassemia:

--> Red blood cell indices: microcytic hypochromic anemia, nucleated red blood cells on peripheral blood smear

--> Hemoglobin analysis: decreased amounts of HbA and **increased amounts of hemoglobin F** after age 12 months

-In each at-risk population, **4-10 mutations account for the large majority of HBB disease**

## Others

-Treatment with a **regular transfusion program and chelation therapy** (to reduce transfusion iron overload) --> normal growth and development and extends life expectancy (30s-50s)

-High frequency of β-thalassemias: most likely related to selective pressure from malaria

-Increased HbA2 (alpha2delta2)

# Factor V Leiden Thrombophilia

## Genetics

-Gene F5 (Coagulation factor V; 1q23)

-AD (moderately increased risk for **venous thromboembolism**), AR (significantly increased risk)

## Clinical findings/Dysmorphic features

-Poor anticoagulant response to **activated protein C** (APC) --> increased risk for VT

-Most commonly **deep venous thrombosis (DVT)**

-Heterozygous: 2-3x increased recurrence risk of pregnancy loss

-FVL and **oral contraceptive use**: HETs with 35-50x risk for VT (risk is 1 in 20,000 FVL HETs vs. 1 in 140,000 in wt); HOM with **>100x risk**

## Etiology

-**Heterozygosity: 3%-8% of the US and European** populations; high prevalence in Sweden (10%-15%); extremely rare in Asian, African, and indigenous Australian populations

-Frequency of homozygosity for the Leiden variant is approximately 1:5,000

## Pathogenesis

-G>A substitution affects an **APC cleavage site --> FVL inactivation 10x more slowly and persists longer in circulation** --> increased thrombin generation

## Genetic testing/diagnosis

-Suspected in individuals with:

--> History of 1st/recurrent VTE manifest as DVT or pulmonary embolism, especially in women with history of VTE during pregnancy or in association with estrogen-containing contraceptives

--> A family history of recurrent thrombosis

-**APC resistance assay**: sensitivity and specificity for factor V Leiden approaches 100%

-Identification of a heterozygous or homozygous **c.1691G>A variant** (100%)

## Others

-**Factor II/Prothrombin**: common variant in 3’ UTR (G20210A; AF478696.1: g.21538G>A; **c.\*97G>A**) --> **changes polyA signal** --> **stabilizes mRNA** --> **more prothrombin** produced

-Incidence: ~2% in Caucasians; heterozygotes with 3-fold increased risk

-Oral contraceptives --> **149-fold increased risk for cerebral vein thrombosis**; 16.3-fold increased risk for DVT

# Hemophilia A

## Genetics

-Gene: **F8** (Coagulation factor VIII; Xq28)

-**XLR**

## Clinical findings/Dysmorphic features

-**Deficiency in factor VIII clotting activity** --> prolonged oozing after injuries, tooth extractions, surgery; delayed or recurrent bleeding prior to complete wound healing; excessive bruising

-Severe: diagnosed during first two years; bleeding from minor mouth injuries and large "**goose eggs**" from minor head bumps; **spontaneous** joint bleeds or deep-muscle hematomas; hemarthrosis or intracranial bleed with mild or no trauma

-Moderate: **seldom spontaneous** bleeding; prolonged or delayed oozing after relatively minor trauma; usually diagnosed before age 5-6 year

-Mild: **no spontaneous** bleeding episodes; abnormal bleeding with surgery or tooth extractions

## Etiology

-Birth prevalence of hemophilia A in the United States is approximately **1:6,500** live male births

## Pathogenesis

-Normal Factor VIII circulates as an inactivated clotting cofactor; **gets activated by thrombin**

-**Severe: absent protein, mild-mod: abnormal protein**

## Genetic testing/diagnosis

-Decreased factor VIII clotting activity and normal von Willebrand factor level (severe: <1%, moderate: 1-5%, mild: 6-35%); prolonged activated partial thromboplastin time (aPTT)

-Severe: **F8 intron 22 gene inversion (48%)**/F8 intron 1 gene inversion (3%)/F8 gene del, rearrangement, frameshift, splice, nonsense mutations (40%)/missense mutation (10%)

-Mild-moderate: missense mutation (97%), no intron inversions

## Others

-Approximately 30% of heterozygous females have clotting activity below 40%

-Intravenous infusion of factor VIII concentrate

# Hemophilia B

## Genetics

-Gene: **F9** (Coagulation factor IX; Xq27.1-Xq27.2)

-**XLR**

## Clinical findings/Dysmorphic features

-**Similar to hemophilia A**

-Hemarthrosis or intracranial bleed with mild or no trauma; deep muscle hematomas; prolonged or renewed bleeding after trauma, surgery, tooth extraction, nose bleeds, mouth injury, circumcision; excessive bruising

## Etiology

-Prevalence of is ~ **1: 30,000** live male births worldwide; **~ 1/5 as prevalent as hemophilia A**

## Pathogenesis

-**Factor IX activates Factor X** --> regulates **overall rate of thrombin generation in coagulation**

## Genetic testing/diagnosis

-Prolonged aPTT: severe: <1%; moderate: 1-5%; mild: 6-30% F9 activity

-Sequencing of F9 first (97%-100%); then gene-targeted del/dup(2%-3%)

-Large gene deletions, nonsense mutations, and most frameshift mutations --> severe disease

## Others

-Approx. 30% of females with one pathogenic variant: activity < 40% and bleeding disorder

-Recombinant factor IX concentrate 2-3x/week for severe deficiency; within one hour of trauma

# HFE Hemochromatosis

## Genetics

-Gene **HFE** (Hereditary hemochromatosis protein; 6p21.3)

-AR (**low penetrance**, many homozygotes never develop symptoms)

## Clinical findings/Dysmorphic features

-**High iron absorption by GI mucosa** --> excessive iron storage in liver, skin, pancreas, heart, joints, testes

-Early symptoms: abdominal pain, weakness, lethargy, weight loss

-Clinical signs of advanced iron overload: diabetes mellitus, progressive **increase in skin pigmentation**, hepatomegaly, **hepatic cirrhosis**, **arthropathy** (metacarpophalangeal joints), primary liver cancer, cardiomyopathy, hypogonadism

## Etiology

-Northern European: prevalence of ind. homozygous for p.Cys282Tyr is 2:1,000 to 5:1,000

-**Non-Hispanic whites in US**: prevalence of p.Cys282Tyr homozygotes is 1:200 to 1:400

-Less common in Asians and Hispanics

## Pathogenesis

-**HFE protein binds transferrin receptor 1 and inhibit cellular iron uptake --> LOF mutations lead to increased iron uptake**

## Genetic testing/diagnosis

-Increased **fasting transferrin-iron saturation** on at least 2 occasions

-Targeted mutation testing (60-90% **C282Y/C282Y**; 3-8% **C282Y/H63D**)

## Others

-Treatment --> Clinical HFE hemochromatosis: induction treatment by phlebotomy to achieve serum ferritin concentration ≤50 ng/mL

-Clinical HFE hemochromatosis is **more common in men than women** (monthly period)

# Bruton’s agammaglobulinemia (X-linked agammaglobulinemia)

## Genetics

-Gene: **BTK** (Xq21.3)

-XLR

## Clinical findings/Dysmorphic features

-Recurrent bacterial infections in aff. males in first 2y (**otitis** most common prior to diagnosis)

-Also: conjunctivitis, sinopulmonary infections, diarrhea, skin infections

-60% of individuals are found to have immunodeficiency when they develop a severe, life-threatening infection (pneumonia, empyema, meningitis, sepsis, cellulitis, septic arthritis)

-**Paucity of lymphoid tissue**

## Etiology

-3:1,000,000-6:1,000,000

## Pathogenesis

-BTK expressed in myeloid cells, platelets, B lineage cells --> development/maturation of B cells

## Genetic testing/diagnosis

-Males with early-onset infections, low serum immunoglobulins, absent B cells (CD19+ cells)

-Low but measurable IgG, <1% B Cells (CD19)

-90% BTK sequence variant, 8% gene targeted in/del; 3-5% CMA (larger deletions)

## Others

-Treatment is gamma-globulin substitution (subcutaneous or intravenous every 2-4 weeks)

# Familial Mediterranean Fever

## Genetics

-Gene: **MEFV** (**Pyrin**; 16p13)

-AR

## Clinical findings/Dysmorphic features

-Type 1: recurrent short episodes of inflammation, **serositis** and fever; peritonitis, synovitis, pleuritis, pericarditis, meningitis; **amyloidosis** severe complication: if untreated --> **renal failure**

-Type 2: **amyloidosis as first clinical manifestation** in asymptomatic individual

## Etiology

-Variant **p.Met694Val** in more than 90% of affected Jewish of North African origin

## Pathogenesis

-Mutations result in **increased IL-1 responsiveness** --> increased inflammatory attacks

## Genetic testing/diagnosis

-Sequencing: 75-90%; **no In/Del reported**

-Targeted analysis first: Armenian, Turkish, Arab, North African Jewish, Iraqi Jewish, AJ

## Others

-Up **to 25% of individuals with FMF have only one MEFV pathogenic variant** identified

-If only one mutation: diagnosis of FMF can be confirmed by a **6-month trial of colchicine**

# Aarskog syndrome

## Genetics

-Gene: **FGD1** (**Rho/Rac guanine nucleotide exchange factor**; **Xp11.22**)

-**XLR** (some cases AR or AD)

## Clinical findings/Dysmorphic features

-S**hawl scrotum** (scrotum surrounds penis); cryptorchidism; brachydactyly (short fingers); short stature; cervical vertebral abnormalities; ID in 30%

-High anterior hairline, frontal bossing, **hypertelorism**, anteverted nares

-Milder manifestations in females: hypertelorism, short stature, widow's peak hairline

## Etiology

-Not known

## Pathogenesis

-Unclear: FGD1/Rho GTPase Cdc42 implicated in cytoskeletal organization, potentially in skeletal formation and morphogenesis

## Genetic testing/diagnosis

-**FGD1 sequencing (20%)**

## Others

-**Orchiopexy** (surgery to move undescended testicle into scrotum and permanently fix it there)

# Antley-Bixler syndrome

## Genetics

-Gene: **POR** (NADPH-cytochrome P450 reductase; 7p11.2)

-AR

## Clinical findings/Dysmorphic features

-Ambiguous genitalia, enlarged cystic ovaries, poor masculinization in males, **maternal virilization during pregnancy with an affected fetus**

-Craniosynostosis, choanal stenosis/atresia (nose blockage), stenotic external auditory canals, hydrocephalus

-Neonatal fractures, bowing of the long bones, joint contracture, renal malformations

## Etiology

-Only 140 cases reported

## Pathogenesis

-**Disorder of steroid and cholesterol synthesis** due to cytochrome P450 reductase deficiency

## Genetic testing/diagnosis

-Sterol or steroid abnormalities using GC-MS

-Increased urinary pregnenolone and progesterone metabolites

-POR sequencing (92%); In/Del analysis (2.5%)

# Bardet-Biedl syndrome

## Genetics

-At least **19 genes**: BBS1 (11q13; 23%), BBS10 (12q21.2; 20%), BBS2 (8%)

-AR, 10% **triallelic;** no identifiable variant in 20% of individuals

## Clinical findings/Dysmorphic features

-**Rod-cone dystrophy (**night blindness by age 7-8 yrs, legally blind by age 15.5 yrs); truncal **obesity**; **postaxial polydactyly (pinky or toe)**; **ID**

-Male: hypogonadotropic hypogonadism; female: complex genitourinary malformations

-**Renal** abnormalities: renal disease is a major cause of morbidity and mortality

## Etiology

-1:100,000 (North America), 1:160,000 (Switzerland)

## Pathogenesis

-Defects in **cilia or intra-flagellar transport**

-Defects in the transport of phototransduction proteins from the inner to the outer segments of photoreceptors --> cell death underlies pathogenesis of **retinitis pigmentosa** in BBS

-**Aberrant sonic hedgehog signaling** --> polydactyly in BBS

## Genetic testing/diagnosis

-Diagnosis on clinical findings

-Gene panel, mostly missense; p.M390R variant in exon 12 of BBS1 (30% of individuals)

## Others

-Majority have significant learning difficulties, only a minority have severe impairment

# Branchio-Oto-Renal syndrome

## Genetics

-**EYA1, SIX1, SIX5**

-AD; 100% penetrance

## Clinical findings/Dysmorphic features

-**Malformations of outer, middle, and inner ear:**

--> Conductive, sensorineural, or mixed hearing impairment (>90%)

--> Abnormalities of the pinnae (external part of the ear): preauricular pits (82%), lope ear malformation (36%), preauricular tags (13%)

-**Branchial fistulae and cysts**

-**Renal** malformations (mild renal hypoplasia to bilateral renal agenesis) (67%)

## Etiology

-not known

## Pathogenesis

-EYA proteins are four transcriptional activators --> interact with other proteins --> normal embryologic development

-**EYA1 important for inner-ear, kidney, branchial-arch development**

-**SIX gene family binds EYA proteins** --> nuclear translocation of the resultant protein complex

-SIX1 and SIX5 function as transcriptional activators/repressors --> regulation of organogenesis

## Genetic testing/diagnosis

-Diagnosis established in ind. with clinical features and/or het variant in: EYA1, SIX1, SIX5

-EYA1 (40%; of those 80% seq., 20% In/Del), SIX1 (2%), SIX5 (2.5%), >50% unknown cause

## Others

-**Some individuals progress to ESRD** later in life

# CHARGE syndrome

## Genetics

-**CHD7** (Chromodomain-helicase-DNA-binding protein 7, **8q12.1**)

-**AD**

## Clinical findings/Dysmorphic features

-**C**oloboma, **h**eart defects, choanal **a**tresia, **r**etarded growth and development, **g**enital abnormalities, **e**ar anomalies

-Unilateral/bilateral **coloboma** of iris, retina-choroid, and/or disc with or without microphthalmos (small eye) **(80%-90%)**

-**Cardiovascular malformations** (75%-85%): **conotruncal anomalies** (Tetralogy of Fallot, interrupted aortic arch, perimembranous ventricular septal defect, double-outlet right ventricle, truncus arteriosus), AV canal defects, aortic arch anomalies, ASD, VSD, PDA

-Unilateral/bilateral **choanal atresia or stenosis** (nose closed) **(50%-60%)**

-Growth and developmental delay

-**Cryptorchidism** in males; **hypogonadotropic hypogonadism** in both males and females

-Abnormal outer **ears**, ossicular malformations, **Mondini defect** of the cochlea and absent or hypoplastic semicircular canals **(>90%)**

-**Cranial nerve dysfunction** --> hyposmia or anosmia; unilateral/bilateral facial palsy (40%); impaired hearing, and/or swallowing problems **(70%-90%)**

-Tracheoesophageal (TE) fistula

## Etiology

-At least 1:10,000

## Pathogenesis

-Majority of variants are nonsense and frameshift throughout gene --> haploinsufficiency

-**CHD7** with role in early embryonic development --> chromatin structure and gene expression

## Genetic testing/diagnosis

-CHD7 only known gene (accounts for 60-70%)

## Others

-E**mpiric risk to sibs of a proband is approximately 1%-2% (germline mosaicism)**

-20-25% mortality in the first year

# Coffin-Lowry syndrome

## Genetics

-**RPS6KA3** (Ribosomal protein S6 kinase alpha-3)

-**XLD**; 70%-80% de novo; 20%-30% with >1 additional affected family member

## Clinical findings/Dysmorphic features

-**Severe to profound ID** in males; males <3%ile in height; **soft fleshy hands**, tapering fingers with small terminal phalanges; microcephaly; kyphoscoliosis

-**Stimulus induced drop episodes** (SIDAs)

-Facial features in older males: prominent forehead/eyebrows, full supraorbital ridges, marked ocular hypertelorism, downslanting palpebrae, low nasal bridge, blunt tip, thick alae nasi and septum, large mouth, usually held open, **patulous lips with everted lower lip**, prominent ears

## Etiology

-1:40,000 to 1:50,000

## Pathogenesis

-Unclear; RPS6KA3 part of Ras signaling cascade --> cellular proliferation and differentiation

## Genetic testing/diagnosis

-RPS6KA3 (35-40%), thereof 90-95% seq, 5-10% In/Del

## Others

-Symptoms usually more severe in males than in females --> normal to profound ID in females

# Cornelia de Lange syndrome

## Genetics

-NIPBL, SMC1A, SMC3, HDAC8, RAD21

-**AD (NIPBL, RAD21, SMC3)**, **XLR (SMC1A, HDAC8; almost all *de novo*)**

## Clinical findings/Dysmorphic features

-Growth retardation (prenatal onset; <5th centile throughout life), moderate to severe ID; **hirsutism** (excessive body hair); **upper-limb reduction** (subtle phalangeal abnormalities to oligodactyly); diaphragmatic hernia; **pulmonary valve stenosis and/or VSD**

-Facial features: microbrachycephaly; **synophrys**, **arched eyebrows**; **low‐set posteriorly rotated and/or hirsute ears with thickened helices**; depressed or broad nasal bridge; **upturned nasal tip with anteverted nares**; **long smooth philtrum**; thin vermillion border of the upper lip (midline "drip" appearance); downturned corners of the mouth; high and arched palate with clefts; small widely‐spaced teeth; micrognathia; short neck; ptosis; nystagmus; **long eyelashes**

## Etiology

-Approx. 1:50,000 for the classic form of CdLS (ind. with milder features under-diagnosed)

## Pathogenesis

-Unknown, majority of mutations are truncating --> haploinsufficiency

-Cohesinopathy; mutations in cohesin structural/regulatory proteins --> cohesin loading defects

## Genetic testing/diagnosis

-Serial single-gene testing/multigene panel/more comprehensive genomic testing

-**NIPBL (60%), SMC1A (5%), HDAC8 (4%), SMC3 (1-2%), RAD21 (<1%)**

## Others

-Many individuals demonstrate autistic and self-destructive tendencies

-Frequent: cardiac septal defects, GI issues, HL, myopia, cryptorchidism/hypoplastic genitalia

# Cri-du-Chat (5p minus syndrome)

## Genetics

-Partial or complete **deletion of chromosome 5p; deletion 5p from band 5p15.2 to 5pter**

-**12% due to unequal segregation of a translocation or recombination involving a pericentric inversion in one of the parents**

-85% sporadic de novo deletions (**80% are on the paternal chromosome**)

## Clinical findings/Dysmorphic features

-**Cat-like cry** (abnormal laryngeal development); slow growth; ID; hypotonia; strabismus

-Facial features: microcephaly; round face; hypertelorism; micrognathia; epicanthal folds; low‐set ears; broad nasal bridge; short philtrum

## Etiology

-Incidence ranges from 1:15,000 to 1:50,000 live-born infants; slight female predominance

## Pathogenesis

-Loss of CTNND2 is associated with severe ID

## Genetic testing/diagnosis

-Most on karyotype, few are submicroscopic and diagnosed by FISH

## Others

-Cat-like cry only when deletion limited to band 5p15.32

-Study of deletions from 5p15.2 to 5p13 found no correlation with size and degree of ID

# Fryns syndrome

## Genetics

-No gene known

-AR

## Clinical findings/Dysmorphic features

-Most common autosomal recessive syndrome associated with congenital diaphragmatic hernia

-**Diaphragmatic defects** (diaphragmatic hernia, hypoplasia or agenesis); **pulmonary hypoplasia; distal digital hypoplasia** (nails, terminal phalanges); genitourinary malformations

-Agenesis of the Corpus Callosum; optic and olfactory tract hypoplasia; encephalocele

-Facial: coarse facies; hypertelorism; broad/flat nasal bridge; thick nasal tip; long philtrum; low-set/poorly formed ears; tented upper lip; macrostomia (wide mouth); micrognathia

## Etiology

## -7 in 100,000 live births in a French population

## Pathogenesis

-Not known

## Genetic testing/diagnosis

-Based on clinical findings; several different chromosome aberrations have been described in individuals who have previously received a diagnosis of Fryns syndrome

## Others

-Majority are stillborn or die in early neonatal period, 14% survive longer

# Greig Cephalopolysyndactly Syndrome

## Genetics

-**GLI3** (Zinc finger protein GLI3; 7p13)

-AD

## Clinical findings/Dysmorphic features

-**Preaxial polydactyly** or mixed **pre-and postaxial polydactyly**; cutaneous syndactyly; true widely spaced eyes; macrocephaly/**hydrocephalus**; prominent forhead; developmental delay; ID; seizures (<10%)

-Features highly variable, ranging from very mild to severe

-ID more common in those with large (>300 kb) deletions including GLI3

## Etiology

-GCPS is rare and pan-ethnic; prevalence is unknown; ~ 100 cases are known

## Pathogenesis

-GLI proteins regulate genes distal to sonic hedgehog in the SHH pathway

-Pathogenesis of GCPS is haploinsufficiency

## Genetic testing/diagnosis

-GLI3 is only gene; GLI3 alterations (i.e., cytogenetic abnormalities involving GLI3 or pathogenic variants of GLI3) **in more than 75%** of typically affected individuals

-Seq: 70%, In/Del: 5-10%, LoH (detects GLI3 deletions): 50-75%

## Others

-**Allelic with Pallister-Hall syndrome (bifid epiglottis)** --> GCPS is caused by pathogenic variants of all types, whereas PHS is caused by truncating variants and one splice variant that generates a frameshift

# Joubert syndrome

## Genetics

-34 genes are known; **TMEM67** (6-20%), **AHI1** (7-10%), **CPLANE1** (8-14%), CC2D2A (8-11%), CEP290 (7-10%), NPHP1 (1-2%), TMEM216 (2-3%)

-**33 AR, 1 XLR (OFD1); digenic inheritance has been reported; M:F, 2:1**

## Clinical findings/Dysmorphic features

-1) Cerebellar/brain stem malformation: **molar tooth sign** (MRI: cerebellar vermis hypoplasia)

-2) Hypotonia in infancy --> ataxia later in life

-3) DD/ID

-Additional findings: oculomotor apraxia (difficulty in smooth visual pursuits and jerkiness in gaze tracking; **abnormal eye movements**); **retinal dystrophy**, renal disease, ocular **colobomas**, occipital encephalocele, hepatic fibrosis, polydactyly, oral hamartomas, endocrine abnl

## Etiology

-Approx. 1:100,000

## Pathogenesis

-All proteins **localize to primary cilium and/or basal body and centrosome** --> play role in formation, morphology, and/or function of these organelles

## Genetic testing/diagnosis

-Molecular diagnosis can be established in 62%-94% of individuals with a clinical diagnosis

-Combination of gene-targeted (multigene panel) + genomic testing (genomic sequencing)

-Targeted testing in some ethnicities first: AJ --> p.Arg73Leu in TMEM216; Dutch --> p.Arg2904Ter in CPLANE1; French Canadian --> several variants in CPLANE1, CC2D2A, NPHP1, and TMEM231; Japanese --> c.6012-12T>A in CEP290

## Others

-Apnea monitoring, G tube if dysphagia, surgery for eye disease, dialysis for nephronophthisis

**-Ciliopathies: conditions caused by defects in proteins important in ciliary function --> share many features including renal disease, retinal dystrophy, polydactyly**

# Kabuki syndrome

## Genetics

-**KMT2D** (75%, AD; MLL2), KDM6A (3-5%, XLR; Lysine-specific demethylase 6A)

## Clinical findings/Dysmorphic features

-Facial: **long palpebral fissures with eversion of the lateral third of the lower eyelid**; arched and broad eyebrows; short columella with depressed nasal tip; large, prominent, cupped ears

-**Fetal finger pads**; mild to moderate ID (IQ<80); joint laxity; high palate; hypotonia; short stature; CHD; CL/P; scoliosis; renal anomalies; hearing loss; speech delay

## Etiology

-Approx. 1:32,000 – 1:86,000

## Pathogenesis

-KDM6A and KMT2D part of ASCOM complex --> removes repressive epigenetic marks and deposit activating methylation marks on chromatin

## Genetic testing/diagnosis

-Diagnosis of KS in a proband with a history of infantile hypotonia, DD, and/or ID AND one or both of the following:

1) typical dysmorphic features (long palpebral fissures with eversion of the lateral third of the lower eyelid, and ≥2 of the following: arched/broad eyebrows with lateral third displaying notching/sparseness; short columella with depressed nasal tip; large, prominent, cupped ears; persistent fingertip pads)

2) heterozygous variant in KMT2D or heterozygous or hemizygous pathogenic variant in KDM6A

-KMT2D (99% sequencing); KDM6A (80% sequencing, 20% InDel)

## Others

-Risk for immunodeficiency

# 1p36 Deletion Syndrome

## Genetics

-Genes unknown; contiguous gene deletion syndrome

-**Terminal deletion of 1p36; F:M, 2:1**

## Clinical findings/Dysmorphic features

-Craniofacial features: straight eyebrows, deeply set eyes, midface retrusion, wide and depressed nasal bridge, long philtrum, pointed chin, large, **late-closing anterior fontanel (77%),** **microbrachycephaly** **(65%), epicanthal folds (50%)**, posteriorly rotated, low-set, abnormal ears

-DD/ID of variable degree in 100%; hypotonia in 95%; seizures (44%-58%); structural brain abnormalities (88%); congenital heart defects (71%); eye/vision problems (52%) and hearing loss (47%); skeletal anomalies (41%); brachy/camptodactyly and short feet; abnormalities of the external genitalia (25%); renal abnormalities (22%)

## Etiology

-Between 1:5,000 and 1:10,000 births

## Pathogenesis

-**No genes** have been associated with clinical features of 1p36 deletion syndrome

## Genetic testing/diagnosis

-Conventional G-banded cytogenetic analysis, FISH, CMA can be used to detect deletions

-Complexity of some deletions may be detected only by CMA.

## Others

-**Most common terminal deletion syndrome**; **majority maternally derived**

# Prader-Willi Syndrome

## Genetics

-**15q11.2-q13**; 4 distinct regions; 3 common deletion breakpoints within segmental duplication

-Penetrance is complete

## Clinical findings/Dysmorphic features

-Severe hypotonia and feeding difficulties in early infancy --> **excessive eating** and gradual development of morbid obesity in later infancy/early childhood

-Delayed motor milestones/language development; some degree of cognitive impairment

-Temper tantrums, **stubbornness**, manipulative behavior, obsessive-compulsive features

-**Hypogonadism** in both males and females (manifests as genital hypoplasia, incomplete pubertal development, infertility)

-Short stature (if not treated with growth hormone); characteristic facial features; strabismus; scoliosis; **thick/sticky saliva**

## Etiology

-1:10,000 to 1:30,000

## Pathogenesis

-Genomic and epigenetic changes causing PWS all lead to a loss of expression of the normally paternally expressed genes on chromosome 15q11.2-q13

-PWS paternal-only expressed region:

--> 5 protein-coding genes (MKRN3, MAGEL2, NECDIN, bicistronic SNURF-**SNRPN**)

--> NPAP1 (intron-less gene; biallelically expressed in testis, only from paternal allele in brain)

--> Cluster of C/D box snoRNAs and antisense transcripts (incl. antisense transcript to UBE3A)

-AS maternally-only expressed region: with maternally expressed genes UBE3A and ATP10A

## Genetic testing/diagnosis

-DNA methylation analysis --> abnormal parent-specific imprinting within the PW critical region

-**70% have paternal deletions in 15q11q13; 25% have maternal uniparental disomy; <5% have methylation defects; <1% have translocations involving the 15q11q13 region**

-DNA methylation analysis (e.g. MS-MLPA) at 5' SNRPN locus will identify imprinting defects

## Others

-Risk to the sibs of affected child depends on genetic mechanism:

--> Less than 1% if affected child has deletion or uniparental disomy

--> Up to 50% if the affected child has an imprinting defect

--> Up to 25% if a parental chromosome translocation is present

-Prenatal testing is possible for pregnancies at increased risk if underlying mechanism is known

-**SNRPN is methylated on maternal allele**

# Rubinstein-Taybi syndrome

## Genetics

-**CREBBP** (CREB-binding protein), **EP300** (histone acetyltransferase-p300)

-AD; mostly de novo; empiric recurrence risk for sibs is less than 1%

## Clinical findings/Dysmorphic features

-**Broad and often angulated thumbs and great toes;** short stature; moderate to severe ID

-Facial: downslanted palpebral fissures, **low-hanging columella**, high palate, **grimacing smile**, and **talon cusps** ("cusp-like" projections located on the inside surface of the affected tooth)

## Etiology

-Prevalence of 1:100,000 to 1:125,000 in the Netherlands

## Pathogenesis

-CREBBP mutations cause abnormal histones-acetylation

## Genetic testing/diagnosis

-CREBBP and EP300 only genes known to be associated with Rubinstein-Taybi syndrome

-CREBBP: FISH (~10%) and sequencing (40-60%), EP300 (~3%-8%); 30% unknown

# Smith-Magenis syndrome

## Genetics

-Deletion or mutation of **RAI1** (Retinoic acid-induced protein 1; **17p11.2**)

-Deletions are de novo; SNVs can be de novo or inherited

## Clinical findings/Dysmorphic features

-Mild-moderate infantile hypotonia, feeding problems, FTT

-Short stature, brachydactyly, ophthalmologic abnormalities, early speech delay with or without hearing loss, peripheral neuropathy, sleep problems; mild-moderate ID

-Stereotypic **maladaptive behaviors** (self-injurious behaviors, inattention, hyperactivity, impulsivity, **disobedience**, “**self-hug**” **and** “**lick and flip” page** **motion**)

-Facial: brachycephaly; midface retrusion; relative prognathism with age; broad, square‐shaped face; everted**, "tent"-shaped vermilion** of the upper lip with mild micrognathia; **deep‐set, close‐spaced eyes**; coarsening face over time

## Etiology

-Prevalence ~1:15,000

## Pathogenesis

-RAI1 functions in transcriptional regulation --> haploinsufficiency as disease mechanism

## Genetic testing/diagnosis

-**Visible interstitial deletion of chromosome 17p11.2:** routine G-banded analysis with adequate resolution (≥550 band); can be overlooked particularly when the indication is not SMS

-FISH or aCGH required in cases of submicroscopic deletions and/or to resolve equivocal cases

-90% have FISH-detectable deletion and of those ~70% have the common 3.5-Mb deletion

# Triploidy

## Genetics

-69,XXY > 69,XXX (**69,XYY very rare**)

-**sporadic**, no increased risk of recurrence

## Clinical findings/Dysmorphic features

-Dysplastic calvaria (skullcap) with large posterior fontanelle (**incomplete skull ossification**), **classic 3/4 finger syndactyly**, ASD, VSD, hydrocephalus, holoprosencephaly

## Etiology

-The frequency of triploidy in live births is 1:10,000; males represent 51-69 % of all cases

-More than 99% lost in first trimester; accounts for 6-10% of all spontaneous abortions and ~20% of all chromosomally abnormal spontaneous abortions

## Pathogenesis

-**85% are** **diandric** (2 paternal, 1 maternal) --> **well grown fetus**, slightly smaller head size, **large placenta** (**partial mole**), usually do not survive to term; 0.5% risk of gestational trophoblastic disease (abnormal growth of cells inside a woman's uterus), 0.1% risk of choriocarcinoma

-**15% are** **digynic** (2 maternal, 1 paternal): **growth retarded fetus** with macrocephaly, **small & fibrotic placenta**, can survive to birth

**-Complete mole** (diploid – **all paternal**): **15% risk of gestational trophoblastic disease**; **3% risk of** **choriocarcinoma**

**-Ovarian teratomas arise through duplication of egg genome (contain all germ layer)**

## Genetic testing/diagnosis

-Prenatal US, maternal serum hCG low

-Karyotype

# Trisomy 13 (Patau syndrome)

## Genetics

-Full/mosaic/partial trisomy of chromosome 13

## Clinical findings/Dysmorphic features

-Sloped forehead, malformed ears, **cleft lip and palate**

-Eye anomalies: microphthalmia, **iris coloboma**, **hypotelorism**

-CNS: Holoprosencephaly, microcephaly, severe ID, meningomyelocele (type of spina bifida), agenesis of the corpus callosum, enlarged cisterna magna (opening to cerebellum)

-**CHD**: ventral septal defect, hypoplastic left heart, double-outlet right ventricle

-Renal abnormalities: hydronephrosis, polycystic kidneys, hydroureter

-Genitalia abnormalities: Male --> cryptorchidism, hypospadias, anomalous scrotum; Female --> bicornuate uterus, duplicated system

-**Postaxial polydactyly**; IUGR; cutis aplasia; seizures, HL; **omphalocele** (abdominal organs are outside of the body)

## Etiology

-Least common of the live born trisomy disorders (1/15,000-25,000 liveborn infants)

-44% die in the first month, >70% die within one year

## Pathogenesis

-**75% are due to maternal nondysjunction**, 20% to a translocation, and 5% to mosaicism

## Genetic testing/diagnosis

-Karyotype is diagnostic

## Others

-Mosaic T13 with broad phenotype (full T13 - mild ID/physical features and longer survival)

# Trisomy 18 (Edwards syndrome)

## Genetics

-Full (94%), mosaic (<5%), or partial (~2%) trisomy of chromosome 18q

## Clinical findings/Dysmorphic features

-**Clenched hands: 2 over 3 and 5 over 4**

-IUGR, ID

-**Rocker bottom feet**, **small fingernails**, short sternum

-Craniofacial disproportion: micrognathia, prominent occiput, microphthalmia (small eye/eyes) -CHD: VSD, ASD, PDA (patent ductus arteriosus); multiple dysplastic valves

-Generalized muscle spasm; renal anomalies

## Etiology

-Second most common autosomal trisomy; 1/6000 liveborn infants; 60% female

-**95% spontaneously abort;** 50% die in first week, 90% die by one year

## Pathogenesis

-Less than 1% due to a translocation

-**Maternal nondysjunction (97%)**, mosaicism (10%)

## Genetic testing/diagnosis

-Echo, abdominal US; maternal serum screen: **low AFP, hCG, and UE3**

## Others

-Causes of death: central apnea, cardiac failure, respiratory insufficiency

-Maternal age effect

# Trisomy 21 (Down syndrome)

## Genetics

-21q22.1-21q22.3 --> DS critical region (but, cases of dup outside this region who manifest DS)

-Mechanism: 1) T21: 47,XX,+21 (~95% of cases; **1% rr; 1.4% rr if mother <30y**); 2) Rob Translocation: 46,XX,rob(14;21) **(~4%; rr depends on carrier parent: mother carrier: 10-15%; father is carrier: <5%)**; 3) Mosaic T21: (~2%; may be milder)

## Clinical findings/Dysmorphic features

-**Upslanting palpebral fissures**; **excess nuchal skin**; auricular dysplasia; flat facial profile; **macroglossia**; hypodontia; **palmar crease**; clinodactyly; pelvic changes

-Mild-mod ID; hypotonia; growth delay; joint hyperflexibility; **abnormal moro reflex**

-Strabismus, adult cataracts, myopia (nearsightedness), conductive HL; hypogenitalism

-CHD: **AV canal** (hole in the center of the heart; located between atria and ventricles) **almost pathognomonic**; most common: VSD

-Duodenal atresia; hirschprung disease; thyroid disease; early onset **Alzheimers**

-Transient myeloproliferation, **ALL**

## Etiology

-Most common and best-known chromosome aneuploidy --> **1 in 800 live births**

## Pathogenesis

-**95% de novo**, 5% due to Robertsonian translocation or isochromosome 21

-**90% due to maternal meiosis nondisjunction** (**3⁄4 MI error, 1⁄4 MII error**)

## Genetic testing/diagnosis

-Prenatal US abnormalities detected in 50%; maternal serum screen: **high free beta human choriogonadotropin, low PAPP-A**

-Maternal fetal free DNA testing, karyotype is diagnostic

## Others

-First described clinically in 1866 by Langdon Down

-Maternal age effect

-Supportive care, overall life expectancy is reduced

# VACTERL (VATER) Association

## Genetics

-Unknown, eventually: FGF8, FOXF1, HOXD13, LPP, TRAP1, ZIC3

-Sporadic

## Clinical findings/Dysmorphic features

-**Vertebral** defects **(V), 70%**

-Anorectal malformations/**Anal atresia** **(A**), 33%

-**Cardiac** defects **(C), 75%**: VSD, PDA, TOF

-Tracheoesophageal fistula with or without **esophageal atresia** **(TE), 70%**

-**Renal** malformations **(R), 50%**

-**Limb** **(L), 70%**: **polydactyly**, humeral hypoplasia, radial aplasia, **proximally placed thumb**

## Etiology

-Frequency: 1/10,000 to 1/40,000

## Pathogenesis

-unknown

## Genetic testing/diagnosis

-Diagnosis requires 3 of 7 features and it is a diagnosis of exclusion --> rule out aneuploidy with karyotype, Fanconi anemia with DEB testing, and Townes- Brocks syndrome by SALL1 seq

## Others

-A variant is VACTERL with hydrocephalus which can be AR or XL

# Wolf-Hirschhorn Syndrome (4p-, Monosomy 4p)

## Genetics

-**4p deletion**, critical region with two genes: **WHSC1 and WHSC2** of unknown significance

## Clinical findings/Dysmorphic features

-“**Greek warrior helmet**" appearance of nose (wide bridge continuing to forehead)

-Microcephaly, facial asymmetry, ptosis, structural brain anomalies, CL/P; high forehead with prominent glabella; ocular hypertelorism; **epicanthus**; highly arched eyebrows; short philtrum; downturned mouth; micrognathia; poorly formed ears with pits/tags

-**CHD** (ASD>PVS>VSD>PDA>AI>TOF)

-Intrauterine/postnatal growth retardation, hypotonia; ID of variable degree, seizures

-**IgA deficiency**

## Etiology

-50%-60% have a de novo pure deletion of 4p16; **40%-45% have an unbalanced translocation with both a deletion of 4p and a partial trisomy of a different chromosome arm**

-Approximately 1:50,000 births

-**2:1 female/male ratio**

## Pathogenesis

-WHS is true contiguous gene syndrome with contribution of genes within a **1.6-Mb region**

## Genetic testing/diagnosis

-Heterozygous deletion of WHSCR on chromosome 4p16.3 by CMA, conventional G-banded cytogenetic analysis or FISH

# X-linked adrenoleukodystrophy

## Genetics

-**ABCD1** (ATP-binding cassette sub-family D member 1) --> Adrenoleukodystrophy protein

-**95% inherited**; ~ 4.1% have de novo variant

## Clinical findings/Dysmorphic features

-X-ALD affects the **nervous system** white **matter and the adrenal cortex**

-Three main types:

1) **Childhood cerebral form** (35-40%): between ages 4-8; first ADHD/hyperactivity; progressive impairment of cognition, behavior, vision, hearing, motor function --> **total disability within six months to two years**; most have impaired adrenocortical function at the time that neurologic disturbances are first noted; **symmetric enhanced T2 signal in the parieto-occipital region**

2) **Adrenomyeloneuropathy** (**AMN**; 40-45%): in 20s or middle age; **progressive stiffness** and weakness of the legs, **sphincter disturbances**, sexual dysfunction; often, **impaired adrenocortical function**; all symptoms are progressive over decades; 60% of heterozygous women (>40 yr-old) manifests AMN; 35% of male with AMN develop cerebral demyelination

3) **Addison disease** only (10%): between age two years and adulthood (most commonly by age 7.5 years); primary adrenocortical insufficiency, **without evidence of neurologic abnormality**

## Etiology

-Prevalence is estimated at between 1:20,000 and 1:50,000

## Pathogenesis

-**Peroxisomal disorder**, **accumulation of saturated VLCFA**

-**ALDP located in peroxisomal membrane**; required for **transport of VLCFA into peroxisome**

## Genetic testing/diagnosis

-Diagnosis of X-ALD: in a male proband with suggestive clinical findings and **elevated VLCFA;** in a female proband with detection of a heterozygous ABCD1 variant and elevated VLCFA

-**MRI always abnormal in boys with cerebral disease** (often provides the first diagnostic lead)

-Diagnosis based on elevations in VLCFA in plasma or cultured fibroblasts: **concentration of C26:0; Ratio of C26:0/C22:0 and C24:0/C22:0**

-ABCD1 seq (92%); ABCD1 del/dup (6%)

## Others

-20% of females who are carriers develop neurologic manifestations (AMN) but with later onset (age ≥35 years) and milder disease; carrier females do not have **adrenal insufficiency**

-Corticosteroid replacement, BMT if diagnosed after changes visible on brain MRI but before significant neuropsychological problems develop

-**Lorenzo**’**s oil**

# Early onset familial Alzheimer disease

## Genetics

-**PSEN1** (Presenelin-1, 14q24.3), **APP** (Amyloid beta A4, 21q21), **PSEN2** (Presenilin-2, 1q31-q42)

-AD

## Clinical findings/Dysmorphic features

-Dementia, confusion, poor judgment, language disturbance, **agitation**, withdrawal, hallucinations

**-Early onset: <age 60**

## Pathogenesis

-Enhanced production of the 42 amino acid APP C-terminal degradation product (Aβ42) at the expense of the 40 amino acid C-terminal APP C-terminal degradation product (Aβ40) --> Aβ42 is toxic to cells in culture, prone to aggregation, and found in plaques

-**Triple dose of APP may explain Alzheimer**’**s in Trisomy 21**

## Genetic testing/diagnosis

-Gross cerebral cortical atrophy

-Post mortem: **beta-amyloid plaques**, intraneuronal neurofibrillary tangles, amyloid angiopathy

-Sequencing: PSEN1 (20-70%), APP (10-15%), PSEN2 (rare)

## Others

-EOFAD: 1-6% of all Alzheimer’s, 60% of which is familial, and 13% inherited in an AD manner

-**LOFAD: might be associated with APOE e4**, but not sensitive or specific --> supports diagnosis

-APOE e2 may be protective

# Angelman syndrome

## Genetics

-**UBE3A** (Ubiquitin protein ligase E3A, 15q11-q13)

-**Loss of the maternally imprinted contribution in the 15q11.2-q13** (AS/PWS) region

## Clinical findings/Dysmorphic features

-Severe DD or ID, severe speech impairment; **gait ataxia** and/or tremulousness of the limbs

-Inappropriate **happy demeanor** that includes **frequent laughing**, smiling, **excitability; excessive saliva production** (vs. PWS)

-Acquired microcephaly by age two years; seizures before 3y, abnormal EEG: pattern of **large amplitude slow-spike wave**

-Facial features: Protruding tongue, **prognathia, wide mouth**, **widely spaced teeth**, strabismus, light hair and eye color

## Etiology

-Prevalence: 1:12,000 - 1:24,000

## Pathogenesis

-Disruption of UBE3A affects neuronal processes of protein degradation and replacement

-Ubiquitin-proteasome pathway is essential for cellular functioning including signal transduction, cell cycle progression, DNA repair, transcriptional regulation

## Genetic testing/diagnosis

**-68% with deletions in 15q11q13**; **11% with UBE3A mutations; 7% with paternal UPD; 3% with methylation defects**; **<1% with translocations involving the 15q11q13 region; 10% with normal molecular and cytogenetic analysis**

-DNA methylation analysis first test --> identifies 80% of AS (**Del+UPD+ID**); if DNA methylation analysis is normal --> testing of UBE3A (additional 10%)

-Testing strategies:

1) Detection of methylation status at SNRPN locus by methylation specific PCR (MS-PCR) or Southern blot analysis

2) Simultaneous assessment of methylation status and genomic dosage at numerous sites across the 15q11-q13 region, by MS-MLPA

## Others

-Imprinting inheritance in AS: inheritance of UBE3A pathogenic variant from dad has no effect who inherit the variant because the mutated UBE3A has been inactivated in dad’s germ cells and because the children also inherit a normally activated UBE3A from mum

-Carrier females transmit the UBE3A pathogenic variant to sons and daughters --> both will have AS since each will have also inherited an inactivated UBE3A from their father

-Recurrence risk: <1% for UPD and del; up to 50% for imprint defect; 100% for paternal UPD with Robertsonian translocation

# CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

## Genetics

-**NOTCH3** (Neurogenic locus notch homolog protein 3; 19p13.2-p13.1)

-AD; mostly inherited; de novo is rare

## Clinical findings/Dysmorphic features

-**Stroks before age 60;** cognitive disturbance; behavioral abnormalities; migraine with aura

## Etiology

-Minimum prevalence 2-4 per 100,000

## Pathogenesis

-NOTCH transmembrane receptors involved in cell fate specification during development

-Pathogenic variants --> loss or gain of a Cys in one of the 34 EGFr domains --> unpaired cys --> disrupted disulphide bridge formation --> aggregation of the mutant extracellular domain

## Genetic testing/diagnosis

-Suspected: **white matter hyperintensities** + family history of stroke and/or vascular dementia

-Brain MRI: **T2 signal abnormalities** in the white matter of the temporal pole and external capsule, subcortical lacunar lesions

-Skin biopsy: electron microscopy shows characteristic **granular osmophilic material** (GOM) within the vascular media close to vascular smooth muscle cells (**pathognomonic**)

-Sequencing of NOTCH3 identifies pathogenic variants in >90%

# Canavan Disease

## Genetics

-**ASPA** (**Aspartoacylase**; 17pter-p13)

-AR

## Clinical findings/Dysmorphic features

-Neurodegenerative disorder associated with **spongy degeneration of white matter of brain**

-Neonatal/Infantile (Severe) Canavan Disease most common

-Infants normal early in life; by 3-5 mths --> hypotonia --> spasticity, **head lag** (inability to support head is constant feature of this disorder), macrocephaly, DD ; HC grows

-DD more obvious with increasing age; delayed in motor skills; not able to sit, stand, walk, talk

-Optic atrophy develops in the second year of life; normal hearing

-Progression: irritable, sleep disturbance, seizures, feeding difficulties, swallowing deteriorates, joint stiffness

-Prognosis: die in first decade of life; with improved medical and nursing care a larger number of children survive beyond the first decade

## Etiology

-**Carrier frequencies from 1:40 to 1:82 in AJ**

## Pathogenesis

-Aspartoacylase catalyzes conversion of **N-acetyl-L-aspartic acid (NAA) to aspartate and acetate** --> deficiency leads to **build up of NAA in brain --> demyelination**

## Genetic testing/diagnosis

-Typical clinical findings + elevated N-acetylaspartic acid (NAA) in urine using gas chromatography-mass spectrometry (**UOA**) and/or biallelic pathogenic variants in ASPA

-3 common mutations account for 99% of disease-causing alleles in AJ (**p.Tyr231Ter, p.Glu285Ala, and p.Ala305Glu)**, 50-55% in Non-Jewish populations (mainly **p.Ala305Glu**)

# Familial Dysautonomia

## Genetics

-**IKBKAP**/ELP1 (IkappaB kinase complex-associated protein/Elongator complex protein 1, 9q31)

-AR

## Clinical findings/Dysmorphic features

-Debilitating/weakening disease present from birth

-Affects **development and survival of sensory, sympathetic, parasympathetic neurons** --> neuronal degeneration progresses throughout life

-**Gastrointestinal dysfunction**, vomiting crises, recurrent pneumonia, altered sensitivity to pain and temperature perception, cardiovascular instability

## Etiology

-Incidence among **AJ** is 1:3,700 live births (corresponds to a carrier frequency of 1:36)

## Pathogenesis

-ELP1: part of the human elongator complex --> creating a permissive chromatin structure for efficient mRNA elongation during transcription

-Predominant splice donor site variant c.2204+6T>C --> expression of ELP1 in a tissue-specific manner (brain expresses mutated ELP1; lymphoblasts and fibroblasts express wild type ELP1)

-p.Arg696Pro disrupts phosphorylation site

## Genetic testing/diagnosis

-Diagnosis by molecular genetic testing of ELP1 (IKBKAP)

-2 variants account for > 99% of mutated alleles in AJ (**c.2204+6T>C** and **p.Arg696Pro)**

**-8 month old with absent tearing, autonomic neuropathy, episodic vomiting, feeding disorder, and absent fungiform papillae**

# Fragile X

## Genetics

-FMR-1 (**FMRP**, Fragile X Mental Retardation Protein, Xq27.3)

-X-linked triplet repeat, **CGG repeat expansion in the 5**’ **UTR**

-**Normal alleles ~5-44**

-**Intermediate alleles ~ 45-54**: 14% of intermediate alleles are unstable and **may expand into premutation when transmitted by the mother**; not known to expand to full mutation

-**Premutation alleles ~55-200**: no fragile X syndrome, but **increased risk for FXTAS/POI**; 56 is smallest repeat known to expand to full mutation in single transmission; not hypermethylated

-**Full-mutation alleles > 200 CGG repeats**: 100s – 1000s repeats typical; hypermethylation of the FMR1 promoter

## Clinical findings/Dysmorphic features

1) Fragile X syndrome:

-FMR1 **full mutation or LoF variant;** moderate ID in affected males/ID in affected females

-Males with FMR1 full mutation accompanied by aberrant methylation: typical facial features (**long face, prominent forehead, large ears, prominent jaw**), connective tissue findings (**joint laxity)**, **large testes** after puberty, behavioral abnormalities (**ASD**)

2) Fragile X-associated tremor/ataxia syndrome (**FXTAS**):

-**In males (and some females) with FMR1 premutation**

-Characterized by late-onset, **progressive cerebellar ataxia and intention tremor**

3) FMR1-related primary ovarian insufficiency (**POI**):

-Age at cessation of menses <40 years; in approx. **20% of females with FMR1 premutation**

## Etiology

-16 to 25:100,000 males affected with fragile X syndrome

## Pathogenesis

->200 repeats lead to silencing by methylation --> FMRP is RNA-binding protein that forms a messenger ribonucleoprotein complex --> associates with polysomes --> inhibitor of translation --> regulates protein synthesis dendrites --> in fragile X: translation of certain messages may be exaggerated because the normal inhibition provided by FMRP is absent

-FXTAS and POI resulting from FMR1 premutations may be manifestations of RNA-mediated toxicity due to increased FMR1 expression

## Genetic testing/diagnosis

- >99% with increased number of CGG trinucleotide repeats (typically >200) --> aberrant methylation of FMR1 promoter; del and SNVs variants can also cause fragile X syndrome

-PCR for the CGG trinucleotide repeat --> high sensitivity for normal and lower premutation range (≤100 to 120 repeats); less sensitive to larger premutations; fails to amplify full mutations

-Southern blot analysis detects all FMR1 alleles including normal, larger-sized premutations, and full mutations and in addition determines methylation status of the FMR1 promoter region

-Methylation can be assessed by PCR-based methods independent of the of CGG repeats

## Others

-CGG repeats expand exclusively during transmission from female carriers

-Risk for expansion depends on number of CGG repeats and presence of AGG triplets

# Huntington Disease

## Genetics

-Gene: HTT (Huntington, **4p16.3**)

-AD

## Clinical findings/Dysmorphic features

-Progressive motor disability involving both involuntary and voluntary movement (**chorea, dysarthria, dysphagia progress to bradykinesia, rigidity, dystonia**)

-**Cognitive** decline (problems with planning or organization)

-Psychiatric disturbances (personality change, affective **psychosis**, schizophrenic psychosis)

-Mean age of onset 35-44 yrs (juvenile onset <20yrs ~10%)

## Etiology

-HD prevalence varies across world regions: 10:100,000 in Europe; less frequent in Japan, China, Korea, Finland, indigenous African populations from South Africa (0.1 to 2 per 100,000)

## Pathogenesis

-Toxic gain of function; non-cell autonomous toxicity; many pathways lead to toxicity

## Genetic testing/diagnosis

-CT or MRI: **characteristic atrophy of caudate and putamen**

-Analysis of repeat by PCR --> heterozygous expansion of **CAG (glutamine) in 1st exon of HTT**

## Others

-> **36 CAG considered HD-causing alleles** (risk of developing the disease); **36 to 39 CAG --> incompletely penetrance**; **> 40 CAG are completely penetrant**

-Adult-onset HD usually with 40 to 55 CAGs while **juvenile onset with >60 CAGs**

**-Maternal expansions are extremely rare**

# Galactocerebrosidase deficiency (Krabbe Disease)

## Genetics

-Gene: **GALC** (Galactocerebrocidase, 14q31)

-AR

## Clinical findings/Dysmorphic features

1) **Infantile-onset (onset <12 months)**: progressive neurologic deterioration in infancy and **death before age two years** (85%-90%) --> **excessive crying to extreme irritability**, feeding difficulties, gastroesophageal reflux disease, spasticity of lower extremities and fisting, **loss of acquired milestones (smiling, head control)**, staring episodes, peripheral neuropathy; average age of death is 13 months (infections or respiratory failure)

2) **Later-onset (onset >12 months, to 5th decade)**: slower disease progression (10%-15%) --> slow development of motor milestones or loss of milestones (e.g. sitting without support, walking), slurred speech, spasticity of extremities with truncal hypotonia, vision loss, **esotropia** (both eyes turns inward), seizures, peripheral neuropathy

## Etiology

-1:250,000 in US; 1:100,000 in Europe

## Pathogenesis

-**Galactocerebrosidase**: liposomal hydrolysis of galactolipids formed during white matter myelination

-Pathologic changes in the peripheral and central nervous system (**globoid cell formation** and **decreased myelin**) may result from **toxic nature of accumulated psychosine** (**galactosylsphingosine**) --> cannot be degraded due to galactocerebrosidase deficiency

## Genetic testing/diagnosis

-More than 200 pathogenic variants, **30-kb deletion** (from large intron 10, extends beyond the end of gene) accounts for **~45% of pathogenic variants in persons of European ancestry**

-CT: nonspecific - diffuse cerebral atrophy of grey and white matter; MRI: **demyelination of the brainstem and cerebellum;** abnormal EEG, low nerve conduction velocity

-Low GALC enzyme activity (0-5% of normal activity)

-GALC targeted mutation analysis: **GALC 30-kb deletion** (45% of Europeans, 35% of Mexicans); c.809G>A mutation (50% of late onset Krabbe); GALC sequencing (virtually 100%)

## Others

-On NBS --> HSCT decreases morbidity and mortality when given to infants before symptoms

-Supportive care to control irritability and spasticity if diagnosed when symptomatic

# Neurofibromatosis type I

## Genetics

-NF1 (Neurofibromin, 17q11)

-AD, **50% de novo**

## Clinical findings/Dysmorphic features

-Multiple **café au lait spots;** axillary and inguinal freckling; multiple **cutaneous neurofibromas**; **Lisch nodules**; choroidal freckling; **plexiform neurofibromas** (50%); learning disabilities (50%)

-Less common but serious: optic nerve and other central nervous system gliomas, **malignant peripheral nerve sheath tumors**, scoliosis, tibial dysplasia, vasculopathy

## Etiology

-Most common dominantly inherited genetic disorder: **incidence 1:3000**

## Pathogenesis

-Neurofibromin GTPase-activating protein (GAP) that negatively regulates Ras pathway

-Increases the hydrolysis of Ras-bound guanosine triphosphate (GTP) --> controls proliferation/acts as a tumor suppressor

## Genetic testing/diagnosis

-**NIH diagnostic criteria** are met in an individual **who has ≥ 2 of**:

1) **≥ 6 café au lait macules (>5 mm in prepubertal ind./>15 mm in postpubertal ind**.

2) **≥ 2 neurofibromas of any type or one plexiform neurofibroma**

3) **Freckling** in the axillary or inguinal regions

4) **Optic glioma**

5) **Two or more Lisch nodules** (iris hamartomas)

6) **A distinctive osseous lesion** such as **sphenoid dysplasia or tibial pseudarthrosis**

7) **A first-degree relative** (parent, sib, or offspring) with NF1 as defined by the above criteria

-Diagnosis usually based on clinical findings, molecular genetic testing is rarely needed, except: --> NF1 is suspected but NIH diagnostic criteria not fulfilled

--> In child with serious tumor (e.g., optic glioma) in whom diagnosis would affect management --> Prenatal or preimplantation genetic diagnosis in a current or future pregnancy

--> Spinal NF1 or NF1 c.2970-2972 delAAT pathogenic variant often do not meet criteria

->500 mutations reported, usually unique to a particular family

## Others

-Majority normal lifespan; surgery for bone malformations or painful or disfiguring tumors; **MEK inhibitors for plexiform neurofibromas**; risk of malignant peripheral nerve sheath tumors in adolescence and young adulthood

-**Vitamin D supplementation**

# Parkinson Disease (Parkin-type)

## Genetics -PRKN (formerly PARK2; parkin, only gene to cause parkin type of early-onset Parkinson)

-AR

## Clinical findings/Dysmorphic features

-Early onset (age <40 years) or, rarely, juvenile onset (age <20 years)

-Lower-limb dystonia (muscles contract uncontrollably); hyperreflexia of lower extremities; well-preserved sense of smell; marked and sustained response to oral administration of **levodopa;** slow disease progression; **absence of dementia in most cases** (prevalence <3%)

## Etiology

-In Europe: parkin type of early-onset Parkinson disease accounts for ~50% of AR parkinsonism

## Pathogenesis

-**Parkin is E3 ubiquitin ligase** --> ubiquitination of proteins --> proteasomal degradation

-Parkin also mediates non-degradative modes of ubiquitination --> required for survival of nigrostriatal dopaminergic neurons

## Genetic testing/diagnosis

-Detection frequency is 80%-90% in familial cases with onset before age 20 years; lower than 10% in individuals with no family history and onset around age 40 years

# Rett syndrome

## Genetics

-Gene: **MECP2** (MECP2, **Xq28**)

-XLD; **pathogenic variant in a male is presumed to most often be lethal** (surviving males: severe neonatal encephalopathy; manic-depressive psychosis, pyramidal signs, Parkinsonian, macro-orchidism)

->**99% are simplex cases** (i.e. single occurrence in family), resulting from de novo variant

## Clinical findings/Dysmorphic features

-Spectrum in females: classic Rett, variant Rett, mild LD

1) Classic:

-Normal psychomotor development during first 6 - 18 months --> short period of developmental stagnation --> **rapid regression in language and motor skills** --> followed by long-term stability

-**Repetitive, stereotypic hand movements replace purposeful hand use**

-Additional findings: **fits of screaming**, **autistic features**, panic attacks, episodic apnea and/or hyperpnea, gait ataxia and apraxia, tremors, seizures, acquired microcephaly

2) Variant:

-Clinically suspected but molecularly unconfirmed Angelman syndrome

-Intellectual disability with spasticity/tremor, mild LD, rarely autism

## Etiology

-Prevalence of Rett syndrome in females: 1:8,500 by age 15 years

## Pathogenesis

-**MECP2 binds methylated CpG islands**

**-**Decreased of LoF --> Disruption of regulated gene expression during development

-Ubiquitously expressed but predominantly neurologic phenotype --> brain tissues more vulnerable or tissue-specific differences in MECP2 expression (alternate transcripts, differentially expressed in brain during development)

## Genetic testing/diagnosis

-Sequencing of exons 1-4, followed by deletion/duplication if sequencing is normal

-Testing of both parents for the identified sequence variation if VUS

**-Sequencing of MECP2 in classic Rett: 80%, In/Del: 8%**

## Others

-Germline mosaicism described

-MECP2 microduplication syndrome (0.3 to 2.3 Mb) --> infantile hypotonia, severe ID, absence of speech, progressive spasticity, recurrent respiratory infections, seizures

-Phase I and II: administration of tri-peptide form of insulin-like growth factor, rhIGF-1 (**mecasermin**)

# Wilson Disease

## Genetics

-Gene: **ATP7B** (Copper-transporting ATPase 2; 13q14.3-q21.1)

-AR

## Clinical findings/Dysmorphic features

-Disorder of **copper metabolism**; hepatic, neurologic, or psychiatric disturbances; 3-50 years

-**Liver** disease: **recurrent jaundice**, simple acute self-limited hepatitis-like illness, autoimmune-type hepatitis, **hepatic failure, chronic liver disease**

-Neurologic presentations: **movement disorders** (**tremors**, poor coordination, loss of fine-motor control, chorea, choreoathetosis) or **rigid dystonia** (**mask-like facies**, rigidity, gait disturbance, pseudobulbar involvement)

-Psychiatric disturbance: depression, neurotic behaviors, disorganization of personality

-**Kayser-Fleischer rings**: frequent, **copper deposition in Descemet's membrane of the cornea**

## Etiology

-1:30,000; carrier frequency 1:90

## Pathogenesis

-Copper-transporting ATPase 2: intracellular transmembrane copper transporter --> incorporating copper into ceruloplasmin and **moving copper out of the hepatocyte into bile**

-Tissue damage due to copper accumulation because of **lack of copper transport from the liver**

## Genetic testing/diagnosis

-Diagnosis established by combination:

1) Biochemical (low serum copper and ceruloplasmin conc., inc. urinary copper excretion)

2) Clinical (**Kayser Fleischer corneal ring**)

3) Detection of biallelic ATP7B pathogenic variants

-ATP7B sequencing (98%) --> H1069Q (35-45% Europeans); R779L (57% Asians); H714Q and delC2337 (40% Russians)

## Others

-Treatment: Chelating agents, liver transplant

# Amyotrophic lateral sclerosis

## Genetics

-**ALS/FTD** --> C9orf72, 23-30%, AD; **ALS1** --> SOD1, 20%, AD; **ALS6** --> FUS/TLS, 4%, AD; AD (AR: ALS2 and SPG20)

## Clinical findings/Dysmorphic features

-**Progressive neurodegenerative disease** involving **upper motor neurons** (UMN, located within brain and brainstem; send axons down the spinal cord to innervate with LMN) and **lower motor neurons** (LMN, located within ventral horn of spinal cord, send axons towards the periphery to innervate skeletal muscles)

-UMN signs: **hyperreflexia**, extensor plantar response, **increased muscle tone**, weakness in a topographic representation

-LMN signs: weakness, **muscle wasting**, **hyporeflexia**, **muscle cramps**, **fasciculations** (small, local, involuntary muscle contraction and relaxation, may be visible under the skin)

-Asymmetric focal weakness of extremities (**stumbling or poor handgrip**) or bulbar findings (dysarthria, dysphagia)

-Mean onset is 56y with no known family history; 46y with >1 one family member (familial ALS)

-Disease duration ~ 3years (death from compromise of the respiratory muscles)

## Etiology

-Prevalence is 4-8:100,000

## Pathogenesis

-**Toxic gain of function**, not enzyme deficiency (SOD1 prevents oxidative damage to cells)

## Genetic testing/diagnosis

-SOD1 mutation (20% familial, 3% sporadic ALS; 50% have p.Ala4Val in exon 1 mutation)

-Multigene panel

## Others

-**Steven Hawkins** **diseases**

-An increased number of GGGGCC (G4C2) hexanucleotide repeats in C9ORF72 can cause ALS

# Charcot Marie Tooth Disease

## Genetics

-**CMT1** (**AD):** **70-80%: 1.5Mb dup of PMP22 on 17p11.2** **(CMT1A); 5-10%: MPZ variant (CMT1B)**

-**CMT2** (**AD): MFN2, MPZ, HSPB1, KIF1B, LMNA**

-CMT intermediate form (AD): DNM2, YARS

-CMT4 (AR): 11 genes known: GDAP1 (CMT4A), MTMR2 (CMT4B1), SBF2 (CMT4B2), SBF1 (CMT4B3), SH3TC2 (CMT4C), NDRG1 (CMT4D), EGR2 (CMT4E), PRX (CMT4F), HK1 (CMT4G), FGD4 (CMT4H), FIG4 (CMT4J)

-**CMTX; XLD: 90% with GJB1** (mainly sequence variants)

## Clinical findings/Dysmorphic features

-CMT affects the peripheral nerves (both motor and sensory nerves)

-**CMT1 (50% of all CMTs)**: **demyelinating peripheral neuropathy**; distal muscle weakness and atrophy; sensory loss; **slow nerve conduction velocity**; often associated with **pes cavus** **and bilateral foot drop**; onset 5-25 years

-**CMT2 (20-40% of all CMTs)**: **axonal** (**non-demyelinating**) peripheral neuropathy; distal muscle weakness and atrophy; mild sensory loss; **normal or near-normal nerve conduction velocities**; clinically similar to CMT1; **typically less severe**; peripheral nerves not enlarged or hypertrophic; subtypes of CMT2 are clinically similar --> distinguished only by molecular genetic findings

-CMT **intermediate** form (rare): combination of myelinopathy and axonopathy

-CMT4 (rare): either myelinopathy or axonopathy; progressive motor and sensory axonal and demyelination; typical CMT phenotype of distal muscle weakness and atrophy associated with sensory loss and, frequently, pes cavus foot deformity

-CMTX (10-20% of all CMTs): moderate to severe motor and sensory neuropathy in affected males; usually mild to no symptoms in carrier females; SNHL and CNS symptoms may also occur

## Etiology

-1 in 3300 worldwide

## Pathogenesis

-Abnormal peripheral myelination

## Genetic testing/diagnosis

-Nerve conduction studies, nerve biopsy

-Gene sequencing, deletion/duplication analysis

# Duchenne & Becker Muscular Dystrophy

## Genetics

-Gene: **DMD** (Dystrophin; **Xp21.2**)

-**XLR, 1/3 de novo, 2/3 inherited**

## Clinical findings/Dysmorphic features

-**DMD**: onset <5 years; **progressive symmetrical muscular weakness**; delayed motor milestones; **waddling gait** and difficulty climbing stairs, running, jumping, standing up from a squatting; **calf hypertrophy**, **wheelchair by age 12**; **dilated cardiomyopathy** in almost all individuals >18y; few survive beyond the 3rd decade --> respiratory complications, progressive cardiomyopathy

-**BMD**: later onset; less severe; **wheelchair after age 16 years**; weakness of quadriceps may be only sign; activity induced cramping; **preservation of neck flexor muscles** (vs.DMD)

-**DMD-associated dilated cardiomyopathy** (**left ventricular dilation** and congestive heart failure); heterozygous females are at increased risk for DCM

## Etiology

-**DMD: 1 in 3,500 males; BMD: 1 in 30,000 males**

## Pathogenesis

-Dystrophin binds actin and other membrane proteins; mutations causing lack of dystrophin expression --> DMD; mutations causing abnormal quality or quantity of dystrophin --> BMD

## Genetic testing/diagnosis

-Increase in serum concentration of **creatine phosphokinase (CK);** **CK 10x nl in DMD, 5x nl in BMD** (unreliable test for carrier females; tends to decrease with age)

-Multiplex PCR: DMD exon del (65% DMD, 85% BMD); Southern or qPCR for gene duplication (6% DMD); DMD seq for small del/ins or SNVs (30% DMD); MLPA or gene-targeted microarray

## Others

-**Pseudohypertrophy**; **Gowers**’ **Maneuver**

-80% of het females no symptoms, but: Turner syndrome (45,X), skewed X-inactivation (balanced X-autosome translocation), UPD for X (from carrier mother or BMD father), compound heterozygosity for 2 DMD variants (carrier mother and BMD father)

-**Germline mosaicism: risk is estimated to be ~10-15% (rr ~7%)**

-Therapy: exon skipping, stop-readthrough, Crispr/Cas

# Friedreich Ataxia

## Genetics

-Gene: **FRDA** (Frataxin, 9q13)

-**AR; GAA triplet repeat expansion in FRDA intron 1**

## Clinical findings/Dysmorphic features

-**Progressive degeneration of the dorsal root ganglia**, posterior columns, corticospinal tracts, dorsal spinocerebellar tracts of the **spinal cord and cerebellum**

-Progressive **limb and gait ataxia** (slurred speech, stumbling, falling, incoordination) < 25 yrs; absent tendon reflexes in the lower extremities

-Within 5 years of disease onset: dysarthria, areflexia, pyramidal weakness of legs, **extensor plantar responses**; distal loss of joint position and vibration sense

-Scoliosis, **pes cavus**, **optic nerve atrophy**, **hypertrophic cardiomyopathy**

## Etiology

-1 in 50,000; carrier frequency: 1:60-1:100

## Pathogenesis

-**Frataxin** is predominantly located in **mitochondria**

-**Carboxy-terminal region** is highly conserved and is target for pathogenic missense variants

-Frataxin binds iron and is required for **synthesis of iron-sulfur clusters** --> synthesis of enzymes in the respiratory chain complexes I–III and aconitase

-**GAA repeat results in transcriptional silencing of FXN**: 1) epigenetic silencing in the sequence flanking the expanded GAA repeat and near the FXN promoter; 2) formation of one or more abnormal DNA structures, which interferes with transcriptional elongation

## Genetic testing/diagnosis

-**GAA triplet repeat expansion in FRDA intron 1** **(96% homozygous)**: **normal 5-33, premutation 34-65, disease causing: 66-1700** repeats; **some comphet for expansion and path variant**

-Electrophysiologic evidence of **axonal sensory neuropathy**

# Hereditary Neuropathy with Liability to Pressure Palsies

## Genetics

-Gene: **PMP22** (**Peripheral myelin protein** **22**, 17p.11.2); **PMP22 del vs. PMP22 dup in CMT1a**

## Clinical findings/Dysmorphic features

-Repeated **focal pressure neuropathies** (i.e. carpal tunnel syndrome, peroneal palsy with foot drop); recovery from acute neuropathy often complete; if not complete, disability usually mild

-Some affected individuals also have signs of a mild to moderate peripheral neuropathy

-Mild to moderate **pes cavus** deformity

-First attack usually in the second or third decade

## Etiology

-2-5 per 100,000

## Pathogenesis

-Decreased PMP22 mRNA and decreased peripheral myelin protein 22 in peripheral nerve cells

## Genetic testing/diagnosis

-PMP22 sequencing (20%), **1.5-Mb PMP22 deletion (80%)**

# Limb-Girdle Muscular Dystrophy

## Genetics

-Genes: **CAPN3** (Calpain 3), **FKRP** (Fukutin related protein), **LMNA** (Lamin-A/C), SGCA/B/D/G (alpha/beta/delta/gamma-sarcoglycan), DYSF (Dysferlin)

-**Mainly AR**, some AD

## Clinical findings/Dysmorphic features

-AR **Sarcoglycan**-LGMD: proximal limb weakness, difficulty running/walking, calf hypertrophy, onset age 3-15 (68% of childhood onset, 10% adult onset)

-AR **Calpain**-LGMD: proximal limb weakness, difficulty running and walking, calf atrophy, onset 2-40 yrs (10-30% AR LGMD)

-AR **Dysferlin**-LGMD: problems running/walking, foot drop, distal and/or pelvic weakness, transient calf hypertrophy, onset 17-23 yrs

## Etiology

-1 in 14,500 to 1 in 123,000 individuals

## Pathogenesis

-Sarcoglycanopathies: **disruption of dystrophin-dystroglycan complex**

-Calpainopathy: impairment of calpain proteolytic activity results in sarcomere remodeling by **promoting ubiquitin-mediated degradation of sarcomeric proteins**

-Dysferlinopathy: **disruption of muscle membrane repair machinery** is responsible for dysferlin-deficient muscle degeneration in dysferlin-null mice

## Genetic testing/diagnosis

-Inc. **serum CK**, dystrophic changes on muscle biopsy, sarcoglycan protein staining

-Gene sequencing (80-99%)

## Others

-Supportive care to promote mobility and ambulation

-Monitor for respiratory and orthopedic complications and for cardiomyopathy

# Myotonic dystrophy type I

## Genetics

-**DMPK** (Myotonin-protein kinase; **19q13.32**)

-**AD**

## Clinical findings/Dysmorphic features

-Multisystem disorder of **skeletal and smooth muscle**, eyes, heart, endocrine system, CNS

-**Mild (50-150 repeats)**: **cataract** (clouding of lens) + mild myotonia (sustained muscle tensing)

-**Classic (100-1000 repeats)**: muscle weakness/wasting, myotonia, cataract, arrhythmia; grip myotonia (**inability to quickly release a hand grip**)

-**Congenital (>2000 repeats)**: hypotonia and severe **generalized weakness at birth;** often with respiratory insufficiency and early death, ID is common

## Etiology

-Worldwide: 1:20,000

## Pathogenesis

-DMPK is serine-threonine kinase --> interact with members of the Rho- GTPases --> substrates include myogenin, the beta-subunit of the L-type calcium channels

-Due to **gain of function RNA mechanism --> CUG repeats attract many RNA splicing proteins --> alter alternative splicing of other genes**, **including the CL-channel** --> myotonia

## Genetic testing/diagnosis

-No DPMK SNVs, deletions or insertions reported, only **CTG repeat expansion in the 3' untranslated region of DMPK**

-Abnormal repeat can reach several thousand, particularly in individuals with congenital DM1

-PCR (detects repeats up to ~100), southern blot (detect repeats>100)

## Others

-**DM2**: **myotonia (90%) and muscle dysfunction** (weakness, pain, stiffness; 82%), less commonly by cardiac conduction defects, iridescent posterior subcapsular cataracts; **CNBP (ZNF9); intron 1** contains a complex repeat motif, (TG)n(TCTG)n(CCTG)n; expansion of the CCTG repeat 75 - 11,000 (mean 5000)

# Nemaline myopathy

## Genetics

-**ACTA1**, **NEB**, TNNT1, TPM2, TPM3; rare: CFL2, KBTBD13, KHLH41

-AR or AD

## Clinical findings/Dysmorphic features

-Weakness, hypotonia, **depressed or absent deep tendon reflexes**

-Weakness usually **most severe in face, neck flexors, proximal limb muscles**

-Age of onset: severe congenital (neonatal) (16%), Amish NM, intermediate congenital (20%), typical congenital (46%), childhood-onset (13%), adult-onset (late-onset) (4%)

## Etiology

-Incidence of 1:50,000 live births

## Pathogenesis

-Ten different genes: **6 encode protein components of the muscle thin filament**, **3 involved in the protein turnover in the muscle sarcomere** via ubiquitin proteasome pathway

## Genetic testing/diagnosis

-Muscle biopsy --> **diagnostic hallmark is the presence of rod-like inclusions (nemaline bodies)** in the sarcoplasm of skeletal muscle fibers with trichrome stain

-NEB sequencing: 50%; ACTA sequencing: 15-25% of NM (ACTA Del/dup analysis: Exon 55)

## Others

-Walking prior to 18 months is predictive of survival

# Spinal muscular atrophy

## Genetics

-Genes: **SMN1 (SMNT), SMN2 (SMNC)** (survival motor neuron protein 1 and 2; 5q12.2-q13.3)

-**AR**

## Clinical findings/Dysmorphic features

-**Arthrogryposis multiplex congenita** (congenital joint contracture in >2 areas of body)

-Progressive **degeneration and** **loss of anterior horn cells in the spinal cord** (i.e. lower motor neurons) **and the brain stem nuclei** --> **muscle weakness and atrophy**

-Onset of weakness ranges from before birth to adolescence/young adulthood

-Weakness is **symmetric, progressive, proximal > distal**

-SMN1-associated SMA spans a continuum without clear delineation of subtypes

-Complications: poor weight gain, FTT, restrictive lung disease, scoliosis, joint contractures

-**Loss of deep tendon reflexes**

## Etiology

-Incidence 4-10 in 100,000; Carrier frequency: 1:50 – 1:100

## Pathogenesis

-**Role for SMN protein in snRNPs** (small nuclear ribonuclear proteins) biogenesis and function

-Reduced SMN lowers the capacity of cells to assemble snRNPs --> altered levels of spliceosomal components and **defects in splicing** --> **impaired production of specific mRNAs and proteins**

## Genetic testing/diagnosis

-Targeted analysis: deletion of **SMN1 exon 7 deletion (95-98%)**, SMN1 sequencing (2-5%)

-Carriers with 2 SMN1 in cis (~4% of the population) will be misdiagnosed as non-carriers

-**Quantitative PCR** and **MLPA** to detect single-exon deletions or duplications (SMN1 and SMN2 are nearly identical --> gene-targeted microarray cannot be used to determine copy number)

-SMN1 sequencing cannot determine whether an inactivating variant is in SMN1 or SMN2 -->

1) Establish that the inactivating variant has previously been reported in SMN1

2) Sequence a long-range PCR product or a subclone of SMN1

## Others

-Increase in SMN2 copies often improves phenotype; absence of both SMN genes --> lethal

-SMN2 predominantly produces protein that is lacking in exon 7 (splice site variant in SMN2)

-Treatment: **SPINRAZA® (nusinersen)**; ASO targeted to SMN2 --> increased exon 7 inclusion

-Newborn with weakness, hypotonia, absent reflexes, and tongue fasciculations

# Syndromic Congenital Muscular Dystrophy

## Genetics

-Fukuyama (FCMD; *FCMD*)

-Muscle‐Eye‐Brain (MEB; *POMGNT1*)

-**Walker‐Warburg** (WWS; *POMT1*/*POMT2*)

-Congenital Muscular Dystrophy Type 1D (MDC1D; *LARGE*)

-**Mostly AR**; but: collagen VI-deficient CMD is AR/AD; LMNA-related CMD is AD (all de novo)

## Clinical findings/Dysmorphic features

-Hypotonia and muscle weakness present at birth or during infancy (**floppy baby**)

-Poor/decreased motor abilities, delay/arrest of motor milestones, joint/spinal deformities

-Onset of manifestations < 2yrs may be a reasonable diagnostic criterion

## Etiology

-Prevalence of 1:125,000

## Pathogenesis

-Disruption of **alpha dystroglycan** (integral component of the dystrophin‐glycoprotein complex)

## Genetic testing/diagnosis

-Muscle biopsy: dystrophic or myopathic pattern; **increased serum creatine kinase**; brain MRI: **Cobblestone complex** (enlarged flat ventricles, flat brainstem, cerebellar hypoplasia)

## Others

-LGMD is defined by muscle weakness in late childhood or adulthood

# Hexosaminidase A deficiency (Tay Sachs Disease)

## Genetics

-Gene: **HEXA** (Hexosaminidase A; 15q23-q24); HEXA encodes alpha chain of the heterodimeric protein β**-hexosaminidase A** (HEX A) (also called **GM2 gangliosidase)**

-AR

## Clinical findings/Dysmorphic features

1) Infantile (Tay-Sachs): progressive weakness, loss of motor skills, decreased attentiveness, **increased startle response** beginning at 3-6 months --> progressive neurodegeneration (seizures, blindness, spasticity, **eventual total incapacitation**) --> **death usually < 4 years**

2) Juvenile (subacute): muscle coordination problems, seizures, vision problems starting as young children

3) Chronic and adult-onset: later onset, rarer, some with bipolar form of psychosis

-**Cherry red spot on eye exam** (accumulation of GM2 gangliosides in the surrounding area)

## Etiology

-Incidence **approximately 1:3600 in AJ births**

-Carrier rate: 1:27, (**c.1274\_1277dupTATC**, p.Tyr427IlefsTer5 accounts for ~ 80%)

## Pathogenesis

-β-hexosaminidase A **cleaves terminal** β**-linked N-acetylgalactosamine** from GM2 ganglioside

-**Excessive and ubiquitous neuronal glycolipid storage** (≤12% of the brain dry weight)

-Enormous predominance is the specific glycolipid **GM2 ganglioside**

## Genetic testing/diagnosis

-Diagnosis relies on **absent/near-absent** β**-hexosaminidase A activity** in serum/white blood cells/other tissues from symptomatic individual (in presence of normal/elevated activity of the β-hexosaminidase B) --> **0-5% infantile TSD vs. <15% juvenile or chronic and adult-onset type**

-more than 130 HEXA pathogenic variants have been detected to date

-Panel of six most common pathogenic variants:

--> 3 x LOF (p.Tyr427IlefsTer5, c.1421+1G>C, c.1073+G>A)

--> p.Gly269Ser (associated with adult-onset form in hom or in comhet state with a null allele)

--> **2 x pseudodeficiency alleles** (p.Arg247Trp and p.Arg249Trp; not associated with neurologic disease but with reduced degradation of synthetic substrate during HEX A enzymatic testing)

## Others

-**Normal-sized liver and spleen (vs. Gaucher)**

-HEX A is composed of 1 alpha and 1 beta subunit; HEX B is composed of 2 beta subunits

# BRCA1 and BRCA2 Hereditary Breast and Ovarian Cancer

## Genetics

-BRCA1 and BRCA2 (Breast cancer type 1 and 2 susceptibility protein; **17q21 an 13q12.3**)

-AD

## Clinical findings/Dysmorphic features

**-BRCA1: Breast, ovarian, prostate cancer**

**-BRCA2: Breast, ovarian, prostate and pancreatic cancer**

## Etiology

-Prevalence of BRCA1/2 pathogenic variants in the general population: 1:400 to 1:500

## Pathogenesis

-LOF of BRCA1 --> defects in DNA repair/transcription, abnl centrosome duplication, **defective G2/M cell-cycle checkpoint regulation**, impaired spindle checkpoint, chromosome damage

-LOF of BRCA2 --> **defects in double-strand breaks repair** (hypersensitivity to ionizing radiation)

## Genetic testing/diagnosis

-Suspected in individuals with personal or family history (1st-, 2nd-, or 3rd-degree relative) of any of the following: 1) **Breast cancer diagnosed < 50 years**; 2) **Ovarian cancer**; 3) **Multiple primary breast cancers** (in one or both breasts); 4) **Male breast cancer**; 5) **Triple-negative** (estrogen receptor-negative, progesterone receptor-negative, HER2 negative); particularly when diagnosed < 60 years; **6) Combination of pancreatic cancer and/or prostate cancer** (Gleason score ≥7) **with breast cancer, and/or ovarian cancer**; 7) Breast cancer diagnosed at any age in an AJ individual; 8) > 2 relatives with breast cancer (one < 50); 9) >3 relatives with breast cancer at any age; 10) Previously identified BRCA1 or BRCA2 pathogenic variant in family

-**BRCA1 (66% of cases; 80% seq, 10% InDel); BRCA2 (34% of cases; 80% seq, 10% InDel)**

## Others

1) **Breast**: 12% in general pop. – **46-87% in BRCA1 / 40-84% in BRCA2**

2) **Ovarian**: 1-2% in general pop. – **40-63% in BRCA1 / 17-27% in BRCA2**

3) **Male breast**: 0.1% in general pop. – **1.2% in BRCA1 / 9% in BRCA2**

4) **Prostate**: 6% in general pop. – **9% in BRCA1 / 15% in BRCA2**

5) **Pancreatic** 0.5% in general pop. – **1-3% in BRCA1 / 2-7% in BRCA2**

# Familial Adenomatous Polyposis

## Genetics

-Gene: **APC** (Adenomatous polyposis coli protein; **5q21-22**)

-AD (15-30% de novo; 75-80% inherited)

## Clinical findings/Dysmorphic features

1) **FAP**:

-Colon cancer predisposition syndrome; **hundreds - thousands of adenomatous colonic polyps**

-Onset ~16 years; by age 35 years --> 95% of individuals have polyps

-Colon cancer risk 100% without colectomy; diagnosis in untreated individuals at ~ 39 years

-Extracolonic manifestations: polyps of gastric fundus and duodenum; osteomas; **dental anomalies**; **congenital hypertrophy of the retinal pigment epithelium (CHRPE)**; soft tissue tumors; desmoid tumors

2) **Attenuated FAP**:

-Multiple colonic polyps (less than 100, average of 30), **more proximally located**

-Diagnosis of colon cancer at a later age than in FAP

-Extracolonic manifestations: gastric and duodenal polyps or cancers

3) **Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS):**

-Gastric fundic gland polyposis, increased risk of gastric cancer, limited colonic involvement

## Etiology

-Prevalence of FAP: 1:7,000 to 1:30,000 live births

## Pathogenesis

-Pathogenic APC variants produce **usually truncated protein** --> no longer binds to GSK-3b --> does **not target beta-catenin for destruction** --> high levels of free cytosolic beta-catenin --> migrates to nucleus --> binds to Tcf-4 or Lef-1 --> **expression oncogenes (c-Myc and cyclin D1)**

## Genetic testing/diagnosis

-APC-associated polyposis condition should be suspected in individuals with any of the following clinical features: 1) **Multiple colorectal adenomatous polyps (at least 10-20)**; 2) **Family history of multiple colorectal adenomatous polyps** (>10 in a single individual, or fewer if >1 relative has multiple polyps, especially if diagnosed at a young age) and/or extracolonic features; 3) **Hepatoblastoma (very rare cancerous tumor, starts in liver)**; 4) Multifocal/bilateral **CHRPE**; 5) **Desmoid** tumor (noncancerous growths in the connective tissue); 6) Cribriform-morular variant of papillary thyroid cancer

## Others

-Colorectal **screening beginning at age 10-12 years for FAP** and in late teens for attenuated FAP

-Mutations in attenuated FAP located in three distinct regions of the APC gene, including the 5′ end spanning exons 3 to 5, exon 9 and the 3′ distal end

-If thousands of polyps and no SNV --> highest yield is to send for del/dup

**-Screening for hepatoblastoma in children identified to have APC variant recommended (10% of children with hepatoblastoma carry a mutation in APC)**

# Hereditary Nonpolyposis Colon Cancer (Lynch syndrome)

## Genetics

-Genes: **MLH1** (DNA mismatch repair protein MLH1), **MSH2** (DNA mismatch repair protein MSH2), **MSH6** (DNA mismatch repair protein MSH6), **PMS2** (PMS1 protein homolog 2), **EPCAM**

-AD

## Clinical findings/Dysmorphic features

-**Increased risk for CRC (50-80%)**, **endometrium cancer (25-60%), stomach (6-13%)**, **ovary (4-12%),** small bowel, hepatobiliary tract, urinary tract, brain, skin

## Etiology

-Prevalence ~ 1:440; accounts for ~ 1%-3% of CRCs and 0.8%-1.4% of endometrial cancers

## Pathogenesis

-Genes involved in **mismatch repair (MMR) pathway** --> functions to identify and remove **single-nucleotide mismatches** or insertions and deletion loops

-**Germline deletions within EPCAM** (not an MMR gene) --> disrupt MMR pathway by inactivating adjacent MSH2 (even though MSH2 itself is not mutated)

## Genetic testing/diagnosis

-**Amsterdam II Criteria**: ≥3 family members (at least one 1st degree) with HNPCC related cancers; 2 successive affected generations; ≥1 or more of the HNPCC-related cancers diagnosed before age 50; exclusion of FAP

-**Bethesda 2004**: CRC diagnosed under age 50yrs; 2 HNPCC related tumors at once; CRC with high MSI in someone <age 60yrs; CRC in ≥ 1st degree relatives with HNPCC related tumor with 1 cancer diagnosed before age 50yrs; CRC diagnosed in ≥ 1st or 2nd degree relatives (any age)

-**MSI** of tumor**; immuno-histochemistry** of tumor for MLH1, MSH2, MSH6 and PMS2

-Sequencing/InDel of MLH1 (50% of cases; 90%/10%); MSH2 (40% of cases; 80%/20%); MSH6 (7-10% of cases; 95%/5%); PMS2 (<5% of cases); EPCAM (1-3%; 0%/100%)

## Others

-**Colonoscopy with removal of precancerous polyps every 1-2y beginning at 20-25y** or 2-5 years before earliest age of diagnosis in family

# Li-Fraumeni Syndrome

## Genetics

-Gene: **TP53** (Cellular tumor antigen P53; **17p13**)

-AD (7-20% de novo)

## Clinical findings/Dysmorphic features

-Cancer predisposition syndrome: 1) **soft tissue sarcoma**; 2) **osteosarcoma**; 3) pre-menopausal **breast cancer**; 4) **brain tumors** (including choroid plexus carcinoma); 5) **adrenocortical carcinoma (ACC)**; 6) leukemias

-LFS-related cancers often occur in childhood or young adulthood

## Etiology

-Frequency of germline TP53 mutation may be as high as 1:5,000 to 1:20,000

## Pathogenesis

## -P53 is an important **TF** --> **in response to cellular stress/damage, p53 gets activated** --> regulates target genes to induce the following processes: cell cycle arrest, apoptosis, senescence, DNA repair

-**Absent p53 --> DNA-damaged cells survive and proliferate --> diverse number of malignancies**

## Genetic testing/diagnosis

-Diagnosis by presence of **all** of the following criteria: 1) **Proband with a sarcoma** (soft tissue tumor) diagnosed before age 45 years; 2) **1st-degree relative with any cancer** before age 45 years 3) **1st or 2nd-degree relative with any cancer** before age 45 years or a sarcoma at any age

-80% of families with features of LFS have identifiable TP53 pathogenic variant

-TP53: seq 95%, In/Del 1%

## Others

-Surveillance:

1) Children and adults undergo comprehensive annual physical examination

2) Children and adults should see physician promptly for lingering symptoms and illnesses

3) Women undergo breast cancer monitoring, with annual breast MRI and twice annual clinical breast examination beginning at age 20-25 years (mammograms = radiation risk)

4) Adults consider routine screening for colorectal cancer with colonoscopy every 2-3 years beginning no later than age 25 years

5) Individuals consider organ-targeted surveillance based on pattern of cancer in their family

-Intensified surveillance with whole-body MRI for adults/children are being evaluated in investigational settings

-NCCN suggests TP53 testing for any woman with breast cancer < 35 if BRCA1/2 is negative

# Multiple endocrine neoplasia type 1 (MEN1)

## Genetics

-Gene: **MEN1** (Menin; 11q13)

-AD

## Clinical findings/Dysmorphic features

-Varying combinations of >20 endocrine and non-endocrine tumors (overproduction of hormones by tumor or by growth of tumor)

-**Parathyroid tumors**: main MEN1-associated endocrinopathy; onset in 90% of individuals is 20-25 yrs with **hypercalcemia** --> hypercalcemia causes lethargy, depression, confusion, anorexia, constipation, nausea, vomiting, dehydration, hypercalciuria, kidney stones, increased bone resorption/fracture risk, hypertension, **shortened QT interval**

-**Pituitary tumors** (most common **prolactinoma**): **oligomenorrhea/amenorrhea/galactorrhea** in females and sexual dysfunction in males

-Well-differentiated endocrine tumors of the **gastro-entero-pancreatic (GEP)** tract

-Carcinoid tumors: non-hormone-secreting, manifest as a large mass after age 50 years

-Adrenocortical tumors: associated with primary hypercortisolism or hyperaldosteronism

-Non-endocrine tumors: facial angiofibromas, collagenomas, lipomas, meningiomas, ependymomas, leiomyomas and café au lait spots

## Etiology

-Prevalence 1:10,000 to 1:100,000

## Pathogenesis

-**Menin** mainly in nucleus; expressed in all tissues --> tissue-specific roles in DNA replication/repair and in transcriptional machinery

-Prevents tumorigenesis through repression of cell proliferation: 1) directly interacting with TFs (e.g., JunD, NF-kB, PPARgamma, VDR); 2) interacting with histone-modifying enzymes (MLL; HDACs; EZH2); 3) acts as TF itself

-Pathogenic variants prevent translocation to the nucleus

## Genetic testing/diagnosis

-Diagnosis: identification of one or both of the following:

1) 2-3 endocrine tumors (i.e. **parathryoid, pituitary, tumors of the GEP tract**)

2) A heterozygous pathogenic variant in MEN1 on molecular testing

-MEN1 sequencing (familial 80-90%; sporadic: 65%)/Indel (1-4%)

## Others

-MEN1 is tumor suppressor that follows **Knudson's two-hit model**

-**PPP: Pituitary, Parathyroid, Pancreatic Islet**

# Multiple Endocrine Neoplasia Type 2 (MEN2)

## Genetics

-Gene: **RET** (proto-oncogene tyrosine-protein kinase receptor RET; 10q11.2)

-AD

## Clinical findings/Dysmorphic features

-3 subtypes:

1) **MEN 2A**: **medullary thyroid carcinoma** (MTC), **pheochromocytoma** (adrenal glands tumor), **parathyroid adenoma/hyperplasia**

2) **MEN 2B**: **MTC**, pheochromocytoma, mucosal neuromas of lips and tongue, **distinctive facies with enlarged lips**, ganglioneuromatosis of the gastrointestinal tract, **"marfanoid" habitus**

3) **FMTC** (familial medullary thyroid carcinoma): MTC only

-**MTC typically occurs in early childhood in MEN 2B, early adulthood in MEN 2A, and middle age in FMTC**

## Etiology

-Prevalence of MEN 2 has been estimated at 1:35,000

## Pathogenesis

-RET: receptor tyrosine kinase (extracellular, transmembrane, intracellular domains)

-**Pathogenic variants in cysteine-rich extracellular domain (609, 611, 618, 620, 634)** **cause ligand-independent RET dimerization --> constitutive activation** **(gain of function)**

## Genetic testing/diagnosis

-Clinical criteria:

-MEN 2A: ≥2 specific endocrine tumors (MTC, pheochromocytoma, parathyroid adenoma/hyperplasia) in a single individual or in close relatives

-FMTC: in families with ≥4 cases of MTC without pheochromocytoma or parathyroid adenoma/hyperplasia

-Select exon testing (majority of pathogenic variants in exons 10, 11, 13-16) --> single-gene testing (sequencing of RET if no pathogenic variant is found by exon testing) --> multigene panel that includes RET and other genes of interest

-No In/Dels since gain-of-function

## Others

-**Prophylactic thyroidectomy (by age 1 for MEN2B, by age 5 for most of MEN2A**), screen for pheochromocytoma annually and prior to any surgery, annual calcitonin stimulation test, annual parathyroid hormone screening

-**Pathogenic variant in codon 918 causes 95% of the MEN 2B phenotype**

# Neurofibromatosis type 2

## Genetics

-Gene: NF2; (Neurofibromin-2/Merlin; 22q12.2)

-AD

## Clinical findings/Dysmorphic features

-Benign nerve tumors (schwannomas, meningiomas, ependymonas, astrocytoma)

-**Hallmark is** **bilateral acoustic/vestibular schwannoma**: onset age 18-24 yrs, hearing loss, tinnitus, **balance problems**

-Cataracts, mononeuropathy, café-au-lait (fewer than in NF1)

## Etiology

-Prevalence of NF2 is 1:60,000; birth incidence of 1:33,000

## Pathogenesis

-Merlin may coordinate processes of growth-factor receptor signaling and cell adhesion

-NF2 is a tumor suppressor, 2nd hit leads to complete LOF when one germline mutation present

## Genetic testing/diagnosis

-NF2 sequencing (75%), dup/del including CMA testing (10-15%)

->400 pathogenic variants: mostly missense, nonsense, splicing variants and small deletions

## Others

-**Somatic mosaicism is frequent**: 30% of ind. with de novo NF2 variant have somatic mosaicism

# PTEN Hamartoma Tumor Syndrome

## Genetics

-Genes: **PTEN** (Phosphatidylinositol-3,4,5-trisphosphate 3-phosphatase; 10q23)

-**AD**

## Clinical findings/Dysmorphic features

-**Cowden syndrome (CS)**: multiple **hamartoma** syndrome; high risk for benign and malignant tumors (**breast (LTR:85%), thyroid (LTR:35%), endometrium (LTR:28%)**); **macrocephaly**; **trichilemmomas** (benign cutaneous neoplasm); **papillomatous papules**; present by late 20s

-**Bannayan-Riley-Ruvalcaba syndrome (BRRS)**: congenital disorder characterized by **macrocephaly**, intestinal hamartomatous polyposis, lipomas, **pigmented macules of the** **glans penis (Koppe)**

-**PTEN-related Proteus syndrome (PS)**: complex, highly variable; congenital malformations and hamartomatous overgrowth of multiple tissues, connective tissue nevi, epidermal nevi, hyperostosis (excessive bone growth)

## Etiology

-1 in 200,000

## Pathogenesis

-PTEN is major phosphatase for phosphoinositide-3,4,5-triphosphate --> **downregulates PI3K/AKT pathway**

-Majority (76%) of germline pathogenic variants: truncated or dysfunctional PTEN; many missense variants are functionally null (**haploinsufficiency**)

-**PTEN is absent --> phosphorylation of AKT1 is uninhibited** --> inability to activate cell cycle arrest and/or to undergo apoptosis; mitogen-activated protein kinase (MAPK) pathway is dysregulated, leading to abnormal cell survival

## Genetic testing/diagnosis

-Identification of a heterozygous germline pathogenic variant in PTEN

-Sequence analysis of PTEN first --> gene-targeted deletion/duplication --> PTEN promoter seq

# Tuberous Sclerosis Complex

## Genetics

-Genes: TSC1 (Hamartin, 9q34; 26% of cases), TSC2 (Tuberin; 16p13; 69% of cases)

-**AD (2/3 de novo)**

## Clinical findings/Dysmorphic features

-Skin: **hypomelanotic macules**, confetti skin lesions, facial angiofibromas, **shagreen patches** (rough, elevated), fibrous cephalic plaques, **ungual fibromas** (under toenails)

-Brain: cortical tubers, subependymal nodules, cortical dysplasias, **subependymal giant cell** **astrocytomas**, seizures, ID/DD, psychiatric illness

-Kidney: **angiomyolipomas**, cysts, renal cell carcinomas

-Heart: rhabdomyomas, arrhythmias

-Lungs: lymphangioleiomyomatosis, multifocal micronodular pneumonocyte hyperplasia

-CNS tumors: leading cause of morbidity/mortality; renal disease: 2nd

## Etiology

-Incidence may be as high as 1:5,800 live births

## Pathogenesis

-**Hamartin and tuberin** form heterodimers --> regulate cell growth and proliferation; key **regulators of AKT/mTOR** signaling pathway; participate in several other signaling pathways (MAPK, AMPK, b-catenin, calmodulin, CDK, autophagy, cell cycle pathways)

-Most pathogenic variants are LoF --> uncontrolled cell growth and cell proliferation --> formation of hamartomas

## Genetic testing/diagnosis

-Sequence analysis and gene-targeted del/dup of TSC1 and TSC2

-TSC1 sequencing (10% familial, 15% sporadic) and TSC2 sequencing (14% familial and 53% sporadic); InDel: ~1%

-Somatic mosaicism for pathogenic variant should be considered

## Others

-TSC2/PCKD contiguous gene deletion syndrome with features of TSC and PKD --> renal cysts!

# Von Hippel-Lindau Syndrome

## Genetics

-Gene: VHL (Von Hippel-Lindau disease tumor suppressor; 3p25)

-AD

## Clinical findings/Dysmorphic features

-**Hemangioblastomas** (CNS tumors, originate from vascular system) of brain, spinal cord, retina:

-->cerebellar: associated with headache, vomiting, gait disturbances, ataxia

-->spinal: usually present with pain (cord compression may cause sensory/motor loss)

-->retinal: may be the initial manifestation and may cause vision loss

-Renal cysts and **clear cell renal cell carcinoma** (in 70%, leading cause of death)

-**Pheochromocytoma** (adrenal glands tumors), pancreatic cysts, neuroendocrine tumors; **endolymphatic sac tumors (can cause HL);** epididymal and broad ligament cysts

## Etiology

-Incidence approx. 1 in 36,000 births; de novo mutation rate: 4.4x10-6 gametes per generation

## Pathogenesis

-pVHL is tumor suppressor --> variety of functions including transcriptional regulation, post-transcriptional gene expression, apoptosis, extracellular matrix formation, ubiquitinylation

-**Regulation of hypoxia-inducible genes through targeted ubiquitinylation and degradation of HIF1α** --> disruption of VHL results in renal cell carcinoma, hemangioblastoma, and other highly vascularized tumors

## Genetic testing/diagnosis

-Sequence analysis of the VHL coding region, intron 1, and flanking sequences

-VHL sequencing: 89%; Del/Dup: 11%; 35% of patients with VHL have missense mutations!

## Others

-**Arginine codon 167** is considered a mutational hot spot

# Xeroderma Pigmentosum

## Genetics

-Genes: DDB2 (3%), **ERCC1**, **ERCC2** (20-30%), ERCC3 (1%), ERCC4 (~5%), ERCC5 (3-9%), POLH (10-25%), **XPA** (10-50%), **XPC** (3-43%)

-AR

## Clinical findings/Dysmorphic features

-Sun sensitivity (severe sunburn with blistering, persistent erythema on minimal sun exposure); marked freckle-like pigmentation of the face before age 2 yrs

-Sunlight-induced ocular involvement (photophobia, keratitis, atrophy of the skin of the lids)

-More than **1000x increased risk of sunlight-induced cutaneous neoplasms** (basal cell carcinoma, squamous cell carcinoma, melanoma)

-**25% have neurologic manifestations** (acquired microcephaly, diminished or absent deep tendon stretch reflexes, progressive SNHL, progressive cognitive impairment)

-Most common causes of death: skin cancer, neurologic degeneration, internal cancer

-Median death: XP w neurodegeneration (29 years); XP w/o neurodegeneration (37 years)

## Etiology

-Prevalence is 1:1,000,000 in US and Europe

## Pathogenesis

-DNA repair system: **senses, excises, repairs UV-induced dipyrimidine** photoproducts --> if defective: replication errors and subsequent tumorigenesis

## Genetic testing/diagnosis

-Founder variant testing can be considered (XPA: India, Japan, Tunisia; XPC: North Africa; ERCC2: Iraqi Jewish; POLH: Tunisia, North Africa, Japan, Basque)

-Multigene panel

# Beckwith-Wiedemann Syndrome

## Genetics

-Gene: **IGF2** and **H19** in domain 1; **CDKN1C**, **KCNQ10T1**, and **KCNQ1** in domain 2

-**AD in 15%**

## Clinical findings/Dysmorphic features

-**Neonatal hypoglycemia**, **macrosomia** (large baby, 90%), **macroglossia** (50%), **ear creases/pits,** hemihyperplasia, omphalocele (organs, including liver, outside abdomen with covering membrane vs. Gastroschisis has no sac and is likely caused by a rupture of a hernia of the cord)

-**Embryonal tumors** (**e.g. Wilms tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma**)

-Visceromegaly, adrenocortical cytomegaly

-Renal: medullary dysplasia, nephrocalcinosis, medullary sponge kidney, nephromegaly)

-Clinical spectrum (affected ind. may have many of these features or only one)

-Early death may occur from prematurity, hypoglycemia, cardiomyopathy, macroglossia, tumors

## Etiology

-Prevalence of 1:10,000

## Pathogenesis

-**Domain 1:** imprinted genes **H19** and **IGF2** (H19: ncRNA may function as tumor suppressor; IGF2: potent fetal growth factor):

**--> IC1 unmethylated on mat allele --> CTCF binds DNA --> prevents enhancer to activate IGF2 --> IGF2 is not expressed/H19 is expressed**

--> **IC1 methylated on pat allele --> CTCF cannot bind --> IGF2 expressed/H19 not expressed**

-**Domain 2**: imprinted genes **CDKN1C**, **KCNQ1**, and **KCNQ1OT1;** IC2 in promoter for KCNQ1OT1:

--> **IC2 methylated on mat allele** --> **KCNQ1OT1 not expressed/CDKN1C and KCNQ1 are expressed**

**--> IC2 not methylated on pat allele** --> **KCNQ1OT1 expressed/CDKN1C and KCNQ1 are not expressed**

-Loss of methylation at IC2 on the maternal chromosome --> biallelic expression of the normally paternally expressed KCNQ1OT1 and reduced CDKN1C and KCNQ1 expression

## Genetic testing/diagnosis

-Cytogenetically detectable abnormalities on 11p15 only in < 1%

-Causes: **1) Hypomethylation on maternal IC2 (50%); 2) Paternal UPD for 11p15 (20%), 3) unknown (20%) 4) Hypermethylation on maternal IC1 (5%), 5) Maternal CDKN1C SNV in ~40% of familial cases and 5%-10% of cases with no family history**

## Others

-Screening for embryonal tumors: **abdominal US every 3 months until 8y**

-Serum AFP concentration is monitored in the first few years of life for hepatoblastoma

-**pUPD of 11p15 and gain of met at IC1 --> highest risk for WT and hepatoblastoma**

# Sotos Syndrome

## Genetics

-Gene: **NSD1** (Histone-lysine N-methyltransferase, H3 lysine-36 and H4 lysine-20 specific; 5q35) -**AD (95% de novo); microdeletion of 5q35 or pathogenic variants in NSD1**

## Clinical findings/Dysmorphic features

1) Distinctive facial: broad and prominent forehead, sparse frontotemporal hair, downslanting palpebral fissures, **malar flushing** (reddish cheeks), long and narrow face, long chin

2) Learning disability: early developmental delay, mild to severe intellectual impairment

3) Overgrowth (height and/or head circumference ≥2 SD above mean)

4) Others: behavioral problems, advanced bone age, cardiac anomalies, cranial MRI/CT abnormalities, joint hyperlaxity/pes planus, maternal preeclampsia, neonatal jaundice, neonatal hypotonia, renal anomalies, scoliosis, seizures

## Etiology

- 1:14,000 live births

## Pathogenesis

-**Haploinsufficiency of NSD1** (may be related to genes affecting growth)

## Genetic testing/diagnosis

-**MLPA or FISH for** **5q35 microdeletion including NSD1** (1.9Mb): ~15% (50% in Japanese)

-NSD1 sequencing: 27-93% (12% in Japanese)

-Caused by NAHR! (see 22q11.2 deletion syndrome!)

# Ataxia with Oculomotor Apraxia Type 1 and Type 2

## Genetics

-Gene: APTX (AOA1; Aprataxin; 9p13.3), SETX (AOA2; Probable Helicase Senataxin; 9q34)

-AR

## Clinical findings/Dysmorphic features

-Childhood onset: slowly progressive **cerebellar ataxia** --> **oculomotor apraxia** (defect of controlled, voluntary, purposeful eye movement); severe primary motor peripheral axonal motor neuropathy

-First manifestation: progressive **gait imbalance** (mean age of onset: 4.3 yrs) --> **dysarthria (slurred or slow speech)** --> upper-limb dysmetria with mild intention tremor

-Oculomotor apraxia: few years after onset of ataxia, progresses to external ophthalmoplegia (paralysis of the muscles surrounding the eye)

-All affected individuals: areflexia followed by a peripheral neuropathy and **quadriplegia (paralysis --> partial or total loss of use of all four limbs and torso)** with loss of ambulation

-Intellect remains normal in some individuals

## Etiology

-0.5 in 100,000 for AOA1

## Pathogenesis

-Aprataxin plays role in **DNA-single-strand break repair and double-strand break repair** --> **enhanced sensitivity to agents that cause DNA breaks**

## Genetic testing/diagnosis

-Sequencing APTX (increased incidence in Portugal and Japan) and SETX

-Mutation detection rate unknown

## Others

-AOA2: onset 3-30 years with cerebellar atrophy, axonal sensorimotor neuropathy, oculomotor apraxia, elevated serum concentration of AFP

# Cockayne Syndrome

## Genetics

-Gene: ERCC6, ERCC8 (DNA excision repair protein ERCC-6 and ERCC-8)

-AR

## Clinical findings/Dysmorphic features

1) CS type I (**moderate**): normal prenatal growth; **onset of growth delay and DD in the first 2 yrs**; full manifestation: height, weight, HC far below 5th %tile; progressive impairment of vision/hearing, central/peripheral NS dysfunction --> severe disability; **death in 1st or 2nd decade**

2) CS type II (**severe**): growth failure at birth; little or no postnatal neurologic development; **congenital cataracts** or other structural anomalies of the eye; early postnatal contractures of spine (kyphosis, scoliosis) and joints; **death usually occurs by age 7 years**

3) CS type III (mild): normal growth and cognitive development or late onset

4) Xeroderma pigmentosum-Cockayne syndrome (XP-CS): facial freckling and early skin cancers (typical of XP) + intellectual disability, spasticity, short stature, and hypogonadism (typical CS)

## Etiology

-Minimum incidence at 2.7 per million births

## Pathogenesis

-**Abnormal transcription-coupled nucleotide excision repair** (preferential **removal of UV-induced pyrimidine dimers and other transcription blocking lesions**)

## Genetic testing/diagnosis

-Gene sequencing and/or Del/Dup of ERCC6 (75%), ERCC8 (25%)

## Others

-XP-CS: no skeletal involvement, no facial phenotype, no CNS dysmyelination and calcifications

-CS --> no increased cancer risk

# Hutchinson-Gilford Progeria Syndrome

## Genetics

-Gene: LMNA (Lamin-A/C; 1q21.2)

## Clinical findings/Dysmorphic features

-Onset in childhood: **accelerated aging;** profound FTT during the first year

-Characteristic facial features: disproportionately large head for the face, **narrow nasal ridge**, narrow nasal tip, thin vermilion of upper and lower lips, small mouth, retro- and micrognathia

-Common features: **loss of subcutaneous fat**, delayed eruption and loss of primary teeth, abnormal skin with small outpouchings over the abdomen and upper thighs, alopecia, nail dystrophy, coxa valga (deformity of the hip), progressive joint contractures

-Later: low-frequency conductive HL, dental crowding, partial lack of secondary tooth eruption

-Motor and mental development is normal

-Death occurs as a result of severe atherosclerosis, cardiac disease (myocardial infarction or heart failure) or cerebrovascular disease (stroke) between 6 and 20 years

## Etiology

-1 in 20,000,000

## Pathogenesis

-**c.1824C>T, p.Gly608=** leads to **activation of cryptic splice site in exon 11** --> production of a prelamin A that **lacks 50 amino acids near the C terminus** --> still retains the CAAX box and is therefore farnesylated, but is missing the site for endoproteolytic cleavage of the final 16 amino acids along with the farnesyl moiety --> resulting protein, named **progerin**

-Lack of farnesyl cleavage --> **long-term progerin association with inner nuclear membrane**

## Genetic testing/diagnosis

-Classic genotype: heterozygous for c.1824C>T, p.Gly608= (~90% of individuals with HGPS)

-Non-classic genotype: characteristic clinical features and het for another LMNA pathogenic variant in exon 11 or intron 11 (~10% of individuals with HGPS)

# Alpha-1 Antitrypsin Deficiency

## Genetics

-Gene: **SERPINA1** (alpha-1 antitrypsin; 14q32.1)

-**AR**

## Clinical findings/Dysmorphic features

-**Adult** **chronic obstructive pulmonary disease (COPD); lower lobe emphysema (damage to the air sacs (alveoli) in the lungs)**

-Childhood and adult liver disease **(obstructive jaundice and raised transaminases in kids**; **cirrhosis and fibrosis in adults)**

-Age of onset: 60’s; **40-50yrs in** **smokers**

## Etiology

-**One of the most common metabolic disorders** in individuals with northern European heritage

-1 in 5,000-7,000 in North America and 1 in 1,500-3,000 in Scandinavia

## Pathogenesis

-Low concentrations of alpha1-antitrypsin (AAT), a serine protease inhibitor (serpin)

-**Lung**: AAT expressed in and secreted by liver --> main function is to protect lung from proteolytic damage by binding and inhibiting neutrophil elastase (always in lung and increased in smokers) --> excessive destruction of elastin in the alveolar walls **("toxic loss of function"**)

-**Liver**: defective AAT polymerizes in hepatocytes ("loop-sheet polymerization") --> decreased secretion and intra-hepatocyte accumulation of AAT **("toxic gain of function")**

## Genetic testing/diagnosis

-Diagnosis:

1) Low serum conc. of AAT (most commonly used technique is nephelometry) --> nl: 100-220 mg/dL; in AATD with lung disease usually <57 mg/dL + either 2) or 3)

2) Functionally deficient AAT protein variant by protease inhibitor (PI) typing (by polyacrylamide gel **isoelectric focusing (IEF)** electrophoresis of serum)

3) Detection of biallelic SERPINA1 pathogenic variants

-**PI\*M**: most common allele in all populations

-**PI\*Z**: most common pathogenic allele --> deficient AAT ; **homozygous individuals (PI\*ZZ) have severe AATD**

-PI\*S: pathogenic --> deficient AAT; clinical consequence in the compound heterozygous state with 2nd pathogenic allele (e.g. PI\*SZ) and when serum AAT level is <57 mg/dL.

-Null alleles (designated PI\*QO) --> Pathogenic alleles --> no mRNA/no protein

-Targeted mutation testing of **SERPINA (PI\*Z: 95% E342K)**

## Others

-AATD should be suspected in individuals with: 1) Chronic obstructive pulmonary disease (i.e., emphysema, persistent airflow obstruction, and/or chronic bronchitis) 2) AND/OR any of the following: liver disease at any age, including obstructive jaundice in infancy; C-ANCA positive vasculitis (i.e., GPA); necrotizing panniculitis

# Cystic Fibrosis and Congenital Absence of the Vas Deferens

## Genetics

-Gene: CFTR (cystic fibrosis transmembrane conductance regulator; 7q31.2)

-AR

## Clinical findings/Dysmorphic features

-CF: multisystem disease affecting epithelia: respiratory tract, exocrine pancreas, intestine, hepatobiliary system, exocrine sweat glands

-Progressive obstructive lung disease with bronchiectasis; pulmonary disease (**Staphylococcus aureus and Pseudomonas aeruginosa**)

-Pancreatic insufficiency and malnutrition

-Recurrent sinusitis and bronchitis

-Male infertility: Congenital Absence of the Vas Deferens (CAVD); > **95% of males are infertile**

-Pulmonary disease is major cause of morbidity and mortality

-**Meconium ileus** occurs at birth in 15%-20% of newborns with CF

## Etiology

-**Most common life-limiting AR disorder** in individuals of northern European background; incidence of CF is 1:3,200 live births in this population; ~30,000 affected persons live in the US

-Carrier frequencies: AJ 1:29; NE background 1:28; African American 1:61; Asian American 1:118

## Pathogenesis

-CFTR is **cell membrane chloride channel** --> 4 mutation classes: I. reduced/absent synthesis, II. block in protein processing, III. block in regulation of chloride channel, IV. altered conductance of chloride channel

## Genetic testing/diagnosis

-Diagnosis of CF established in

1) Proband with ≥ characteristic phenotypic features + evidence of defective CFTR function (2 elevated sweat chloride values/biallelic CFTR variants/transepithelial nasal potential difference)

2) Infant with **elevated trypsinogen on NBS** + biallelic CFTR variants or elevated sweat chloride

3) CAVD in male with azoospermia + absence of vas deferens on palpation or biallelic CAVD-causing CFTR variants

-Targeted analysis can be performed first: panel of 23 pathogenic variants

--> **Detection rates: 97% in Ashkenazi Jewish, 88.3% in non-Hispanic whites, 69% in African Americans, 57% in Hispanic Americans**

-Sequencing and del/dup of CFTR if only one or no pathogenic variant is found

## Others

-Poly T tract in intron 8 is associated CFTR-related disorders --> 7T/9T are polymorphic variants; 5T (5% of people) is variable penetrant variant --> 90% lacks exon 9

-Poly T testing as reflux if R117H is detected (not primary test, indication is CF and not CAVD)

-TG tract lies just 5' of the poly T--> longer TG tract (12 or 13) in conjunction with 5T has strongest adverse effect on proper splicing

-**Kalydeco (Ivacavftor**): approved by FDA in 2012 for G551D for kids >6 years; 37 mutations approved July 2017; now approved for patients >2 years --> helps defective CFTR to function (potentiator, opens channel; Phe508del2 not enough CFTR at membrane for Kalydeco to work)

-**Symdeko (Ivacavftor/Tezacaftor or Lumacaftor**): FDA approved for patients > 12 years; also for p.Phe508del2 (Tezacaftor helps to get CFTR to membrane; Ivacaftor opens the channel)

# Alport Syndrome

## Genetics

-Gene: COL4A3, COL4A4, or COL4A5 (Collagen alpha-3(IV) chain/ 4(IV) chain/ 5(IV) chain

-**AR/AD: COL4A3 and COL4A4; XLR: COL4A5;** 2/3 XLAS; 15% ARAS; 20% ADAS

## Clinical findings/Dysmorphic features

-Spectrum: progressive renal disease with cochlear and ocular abnormalities (Alport) to isolated hematuria with benign course (thin basement membrane nephropathy)

-Renal disease progresses: **microscopic hematuria (blood in urine)** (microhematuria; 100% of affected males and > 90% of affected females with XLAS; 100% of males and females with ARAS) to **proteinuria**, **progressive renal insufficiency**, **end-stage renal disease** (ESRD) in all males with XLAS, and in all males/females with ARAS

-**Progressive SNHL** is usually present by late childhood or early adolescence

-Ocular findings: **virtually pathognomonic: anterior lenticonus** (localized, cone-shaped deformation of the anterior or posterior lens surface); maculopathy (whitish or yellowish flecks or granulations in the perimacular region); corneal endothelial vesicles (posterior polymorphous dystrophy); recurrent corneal erosion

-In ADAS: ESRD is delayed until later adulthood, SNHL is late in onset, ocular involvement is rare

## Etiology

-Prevalence estimated at 1:50,000 live births

## Pathogenesis

-**Type IV Collagen**: ubiquitously; major collagen component of basement membranes

-Abnormal secretion of collagen alpha 3,4, 5 chains

## Genetic testing/diagnosis

-Multigene panel: COL4A5 (80-85% of AS cases; Seq: 85-90%; Indel: 10-15%)

# Polycystic Kidney Disease (AD and AR)

## Genetics

-Gene: PKD1/PKD2 (Polycystin-1; 16p13.1/Polycystin-2; 4q21); PKHD1 (Fibrocystin; 6p21.1-p12)

-**AD (PKD1, PKD2) and AR (PKHD1)**

## Clinical findings/Dysmorphic features

1) ADPKD:

-**Generally late-onset** multisystem disorder with **bilateral renal cysts, liver cysts, increased risk of intracranial aneurysms** (5x increased); ~50% with ESRD by age 60 years

-Others: cysts in pancreas; seminal vesicles; arachnoid membrane; dilatation of aortic root and dissection of thoracic aorta; mitral valve prolapses; abdominal wall hernias

2) ARPKD:

-**Congenital hepatorenal fibrocystic syndrome**; renal/liver-related morbidity/mortality in kids

-Majority presents in **neonatal** **period** with **enlarged echogenic kidneys**: renal disease with nephromegaly, hypertension, varying degrees of renal dysfunction (>50% ESRD in 1st decade)

-Pulmonary hypoplasia due to oligohydramnios in a number of affected infants (~30% of these infants die in the neonatal period or within the first year of life from respiratory insufficiency)

-Others: subset with hepatosplenomegaly; histologic hepatic fibrosis present at birth

## Etiology

-ADPKD: **most common potentially lethal single-gene disorder**; prevalence at birth is ~ 1:1,000; it affects ~300,000 persons in the US

-ARPKD: incidence is estimated at 1:10,000 to 1:40,000

## Pathogenesis

-PKD-related proteins are involved with function of the **primary cilia** (located on apical surface of most epithelial cells including kidney tubule and biliary cells)

-Fibrocystin, polycystin-1 and polycystin-2 interact at molecular level in addition to direct interactions of the protein products --> these **cystoproteins** exist as multimeric protein complexes at multiple sites including primary cilia

## Genetic testing/diagnosis

-ADPKD: **PKD1 (78% of cases**; 97%/3%); **PKD2 (12% of cases**; 97%/3%); GANAB (0.3% of cases); DNAJB11 (0.1% of cases); unknown (7% of cases)

-ARPKD: **PKHD1 (73% of cases**/1-2%); DZIP1L (<1%/?)

## Others

-PKD2 mutations show later onset and slower rate of progression. ESRD age 60 yrs

-**TSC2/PKD1 contiguous gene syndrome**

# Achondroplasia

## Genetics

-Gene: **FGFR3** (Fibroblast growth factor receptor 3; 4p16.3)

-AD **(80% de novo)**

## Clinical findings/Dysmorphic features

-**Rhizomelic** (proximal limb) shortening of the limbs; macrocephaly; frontal bossing; midface retrusion; trident hand

-In infancy: hypotonia is typical, developmental motor milestones often delayed

-Intelligence and life span are usually near normal

-Complications: **craniocervical junction compression**, **obstructive sleep apnea**, middle ear dysfunction, kyphosis, spinal stenosis

## Etiology

-Most common form of inherited disproportionate short stature; 1:26,000-1:28,000 live births

## Pathogenesis

-FGFR-3: membrane-spanning tyrosine kinase receptor: extracellular ligand-binding domain (three immunoglobulin (Ig) subdomains), **transmembrane domain**, a split intracellular tyrosine kinase domain

-**WT-FGFR-3: neg. regulator of bone growth** (inhibition of chondrocyte proliferation and diff.)

-p.Gly380Arg in transmembrane domain --> constitutive activation and excess inhibitory signaling in growth plate chondrocytes

## Genetic testing/diagnosis

-Individuals with typical findings do not need molecular confirmation of the diagnosis

-**c.1138G>A (p.Gly380Arg)** in 98% and **c.1138G>C (p.Gly380Arg)** in 1%

## Others

-Family of bone dysplasias (hypochondroplasia, achondroplasia, SADDAN dysplasia, thanatophoric dysplasia type I and II) due to FGFR3 variants --> graded FGFR-3 activation

-De novo mutations occur **exclusively on paternally-derived allele**

# Cleidocranial Dysplasia Spectrum Disorder

## Genetics

-Gene: **RUNX2** (Runt-related transcription factor 2; 6p21)

-AD (high proportion de novo)

## Clinical findings/Dysmorphic features

-Skeletal dysplasia with clinical continuum ranging from classic CCD **(1) delayed closure of the cranial sutures, 2) hypoplastic or aplastic clavicles, 3) dental abnormalitie**s) to mild CCD to isolated dental anomalies without the skeletal features (most with classic form and normal ID)

-**Wide-open fontanelles at birth** (may remain open throughout life)

-**Clavicular hypoplasia** (narrow, sloping shoulders that can be opposed at the midline)

-**Dental anomalies** (supernumerary teeth, eruption failure of permanent teeth)

-Increased risk of developing recurrent sinus infections, recurrent ear infections leading to conductive hearing loss, upper-airway obstruction

## Etiology

-1 in 1,000,000

## Pathogenesis

-**RUNX2 is TF** involved in osteoblast differentiation and skeletal morphogenesis; osteoblast differentiation during intramembranous ossification and chondrocyte maturation during endochondral ossification --> pathogenic variants in RUNX2 result in haploinsufficiency

## Genetic testing/diagnosis

-X-ray: clavicular hypoplasia, open sutures, **wormian bones** (extra bone pieces within a suture), poor or absent sinus pneumatization, hypoplastic scapulae, wide symphysis pubis and sacroiliac joints, large femoral neck and epiphyses, **pseudoepiphyses of the metacarpals and metatarsals**, deformed and short middle phalanges, osteopenia

-RUNX2: 70% of cases (Seq: 60%; Indel: 10%)

## Others

-**Cleido=Clavicula; w**omen with CCD have **increased rate of Caesarian section** in childbirth

# Diastrophic Dysplasia

## Genetics

-Gene: **SLC26A2** (Sulfate transporter; 5q32-q33.1)

-AR

## Clinical findings/Dysmorphic features

-Short limbs, normal-sized skull, **hitchhiker thumbs**, small chest, large joint contracture, cleft palate, cystic ears **(cauliflower ears)**, ulnar deviation of fingers, clubfoot, low tone, early osteoarthritis; spinal (scoliosis, exaggerated lumbar lordosis, cervical kyphosis); normal IQ

## Etiology

-Approximately 1:100,000

## Pathogenesis

-**Impaired activity of the sulfate transporter in chondrocytes and fibroblasts** --> synthesis of **unsulfated proteoglycans due to intracellular sulfate depletion -->** affects composition of the extracellular matrix and leads to impaired proteoglycan deposition --> necessary for proper enchondral bone formation

## Genetic testing/diagnosis

-**SLC26A2 only gene**; targeted testing --> then sequencing --> then InDel

-Most common variants: p.Arg279Trp (37% of the disease alleles), p.Arg178Ter (13%), c.-26+2T>C (8%), p.Cys653Ser (6%); most cases of DTD (97%) are due to com-het variants

## Others

-Incorporation of sulfate into macromolecules can be studied in cultured chondrocytes and/or skin fibroblasts through double labeling with 3H-glycine and 35S-sodium sulfate

# FGFR-Related Craniosynostosis Syndromes

## Genetics

-Gene: **FGFR1, FGFR2, FGFR3** (Basic fibroblast growth factor receptor 1, 2, and 3)

-AD

## Clinical findings/Dysmorphic features

-Premature fusion of one or several sutures of the skull

-Comprises 8 syndromes: 1) **Pfeiffer syndrome**; 2) **Apert syndrome**; 3) **Crouzon syndrome**; 4) **Beare-Stevenson syndrome**; 5) **FGFR2-related isolated coronal synostosis**; 6) **Jackson-Weiss syndrome**; 7) **Crouzon syndrome with acanthosis nigricans**; 8) **Muenke syndrome**

-Muenke syndrome: unilateral coronal synostosis or megalencephaly without craniosynostosis

-FGFR2-related isolated coronal synostosis: uni- or bicoronal craniosynostosis only

-The other 6: bicoronal craniosynostosis or cloverleaf skull, distinctive facial features, variable hand and foot findings

1) **Pfeiffer**: DD/ID; extreme proptosis; cloverleaf skull; **broad and medially deviated thumbs and great toes (towards each other)**; ankylosis of elbows; knees; brachydactyly

2) **Apert**: varying degrees of DD/ID (50%; related to timing of craniofacial surgery); **turribrachycephaly** (high, prominent forehead); midface hypoplasia; soft tissue and bony ("**mitten glove**") syndactyly of fingers and toes; **fused cervical vertebrae (68%)**

3) **Crouzon**: significant **proptosis**; external **strabismus** (one eye looks outwards); mandibular prognathism; normal ID and normal extremities; progressive hydrocephalus (30%)

4) Beare-Stevenson: ID; midface hypoplasia; abnormal ears; widespread cutis gyrata and AN; skin tags; bifid scrotum; normal extremities

5) FGFR2-related isolated coronal synostosis: ID normal; extremities normal

6) Jackson-Weiss: normal ID; mandibular prognathism; broad and medially deviated great toes; normal hands

7) Crouzon with acanthosis nigricans**: 5% of individuals with Crouzon have AN (pigmentary changes in the skin fold regions)**

8) **Muenke**: some with pathogenic variant have no clinically apparent abnormalities; normal to mild ID; uni- or bilateral coronal craniosynostosis, or only megalencephaly; midface hypoplasia; ocular hypertelorism; **carpal-tarsal fusion** diagnostic if present; brachydactyly; bilateral, symmetric, low- to mid-frequency SNHL

## Etiology

-Prevalence all together: 1 in 2,100 to 1 in 3,000 at birth

## Pathogenesis

-Two common **Apert** muts (**98% of syndrome, FGFR2, p.Pro253Arg and p.Ser252Trp)** are at same location as **FGFR1 mut in Pfeiffer and the FGFR3 mut in Muenke:** **linker region between Ig-like loops II and III** --> area critical in ligand binding; replacement of Pro for a bulkier Arg may alter the orientation of IgII and IgIII loops

-Both variants augment receptor binding affinity --> **Gain-of-Function**

## Genetic testing/diagnosis

-**Pfeiffer syndrome (5% FGFR1 - p.Pro252Arg; 95% FGFR2 – 80% in exon 8 and 10**)

-**Apert syndrome: targeted analysis of FGFR2 for p.Ser252Trp and p.Pro253Arg** --> sequencing of FGFR2 --> partial-gene insertions/deletions

-**Crouzon syndrome: FGFR2 – 80% in exon 8 and 10**

-**Crouzon syndrome with AN: usually caused by FGFR3 p.Ala391Glu**

-**Muenke syndrome: 100% p.Pro250Arg in FGFR3**

-FGFR2-related isolated coronal synostosis: combination of uni- or bicoronal craniosynostosis and identification of FGFR2 pathogenic variant

## Others

-**Saethre-Chotzen Syndrome: TWIST1**, big toes pointing away from each other

# Hereditary Multiple Osteochondromas

## Genetics

-Gene: EXT1, EXT2 (Exostosin-1, Exostosin-2)

-AD

## Clinical findings/Dysmorphic features

-Growths of **multiple osteochondromas** (benign cartilage-capped bone **tumors that grow outward from the metaphyses of long bones**)

-Osteochondromas associated with reduction in skeletal growth, bony deformity, restricted joint motion, shortened stature, premature osteoarthrosis, compression of peripheral nerves

-Median age of diagnosis is 3 yrs; nearly all affected individuals are diagnosed by age 12 years

-**Low risk for malignant degeneration** to osteochondrosarcoma (lifetime risk (~1%))

## Etiology

-1 in 50,000 in DC

## Pathogenesis

-EXT1/2 encode glycosyltransferases; mutations lead to actin accumulation and cytoskeletal abnormalities

## Genetic testing/diagnosis

-Combination of sequence analysis and InDel of coding regions of EXT1 and EXT2 --> pathogenic variants in 70%-95% of affected individuals

# Hypochondroplasia

## Genetics

-Gene: **FGFR3** (Fibroblast growth factor receptor 3; 4p16.3)

-AD

## Clinical findings/Dysmorphic features

-Short stature; stocky build; rhizo- or mesomelia; limited elbow extension; brachydactyly; mild joint laxity; macrocephaly; scoliosis; genu varum (O-beine); lumbar lordosis; **no trident hand; normal face;** adult onset osteoarthritis; mild to moderate ID and/or LD might be present

-Skeletal features very similar to achondroplasia but milder; medical complications common to achondroplasia (spinal stenosis, tibial bowing, obstructive apnea) are less frequent

## Etiology

-May approach the prevalence of achondroplasia (i.e., 1 in 15,000 - 40,000 live births)

## Pathogenesis

-FGFR3 normally functions as a negative regulator of bone growth

-FGFR3 pathogenic variants --> constitutive activation of the receptor tyrosine kinase (but to lesser degree than these other pathogenic variants)

## Genetic testing/diagnosis

-70% are heterozygous for a pathogenic variant in FGFR3; **locus heterogeneity**

-Targeted mutation analysis: **p.Asn540Lys(C1620A) (70%), p.Asn540Lys(C1620G) (30%)**

# COL1A1-2-Related Osteogenesis Imperfecta

## Genetics

-Gene: **COL1A1** (Collagen α1(I) chain; 17q21.33), **COL1A2** (Collagen α2(I) chain; 7q21.3)

-Encode the **two chains pro α1(I) and pro α2(I) of type I procollagen** --> collagen type I is a **heterotrimer** consisting of **two α 1 chains and one α 2 chain**

-AD and rare AR; **penetrance 100%**

-De novo: **60% of type I and type IV; close to 100% of type III; 100% of type II**

## Clinical findings/Dysmorphic features

-Fractures with minimal trauma; **dentinogenesis imperfecta** (DI); **blue sclera**; adult-onset HL

-**Continuum**: perinatal lethality - severe skeletal deformities/mobility impairments/very short stature - nearly asymptomatic ind. with mild predisposition to fractures/normal dentition/normal stature/normal life span

-Fractures can occur in any bone, but are most common in extremities

-DI: **gray or brown teeth, may appear translucent**, wear down and break easily

-Four types of COL1A1/2-related OI:

-**OI type I: classic non-deforming OI with blue sclerae**

-**OI type II: perinatally lethal OI**

-**OI type III: progressively deforming OI**

-**OI type IV: common variable OI with normal sclerae**

## Etiology

-Prevalence of approximately 6-7:100,000

## Pathogenesis

-**Type I** **(diminished collagen production)**: most ind. with type I have **premature STOP codon in one COL1A1 allele** --> **half the normal quantity of type I procollagen molecules**; some with SNVs --> **amino acid change is located in amino terminus** (amino terminal changes tend to be less disruptive --> collagen chain assembly can still initiate as usual at the carboxy terminus)

-**Types II, III, and IV** **(structurally defective collagens**): mutations produce **structurally abnormal proα1(I) or proα2(I) chains**; mostly substitutions in triple helix that **replace a glycine** with a more bulky residue --> disrupts formation of triple helix; **ratio wt to mut collagen is 1:3 if proα1(I) is mutated and 1:1 if proα2(I) is mutated**

-Phenotype depends on: specific collagen affected, location of the substitution, nature of the substituting residue, but:

--> Substitutions in proα1(I) more in patients with OI types III and IV and more often lethal

--> Replacement of glycine (neutral) with charged (aspartic acid, glutamic acid, arginine) or large residue (tryptophan) --> very disruptive and associated with severe (type II)

## Genetic testing/diagnosis

-Diagnosis:

1) Family history, a history of fractures, characteristic physical findings

2) X-ray: **fx of varying ages/stages of healing**, **wormian/intrasutural** bones, **"codfish" vertebrae**, osteopenia)

3) Molecular testing of COL1A1 and COL1A2 and/or biochemical analysis of type 1 collagen

-Biochemical testing (i.e. analysis of structure and quantity of type I collagen synthesized in vitro by cultured dermal fibroblasts)

-Suggested diagnostic work flow:

1) Sequencing of COL1A1/2 (eventually follow-up studies to determine pathogenicity)

2) Deletion/duplication analysis (detects additional 1%-2% of pathogenic variants)

3) If no causative COL1A1/2 variant is found, re-review clinical data --> proceed to screening for the non-COL1A1/2-related genetic disorders

## Others

-Treatment: bisphosphonates (slow down bone resorption by shortening the life of osteoclasts and prolonging the life of the osteoblasts)

# Saethre-Chotzen Syndrome

## Genetics

-Gene: **TWIST1** (Twist-related protein 1, 7p21)

-AD

## Clinical findings/Dysmorphic features

-**Coronal synostosis**; facial asymmetry; ptosis; **2/3 hand syndactyly**; mild-mod DD in minority; short; parietal foramina; vertebral fusions; radioulnar synostosis; CP; maxillary hypoplasia; CHD

-**Characteristic appearance of the ear** (**small pinna with a prominent crus**)

-**Broad or duplicated great toes (eventually pointing away from each other)**

## Etiology

-Prevalence estimates range from 1:25,000 to 1:50,000

## Pathogenesis

-Haploinsufficiency by gene deletion/rapid degradation of abnormal protein/altered subcellular localization --> disinhibition of RUNX2 and enhanced osteogenesis

## Genetic testing/diagnosis

-TWIST1 (Seq 72%; InDel 23%)

# Phenylalanine Hydroxylase Deficiency

## Genetics

-Gene: **PAH** (Phenylalanine hydroxylase; 12q23.2)

-AR

## Clinical findings/Dysmorphic features

-**Intolerance to essential amino acid phenylalanine**

-Spectrum: most with severe PAH deficiency (classic PKU) develop profound and irreversible ID

-PHE levels above normal but **below 1200 μmol/L (20 mg/dL)** are at much lower risk for impaired cognitive development in the absence of treatment

-Clinical findings: epilepsy; ID and behavior problems including autistic features; Parkinson-like features; eczema; **decreased skin and hair pigmentation**

-**Progressive white matter disease on brain MRI** (90% of individuals with PAH deficiency)

**-Musty body odor and mousy odor** to urine (phenylacetic acid)

## Etiology

-Frequency: 1:5,000 (Turkey, Ireland) to 1:10,000 (North European and East Asian)

## Pathogenesis

-More than 900 different pathogenic variants in PAH have been identified to date

## Genetic testing/diagnosis

-PAH deficiency detected by NBS in ~100%: presence of hyperphenylalaninemia using tandem mass spectrometry on a blood spot obtained from a heel stick

-Diagnosis established in a proband with:

1) Plasma PHE conc. **persistently above 120 µmol/L (2 mg/dL)** and **altered Phe:Tyr-ratio** (normal: <1; >3 is useful in the diagnosis of PAH deficiency) in untreated state with normal BH4 cofactor metabolism and/or

2) Finding of biallelic pathogenic variants in PAH by molecular genetic testing

-PAH: Seq 97-99%; InDel 1-3%

## Others

-Treatment of classic PKU:

--> **low-protein diet + PHE-free medical formula asap after birth** (plasma PHE conc. of 120-360 µmol/L (2-6 mg/dL))

--> some benefit from adjuvant therapy with sapropterin (**Kuvan**, Tetrahydrobiopterin/BH4)

--> large neutral amino acid (LNAA) compete with PHE at blood brain barrier

-**Tetrahydrobiopterin (BH4) deficiency**: hyperphenylalaninemia from impaired synthesis/ recycling of BH4 (cofactor in the PHE, TYR, TRP hydroxylation reactions)

-**Maternal PKU**/PAH Deficiency: ID (90%), microcephaly (70%), CHD (12%), IUGR --> **maternal PHE conc. of 120-360 µmol/L** during pregnancy is recommended

# Maple Syrup Urine Disease

## Genetics

-Genes: **BCKDHA** (BCKA decarboxylase **(E1) alpha subunit** --> MSUD type 1A; 45%); **BCKDHB** (BCKA decarboxylase **(E1) beta subunit**; MSUD type 1B; 35%); **DBT** (dihydrolipoyl transacylase **(E2) subunit**; MSUD type 2; 20%)

-AR: not digenic --> no individuals are heterozygous for variants in two different genes

## Clinical findings/Dysmorphic features

1) Classic:

-12h after birth: untreated neonates with classic MSUD have **maple syrup odor in cerumen**

-12-24h: **elevated plasma concentrations of BCAAs (leucine, isoleucine, valine)** **+ allo-isoleucine** + disturbance of plasma amino acid concentration ratios

-2-3 days: **ketonuria** (fatty acids are moved from triglyceride stores in the body in response to inadequate intake or availability of carbohydrates); **irritability**; poor feeding

-4-5 days: deepening encephalopathy --> lethargy, intermittent apnea, opisthotonus (spasm of the muscles), **"fencing" and "bicycling"**

-7-10 days: coma and central respiratory failure

2) Intermediate:

-Partial BCKAD deficiency --> manifests intermittently/responds to dietary thiamine therapy

-Experience **severe metabolic intoxication and encephalopathy during catabolic stress**

## Etiology

-Rare in most populations, with incidence estimates of 1:185,000 live births

-Founder variant (c.1312T>A, p.Tyr438Asn) in BCKDHA (E1a) in **Mennonites** (PA, Kentucky, NY, Indiana, Wisconsin, Michigan, Iowa, Missouri) --> carrier 1:10; incidence 1:380 births

## Pathogenesis

-Decreased activity of **branched-chain alpha-ketoacid dehydrogenase complex (BCKAD**) in mitochondria --> catalyzes oxidative decarboxylation of branched-chain keto acids (2nd enzymatic step in the degradative pathway of BCAAs)

-BCKAD with 4 subunits (E1a, E1b, E2, and E3) --> pathogenic variants in both alleles encoding any subunit --> decreased activity of complex --> accumulation of BCAAs and corresponding branched-chain ketoacids (BCKAs) in tissues and plasma

## Genetic testing/diagnosis

-**Increased plasma conc. of leucine;** isoleucine andvaline are also typically elevated; decreased concentrations of other essential and non-essential amino acids --> elevated ratios of leucine to alanine, glutamate, glutamine, tryptophan, methionine, histidine, phenylalanine, tyrosine

-Plasma conc. of **allo-isoleucine (>5 µmol/L; distinctive metabolite in all forms of MSUD)**

-Urinary excretion of branched-chain alpha-hydroxyacids and BCKAs --> gas chromatography-mass spectrometry or dinitrophenylhydrazine (DNPH) test

-BCKAD enzyme activity in a variety of cells including lymphoblasts (< 3%)

## Others

-E3 subunit of BCKAD is shared with pyruvate and alpha-ketoglutarate dehydrogenase complexes --> **MSUD type 3: increased urinary excretion of BCKAs and alpha-ketoglutarate + elevated plasma concentrations of lactate, pyruvate, and alanine**

# Propionic Acidemia

## Genetics

-Genes: PCCA (Propionyl-CoA carboxylase alpha chain, mitochondrial; 13q32.3); PCCB (Propionyl-CoA carboxylase beta chain, mitochondrial; 3q22.3)

-AR

## Clinical findings/Dysmorphic features

-Spectrum: neonatal-onset to late-onset disease

-Neonatal-onset (most common): healthy newborn with poor feeding and decreased arousal --> progressive encephalopathy --> w/o prompt diagnosis and management --> **lethargy, seizures, coma, death**; frequently accompanied by **metabolic acidosis with anion gap, lactic acidosis**, ketonuria, hypoglycemia, hyperammonemia, **cytopenias**

-Late-onset: can be asymptomatic; metabolic crisis under catabolic stress (ill, surgery, fasting)

-Isolated cardiomyopathy in absence of metabolic decompensation or neurocognitive deficits

-Manifestations over time: FTT, ID, seizures, basal ganglia lesions, pancreatitis, cardiomyopathy

-Other reported complications: optic atrophy, HL, ovarian insufficiency, chronic renal failure

## Etiology

-Live-birth incidence is 1:105,000-1:130,000 in the US

## Pathogenesis

-**Organic acidemia** caused by deficiency of propionyl-CoA carboxylase (PCC), a biotin-dependent carboxylase located in mitochondrial inner space

-**PCC converts propionyl-CoA to D-methylmalonyl-CoA** --> enters Krebs cycle as succinyl-CoA

-Propionyl-CoA is common to pathway for degradation of some amino acids (**VOMIT: valine, odd-chain fatty acids, methionine, isoleucine, threonine**) and cholesterol

-Gut bacteria (i.e., Propionibacterium sp.) also produce propionate metabolized through PCC

-Deficiency of PCC: --> toxic effects of free organic acids and ammonia; --> accumulation of propionyl-CoA (inhibits enzymes including oxidative phosphorylation --> decreased energy production); --> decreased production of Krebs cycle intermediates

## Genetic testing/diagnosis

-**Plasma acylcarnitine profile: elevated propionylcarnitine (C3)**

-UOA: elevated 3-hydroxypropionate; presence of: methylcitrate, propionylglycine, lactic acid

-Plasma amino acids: elevated glycine

-PCCA 50% of cases (Seq 78%; Del/Dup 18%); PCCB 50% of cases (Seq 97%; Del/Dup 3%)

## Others

-NBS: acylcarnitine analysis by MS/MS on dried blood spots --> elevated propionylcarnitine (C3); secondary markers: methionine, C3/C2, and C3/C16 ratios

-**Elevated C3** on NBS can be caused by methylmalonic acidemias resulting from **methylmalonyl-CoA mutase deficiency/disorders of intracellular cobalamin metabolism/maternal B12 def**.

# Isolated Methylmalonic Acidemia

## Genetics

-Genes: **MMUT** (methylmalonyl CoA mutase; 60%), **MMAA** (methylmalonic aciduria type A protein; 25%), **MMAB** (methylmalonic aciduria type B; 12%, **MCEE** (Methylmalonyl-CoA epimerase; unknown), **MMADHC**

## Clinical findings/Dysmorphic features

-Complete or partial deficiency of:

1) **Methylmalonyl-CoA mutase**

2) **Methylmalonyl-CoA epimerase**

3) **Defect in transport/synthesis of its cofactor adenosyl-cobalamin** (cblA, cblB, or cblD-MMA)

-Onset: neonatal period to adulthood; periods of relative health and intermittent metabolic decompensation (associated with intercurrent infections and stress)

-Secondary complications: ID (variable); tubulointerstitial nephritis with progressive **renal failure**; "**metabolic stroke**" (acute and chronic basal ganglia injury); pancreatitis; growth failure; functional immune impairment; **optic nerve atrophy**

1) **Neonatal** period: lethargy, vomiting, hypotonia, hypothermia, respiratory distress, severe **ketoacidosis**, **hyperammonemia**, neutropenia, thrombocytopenia; untreated: death < 4weeks

2) **Infantile**/non-B12-responsive: normal at birth, but develop lethargy, vomiting, dehydration, FTT, hepatomegaly, hypotonia, encephalopathy within a few weeks to months of age

3) **Intermediate**/B12-responsive: usually in first months or years of life; anorexia, FTT, hypotonia, DD; protein aversion and/or vomiting/lethargy after protein intake

4) **Atypical** and "benign"/adult: increased, albeit mild, urinary excretion of methylmalonate

## Etiology

-Approximately 1:80,000 newborns

## Pathogenesis

-**Failure to convert methylmalonyl-CoA into succinyl-CoA** during propionyl-CoA metabolism in mt-matrix --> elevated MMA in blood/urine, hypomethioninemia, or variations in other metabolites, such as **malonic acid**

-Suggestive findings: normal B12**; elevated propionylcarnitine (C3)**; **hyperammonemia**; **hyperglycinemia**; **lactic acidosis**; CBC showing **neutropenia, thrombocytopenia, anemia**

## Genetic testing/diagnosis

-Diagnosis: organic acids in plasma and/or urine by gas-liquid chromatography and MS

-Establishing the specific subtype: cellular biochemical studies (14C propionate incorporation, B12 responsiveness, complementation analysis, cobalamin distribution) and genetic testing

-Biallelic pathogenic variants in one of the five genes (MMUT, MMAA, MMAB, MCEE, MMADHC) – with confirmation of carrier status in the parents – can establish the diagnosis

## Others

-MUT form of MMA is unresponsive to vitamin B12 therapy

-Elevated homocysteine in cbl C,D,F

# Isovaleric acidemia

## Genetics

-IVD (Isovaleryl-CoA dehydrogenase)

-AR

## Clinical findings/Dysmorphic features

**-Metabolic ketoacidosis,** “**sweaty feet” odor,** dehydration**, hyperammonemia,** ketonuria**,** vomiting**, hypoglycemia,** FTT

-Can be mild, but decompensations can have **hyperammonemia**, coma, death

-50%: onset few days after birth; poor feeding, vomiting, szs, energy lack; can progress to coma

-50%: onset childhood; may come and go over time; often **triggered by infection** or by eating increased amount of protein-rich foods

## Etiology

-1 in 250,000 in the US

## Pathogenesis

-IVD breaks down BCAA leucine; third step in processing leucine (essential amino acid)

-Isovaleric acid and related compounds build up to toxic levels --> damaging the brain and NS

## Genetic testing/diagnosis

-Plasma acylcarnitine analysis confirms the **increased C5;** urine organic acid analysis will show **isovalerylglycine**; urine acylglycine and acylcarnitine analysis may also be informative

## Others

-Low-leucine / low-protein diet and use medical foods

-Glycine and L-carnitine --> removal of isovaleric acid from body

**-Neonate with acidosis, ketonuria, hyperammonemia, neutropenia and thrombocytopenia**

# GBL1-Related Disorders

## Genetics

-Gene: **GLB1** (β-galactosidase)

-AR

## Clinical findings/Dysmorphic features

-2 phenotypically distinct **lysosomal storage disorders**:

1) **GM1 gangliosidosis**

-Type I (infantile): **onset < 1 yr**; progressive CNS dysfunction --> spasticity, deafness, blindness, decerebrate rigidity; life expectancy 2-3 yrs; infants have **macular cherry-red spots**, DD, regression by 6mths, hepatosplenomegaly, cardiac involvement, coarse facial features, generalized **skeletal dysplasia**

-Type II (late-infantile): **onset 1-3 yrs**, life expectancy 5-10 yrs

-Type II (juvenile): **onset 3-10 yrs**; insidious plateauing of motor and cognitive development followed by slow regression; +/- skeletal dysplasia

-Type III: **onset 2nd - 3rddecade** --> extrapyramidal signs, gait disturbance, cardiomyopathy; similar to Parkinson; ID is common; short stature, kyphosis, and scoliosis of varying severity

2) **Mucopolysaccharidosis type IVB (MPS IVB, Morquio)**

-Skeletal changes, including short stature and skeletal dysplasia

-No clinical sx at birth: severe form at 1-3 yrs, attenuated form in childhood or adolescence

-Significant morbidity: respiratory compromise, obstructive sleep apnea, valvular heart disease, hearing impairment, corneal clouding, spinal cord compression

-Intellect is normal unless spinal cord compression leads to CNS compromise

## Etiology

-GM1 gangliosidosis: 1 in 100,000 to 200,000 newborns

## Pathogenesis

-**β-galactosidase** activity: **Type I ~0%; Type II 1-5%/3-10%; Type III 5-10%; MPS IVB 2-12%**

## Genetic testing/diagnosis

-Specific **GAG pattern** in urine is noted in persons with GM1 gangliosidosis

-**Keratan sulfate** in urine can be diagnostic of MPS IV (does not diff. MPS IVA from MPS IVB)

-GLB1: Seq 99%; InDel <1%

## Others

-GM2 gangliosidosis without skeletal changes or other non-CNS findings

-**MPS IVA is caused by pathogenic variants in GALNS**

# Glycine Encephalopathy (Nonketotic hyperglycinemia)

## Genetics

-Genes: **GLDC (80%; Glycine Dehydrogenase), AMT (20%; Aminomethyltransferase)**

-AR

## Clinical findings/Dysmorphic features

-**Inborn error of glycine metabolism**; defect of glycine cleavage enzyme system (GCS)

-Majority with onset in neonatal period; manifest as progressive lethargy evolving into profound coma and marked hypotonia; 85% have severe NKH and 15% attenuated NKH

-**Neonatal hypotonia, seizures, apnea and hiccups**

## Etiology

-1:76,000

## Pathogenesis

-Accumulation of large quantities of glycine in all body tissues including brain

-Glycine is major **neurotransmitter**: activates inhibitory glycine receptors; co-agonist for excitatory glutamatergic NMDA receptors

## Genetic testing/diagnosis

-GLDC: Seq 80%, InDel 20%; AMT: Seq >99%

-**Elevated isolated glycine in plasma and CSF by quantitative amino acid analysis** + **abnormal CSF/plasma glycine ratio** (**nl ≤0.02; ratio > 0.08 is diagnostic**)

-Diffusion-weighted imaging: diffusion restriction in the **posterior limb of the internal capsule, anterior brain stem, posterior tegmental tracts, cerebellum**

-**Corpus callosum can be thin and shortened but is not absent**

## Others

-**Nonketotic hyperglycinemia vs ketotic hyperglycinemia (MMA/PA)**

-Urine organic acid profile is expected to be normal

# Glycogen storage disease type I (von Gierke disease)

## Genetics

-Genes: **G6PC (Glucose-6-phosphatse; GSDIa; 80%;** 17q21.31**); SLC37A4 (Glucose-6-phosphate exchanger; GSDIb; 20%;** 1q23.3)

-AR

## Clinical findings/Dysmorphic features

-GSDIa and GSDIb are clinically indistinguishable

-Accumulation of glycogen and fat in liver and kidneys --> **hepatomegaly and renomegaly**

-Untreated infants present at 3-4mths: **hepatomegaly**, **lactic acidosis**, **hyperuricemia**, **hyperlipidemia**, **hypertriglyceridemia**, and/or **hypoglycemic seizures**

-Children: **doll-like faces** with **fat cheeks**, thin extremities, short stature, protuberant abdomen

-**Xanthoma** (fatty growths develop underneath the skin) and diarrhea may be present

-Impaired platelet function can lead to a bleeding tendency with frequent **epistaxis**

-Untreated **GSDIb: impaired neutrophil and monocyte function**, chronic neutropenia, IBD --> recurrent bacterial infections, oral and intestinal mucosal ulcers

-Long-term complications: growth retardation, osteoporosis, delayed puberty, gout, renal disease, pulmonary hypertension, hepatic adenomas with potential for malignant transformation, polycystic ovaries, pancreatitis, changes in brain function

-Normal growth and puberty in treated children; most affected individuals live into adulthood

## Etiology

-Incidence of GSDI is 1 in 100,000 individuals

## Pathogenesis

-GSDs: **abnormalities in enzymes/transporters in glycogen synthesis and degradation**

-Glucose is stored as glycogen: **glucose is phosphorylated to glucose-6-phosphate** --> **Glucose-6-phosphate is converted to glucose-1-phosphate** --> **Glycogen synthase catalyzes formation of α-1,4-linkages** --> every 10 glucose, a branching enzyme forms an α-1,6-linkage

-**lack of G6Pase catalytic activity or glucose-6-phosphate exchanger SLC37A4 activity in liver** **--> inadequate conversion of glucose-6-phosphate into glucose through normal glycogenolysis and gluconeogenesis pathways** **causes**:

**1) severe hypoglycemia**

**2) high lactate (due to increased glycolysis)**

**3) high uric acid (glucose-6-phosphate is shunted into the pentose phosphate shunt)**

**4) high triglycerides (increased synthesis of acetyl CoA)**

## Genetic testing/diagnosis

-Hypoglycemia: fasting blood glucose <60 mg/dL (nl 70-120 mg/dL); lactic acidosis: blood lactate >2.5 mmol/L (nl 0.5-2.2 mmol/L); hyperuricemia: blood uric acid >5.0 mg/dL (nl 2.0-5.0 mg/dL); hyperlipidemia: triglycerides >250 mg/dL (nl 150-200 mg/dL) (hypertriglyceridemia causes the plasma to appear "milky"); cholesterol >200 mg/dL (nl 100-200 mg/dL)

-Diagnosis: Biallelic mut in G6PC (GSDIa)/SLC37A4 (GSDIb) or deficient hepatic enzyme activity

-G6PC and SCL37A4: Seq 95%, InDel: rare; targeted: G6PC, p.Arg83Cys in AJ, p.Gln347X in Amish

## Others

-SLC37A4 brings G6P to inner ER membrane where G6Pase enzyme is located

-**Symptoms appear around 3/4 months --> sleep through night and do not eat as frequently**

**-6-month-old boy presents with hepatomegaly, renomegaly, hypoglycemia and lactic acidosis**

**-G6P expressed only in liver: prior to isolation of gene, prenatal diagnosis was not possible**

# Glycogen Storage Disease Type II (Pompe Disease)

## Genetics

-**GAA (α –glucosidase)**

-AR

## Clinical findings/Dysmorphic features

-Infantile-onset: **Cardiomyopathy <12 months**; ~4 mths: hypotonia, muscle weakness, **macroglossia**, **hepatomegaly**, feeding difficulties, FTT, **hypertrophic cardiomyopathy**, HL

-Late-onset (0-70 years):

--> onset < age 12 months: proximal muscular weakness, delayed motor development, lordosis, kyphosis/scoliosis, respiratory insufficiency without cardiomyopathy

--> onset > age 12 months: proximal muscle weakness and respiratory insufficiency; sleep disordered breathing, clinically significant cardiac involvement is uncommon

## Etiology

-Incidence: African Americans 1:14,000, US 1:40,000, European 1:100,000

## Pathogenesis

-**α –glucosidase cleaves α 1,4 and α 1,6-glucosidic linkages during degradation of glycogen**

-Deficiency --> abnl storage of nl glycogen in tissues (mainly **skeletal, smooth, cardiac muscles)**

-α –glucosidase is located in the lysosomes (functions in acidic pH)

## Genetic testing/diagnosis

-NBS: acid alpha-glucosidase (GAA) enzyme activity on dried blood spots

-GAA activity in lymphocytes/cultured fibroblasts (< 10% of normal)

-Elevated creatine phosphokinase (CPK) (10x normal): (as high as 2000 IU/L; normal: 60-305 IU/L) – normal in late onset (also in DMD/BMD)

-GAA: Seq 83-93%, InDel 5-13%; c.-32-13T>G is most frequent pathogenic variant

## Others

-ERT: **Myozyme and Lumizyme are FDA approved (work well --> live longer --> HL)**

-**Pseudodeficiency allele common in Asians; only GSD classified LSD; unlike other GSDs:** **not associated with hypoglycemia**

**-6-mth-old boy with severe hypotonia, massive cardiomegaly, progressive weakness and markedly elevated CPK**

# Fabry disease

## Genetics

-Gene: **GLA** (alpha-galactosidase A, Xq22.1)

-**XLR**

## Clinical findings/Dysmorphic features

1) Classic form (males with < 1% α-Gal A activity): onset in childhood to adolescence; periodic crises of severe pain in extremities (**acroparesthesia**); vascular cutaneous lesions (**angiokeratomas**); **sweating abnormalities** (anhidrosis, hypohidrosis, hyperhidrosis); **corneal and lenticular opacities** (cornea verticillate and fabry cataract) ; proteinuria; **ESRD** (in men in the 3rd -5th decade); most males treated for ESRD develop cardiac and/or cerebrovascular disease (major cause of morbidity and mortality)

2) Non-classical form (males with > 1% α-Gal A activity):

-cardiac variant: 6th-8th decade with **left ventricular hypertrophy**, cardiomyopathy and arrhythmia, proteinuria, but without ESRD

-renal variant: associated with ESRD but without the skin lesions or pain

-cerebrovascular variant: presenting as stroke or transient ischemic attack

## Etiology

-Incidence at 1:50,000 to 1:117,000 males

## Pathogenesis

-Deficiency of **alpha-galactosidase A (α-Gal A)** --> progressive lysosomal **deposition of** **globotriaosylceramide (GL-3)** in cells throughout the body

## Genetic testing/diagnosis

-Deficient α-Gal A enzyme activity in plasma, isolated leukocytes, and/or cultured cells is the most efficient and reliable method in males

-Identification of hemizygous GLA pathogenic variant (>800 mutations identified; most private)

## Others

-Heterozygous females typically have milder symptoms at a later age of onset than males

-ERT is disputable

# Russell-Silver Syndrome

## Genetics

-Abnormalities at imprinted domain on **chromosome 11p15.5**

## Clinical findings/Dysmorphic features

-**IUGR**; postnatal growth deficiency; proportionately short stature, normal head circumference, **fifth-finger clinodactyly**, typical facial features with triangular facies characterized by broad forehead and narrow chin, limb-length asymmetry (hemihypotrophy)

-Significant risk for developmental delay (both motor and cognitive) and learning disabilities

## Etiology

-1 in 100,000

## Pathogenesis

-**IC1 hypomethylation on paternal allele** --> CTCF binds --> blocks transcriptional signals from cis enhancer sequences --> IGF2 is off/biallelic expression of H19

-H19 is an imprinted, maternally expressed non-coding RNA; IGF2 is an imprinted, paternally expressed transcript: insulin-like growth factor II

-Maternal uniparental disomy of chromosome 7 can also cause RSS (loci unknown)

## Genetic testing/diagnosis

1) Chromosome 11p15.5-related RSS:

-Loss of IC1 methylation of paternal 11p15.5 (35-50% of cases) --> methylation analysis

-**Duplication of maternal 11p15.5** (maternal UPD) --> In/Del analysis

2) Chromosome 7-related RSS:

-Maternal UPD (7-10%) --> SNP/marker analysis, methylation specific MLPA

-Deletion/Duplication --> cytogenetic or In/Del analysis

## Others

-RSS caused by epigenetic alterations at IC 1, while BWS is caused by alterations at IC1 and IC2

# WAS-related disorders

## Genetics

-Gene: WAS (**Wiskott-Aldrich** syndrome protein, Xp11.23)

-**XLR**

## Clinical findings/Dysmorphic features

-Spectrum of disorders of **hematopoietic cells** (defects of platelets and lymphocytes): **Wiskott-Aldrich syndrome**, X-linked thrombocytopenia (XLT), **X-linked congenital neutropenia** (XLN)

-Affected males: **thrombocytopenia**, intermittent **mucosal bleeding**, **bloody diarrhea**, intermittent/chronic **petechiae**; eczema; recurrent bacterial/viral infections (mainly ear)

-40% of those who survive early complications develop autoimmune conditions (hemolytic anemia, immune thrombocytopenic purpura, immune-mediated neutropenia, rheumatoid arthritis, vasculitis, immune-mediated damage to kidneys and liver)

-Males with XLT: thrombocytopenia with small platelets; eczema; immune dysfunction, are usually mild or absent

-Males with XLN: congenital neutropenia, myeloid dysplasia, lymphoid cell abnormalities

## Etiology

-Prevalence: 1-4 per 1,000,000

## Pathogenesis

-**WASP** in hematopoietic cells: **signal transduction and actin cytoskeleton organization** in response to external stimuli

-T and B lymphocytes, neutrophils, macrophages, DC of males with WAS-related disorders exhibit defects in migration, anchoring, localization

## Genetic testing/diagnosis

-Male proband with both **congenital thrombocytopenia** (<70,000 platelets/mm3) and **small platelets** + at least one of the following: eczema, recurrent bacterial/viral infections, autoimmune disease(s), malignancy, reduced WASP expression in fresh blood sample

-Identification of hemizygous WAS pathogenic variant is necessary to confirm the diagnosis

# Stickler Syndrome

## Genetics

-Gene: **COL2A1** (AD), COL11A1 (AD), COL11A2 (AD), COL9A1 (AR), COL9A2 (AR), COL9A3 (AR)

## Clinical findings/Dysmorphic features

-**Connective tissue disorder; o**cular findings (myopia, **cataract**, **retinal detachment); HL** (conductive and sensorineural); **midfacial underdevelopment and cleft palate** (either alone or as part of the **Robin sequence**); mild spondyloepiphyseal dysplasia and/or precocious arthritis

-Variable phenotypic expression both within and among families (locus/allelic heterogeneity)

## Etiology

-Incidence among neonates is 1:7,500-1:9,000

## Pathogenesis

**-Haploinsufficiency of type II collagen** --> vestigial gel forms in the retrolental space

## Genetic testing/diagnosis

-COL2A1 (80-90%): Seq 99%; COL11A1 (10-20%): Seq 99%

# Galactosemia

## Genetics

-Genes: **GALT** (galactose-1-phosphate uridylyltransferase; type I), **GALK1** (galactokinase 1; type II) and **GALE** (UDP-galactose-4-epimerase; type III)

-AR

## Clinical findings/Dysmorphic features

1) **Classic galactosemia**/type I/GALT: most common; most severe; if infants not treated promptly with a low-galactose diet --> life-threatening complications within few days after birth: feeding difficulties, lethargy, FTT, **jaundice**, **liver damage**, abnormal bleeding, bacterial infections (**sepsis**), shock, DD, **clouding of lens (cataract**), speech difficulties, ID

2) **Galactokinase deficiency**/type II/GALK1: fewer medical problems than the classic type; affected infants develop **cataracts** but otherwise experience few long-term complications

3) **Galactose epimerase** deficiency/type III/GALE: mild to severe: cataracts, delayed growth and development, ID, liver disease, kidney problems

4) **Clinical variant galactosemia**: 1%-10% residual GALT activity in erythrocytes and/or liver

5) **Biochemical variant galactosemia**: 15%-33% residual GALT enzyme activity in erythrocytes (includes **D2 Duarte biochemical variant state**)

## Etiology

-NBS results: prevalence of classic galactosemia is 1:48,000

## Pathogenesis

-Galactose in many foods; part of larger sugar lactose (in dairy products and baby formulas)

-Pathogenic variant **p.Gln188Arg** largely prevents formation of a GALT-UMP intermediate

-**Duarte D2**: deletion in E-box (carbohydrate response element --> reduced GALT expression)

## Genetic testing/diagnosis

-Classic galactosemia + clinical variant galactosemia: **elevated erythrocyte galactose-1-phosphate** (> 10 mg/dL), reduced GALT activity, and/or biallelic variants in GALT

-Seq of GALT first (95%) --> del/dup analysis if only one or no variant is found (5.2-kb del in AJ)

-Targeted analysis for common variants can be done first in ind. of European or African ancestry

## Others

-**Almost all females with classic galactosemia with premature ovarian insufficiency**

-**100% of classic galactosemia or clinical variant galactosemia can be detected in NBS that include testing for galactosemia in their panel** (clinical variant galactosemia may be missed if NBS only measures blood total galactose level and not erythrocyte GALT enzyme activity)

**-Neonate with emesis, diarrhea, icterus and hepatomegaly**

# Tyrosinemia type I

## Genetics

-Gene: **FAH** (fumarylacetoacetase)

-AR

## Clinical findings/Dysmorphic features

-Untreated: young infants with severe liver involvement or later in first year with **liver dysfunction** and renal tubular dysfunction, growth failure and **rickets;** repeated, often unrecognized, neurologic crises (1-7days) --> change in mental status, abdominal pain, peripheral neuropathy, and/or respiratory failure; death < 10y, typically from liver failure, neurologic crisis, or hepatocellular carcinoma

## Etiology

-1 in 100,000; in general US population, carrier frequency is estimated at 1:100 to 1:150

## Pathogenesis

-**FAH is terminal enzyme in the tyrosine catabolic pathway; fumarylacetoacetate** (FAA) is immediate precursor:

--> accumulates in hepatocytes, causing cellular damage and apoptosis

--> is diverted into succinylacetoacetate and succinylacetone

--> succinylacetone interferes with activity of 2 major hepatic enzymes:

1) parahydroxyphenylpyruvic acid dioxygenase (p-HPPD) --> elevation of plasma tyrosine

2) PBG synthase --> reduced activity of the enzyme δ-ALA dehydratase; reduced heme synthesis; increased δ-aminolevulinic acid (δ-ALA; induces acute neurologic episodes; increased urinary excretion of δ-ALA (see AIP))

## Genetic testing/diagnosis

-NBS: presence of **succinylacetone (MS/MS): pathognomonic for tyrosinemia type 1**

-Supportive findings: increased succinylacetone in blood and excretion in urine; elevated plasma concentration of tyrosine, methionine, phenylalanine

-FAH seq: >95%, In/Del: unknown; targeted p.Pro261Leu first in AJ (> 99% of pathogenic variants in this population); c.1062+5G>A (IVS12+5 G>A) accounts for 87.9% of variants in French-Canadian population; 4 FAH variants (c.1062+5G>A (IVS12+5 G>A), c.554-1G>T (IVS6-1 G>T), c.607-6T>G (IVS7-6 T>G), p.Pro261Leu) account for ~60% of variants in US population

## Others

-Treatment:

1) **Nitisinone/NTBC** (blocks p-HPPD; second step in the tyrosine degradation pathway) --> **prevents accumulation of fumarylacetoacetate and its conversion to succinylacetone**

2) **Low-tyrosine diet** --> > 90% survival rate, normal growth, improved liver function, prevention of cirrhosis, correction of renal tubular acidosis, improvement in secondary rickets

# Arylsulfatase A Deficiency (Metachromatic Leukodystrophy)

## Genetics

-Gene: **ARSA** (Arylsulfatase A) or **Saposin B** (Activator of ARSA)

-AR

## Clinical findings/Dysmorphic features

-Late-infantile: onset < 30 mths; weakness, hypotonia, clumsiness, frequent falls, toe walking, dysarthria --> language, cognitive, motor skills regress --> spasticity, pain, szs, compromised vision and hearing --> tonic spasms, decerebrate posturing, unawareness of surroundings

-Juvenile: onset 30 mths – 16y; decline in school performance and behavioral problems; gait disturbances; progression similar but slower than in late-infantile

-Adult: onset > 16 years; problems in school/job performance, personality changes, emotional lability, psychosis, neurologic symptoms (weakness and loss of coordination progressing to spasticity and incontinence), seizures initially predominate; peripheral neuropathy is common

## Etiology

-Prevalence between 1:40,000 and 1:160,000

## Pathogenesis

-**Lysosomal Sphingolipidosis**; arylsulfatase A (ARSA) enzyme deficiency --> **defect breakdown of sulfatides (3-O-sulfogalactosylceramide)**,

-**Sulfatides: sulfate-containing lipids**; throughout body; greatest abundance in nervous tissue, kidneys, testes; approximately 5% of the myelin lipids

-Sulfatide accumulation in nervous system --> **myelin breakdown (leukodystrophy)** and progressive neurologic disorder

## Genetic testing/diagnosis

-Progressive neurologic dysfunction --> MRI evidence of leukodystrophy

-Abnormally **high sulfatides in urine**

-ARSA: Seq 90-95%; In/Del <1%

## Others

-**Pseudodeficiency (5-15% of normal activity) in ~2% of European Caucasian alleles**

# Urea cycle disorders

## Genetics

-Five catalytic enzymes: 1) **CPS1** (Carbamoylphosphate synthetase I), 2) **OTC** (Ornithine transcarbamylase), 3) **ASS1** (Argininosuccinic acid synthetase), 4) **ASL** (Argininosuccinic acid lyase), 5) **ARG1** (Arginase-1)

-One cofactor-producing enzyme: **NAGS** (N-acetyl glutamate synthetase)

-Two amino acid transporters: 1) SLC25A15/**ORNT1** (Ornithine translocase; ornithine/citrulline carrier), 2) SLC25A13/**Citrin** (aspartate/glutamate carrier)

## Clinical findings/Dysmorphic features

1) **NAGS deficiency: mimic of CPS1 deficiency** (CPS1 inactive w/o **N-acetylglutamate**)

2) **CPS1 deficiency**: most severe UCD; rapidly develop **hyperammonemia** in newborn period

3) **OTC deficiency (XLR)**: as severe as CPS1 deficiency; **~15% of carrier females develop hyperammonemia during lifetime**, many require medical management of hyperammonemia

4) **ASS1 deficiency**: **hyperammonemia** also quite severe; individuals able to incorporate some waste nitrogen into UC intermediates

5) **ASL deficiency**: can present with rapid-onset hyperammonemia in newborn period; ASL past the point in UC at which all the waste N has been incorporated into the cycle --> chronic hepatic enlargement/elevation of transaminases; liver biopsy shows enlarged hepatocytes (fibrosis); **trichorrhexis nodosa** (responds to arginine supplementation)

6) **ARG1 deficiency**: no rapid-onset hyperammonemia; some present earlier with more severe sx; progressive spasticity, tremor, ataxia, choreoathetosis; late-onset hyperammonemia

7) **ORNT1 deficiency** (**Hyperornithinemia-Hyperammonemia-Homocitrullinuria**): variable onset (infancy to adulthood); chronic neurocognitive deficits, hyperammonemic crisis, chronic liver dysfunction

8) **Citrin deficiency**: can manifest in newborns as neonatal **intrahepatic cholestasis** (impaired release of bile from liver cells) --> **bile builds up in liver** --> impaired liver function

## Etiology

-UCDs is estimated to be at least 1:35,000 births

-**OTC deficiency 1:55,000**; ASL deficiency 1:220,000; ASS1 deficiency 1:250,000; ARG1 deficiency 1: 950,000; CPS1 deficiency 1:1,300,000; NAGS deficiency 1:2,000,000

## Pathogenesis

-NH3 is detoxificated to glutamine --> inc. glutamine synthesis in astrocytes --> **cerebral edema**

## Genetic testing/diagnosis

1) **Plasma NH3** **of > 150 μmol/L** (with nl anion gap and nl plasma glucose) --> strong ind. of UCD

2) PAA:

-**Cit is product of proximal (CPS1, OTC, NAGS) and substrate for distal (ASS1, ASL, ARG1)**:

-**CPS1-, NAGS-, OTC- and ORNT1-deficiency: Cit low/absent**

**-ASS1-deficiency: Cit markedly elevated**

**-Citrin deficiency: Cit** **moderate elevated + elevated threonine/serine ratio**

**-ASL deficiency: Cit** **moderate elevated + high argininosuccinic acid (ASA) in plasma/urine**

-**ARG1 deficiency: Cit normal + high arginine (**may be reduced in all other UCDs)

-Plasma **ornithine is elevated in ORNT1 deficiency**, **not elevated in OTC deficiency**

**-Urine homocitrulline is elevated** **ORNT1 deficiency**

-**Urine orotic acid**: **normal/low in CPS1 and NAGS deficiency** and **very high in OTC deficiency (carbamyl phosphate is shunted to pyrimidine synthesis resulting in high orotic acid)**

-Urine orotic acid can also be increased in ARG1 deficiency and ASS1 deficiency

# Glutaric acidemia Type I

## Genetics

-Gene: **GCDH** (**glutaryl-CoA dehydrogenase**; 19p13.13)

-AR

## Clinical findings/Dysmorphic features

-**Macrocephaly at birth (75%)**; **acute encephalopathic** episodes (i.e. illness); sudden onset of hypotonia and severe **movement disorders (choreoathetotic movements)** following an acute episode of dystonia

-Relatively normal development if treated

## Etiology

-Prevalence: 1 in 100,000

-**Prevalence in Amish: 1 in 300**

## Pathogenesis

-Deficiency in glutaryl-CoA dehydrogenase: lysine/tryptophan metabolism (in mt matrix)

-Converts glutaryl-CoA to crotonyl-CoA --> impaired break down of amino acids **lysine, hydroxylysine, tryptophan**

-Accumulating **glutaryl-CoA is metabolized to 3-hydroxyglutaric acid and glutaconic acid**

-Excessive levels of these amino acids/intermediates cause damage to brain (basal ganglia)

## Genetic testing/diagnosis

-Elevated **glutaric acid**, **3-hydroxyglutaric acid**, **glutaconic acid**, glutarylcarnitine --> detected by gas chromatography/MS (organic acids) or tandem MS (acylcarnitines)

-**C5DC level is increased**

## Others

-Sarah’s painting Ruthie’s prayer

-Bleeding in brain or eyes --> **mimics non-accidental trauma/child abuse**

-Treatment:

During crisis: prevent or reverse catabolic state --> **high-energy intake (plus insulin in case of hyperglycemia)**; **reduce production of neurotoxic GA and 3-OH-GA by decrease/omitting natural protein for 24 −48h**; prevent secondary carnitine depletion by **carnitine suppl.**

Long-Term: reduce accumulation of toxic agent glutaric acid; low protein diet which specifically **restricts lysine and tryptophan**; alternatively, they can be put on a lysine free diet with tryptophan supplements for protein biosynthesis; patients are also given carnitine

# Mucolipidosis II (I-cell disease)

## Genetics

-GNPTAB (UDP-N-acetylglucosamine-1-phosphate transferase; 12q23.3)

-AR

## Clinical findings/Dysmorphic features

-Slowly progressive; clinical onset at birth; fatal most often in early childhood

-FTT, contractures in large joints; thickened skin; **coarse facial features**; **hypertrophic gingiva**

-Orthopedic (present at birth): thoracic deformity, kyphosis, clubfeet, deformed long bones, and/or dislocation of hip(s); skeletal radiographs reveal **dysostosis multiplex**

-Cardiac: **thickening and insufficiency of the mitral valve**

-Progressive mucosal thickening --> narrow airways and gradual stiffening of the thoracic cage --> respiratory insufficiency (most common cause of death)

-Breaking of the lumbar vertebrae, a J-shaped sella tursica, and ribs that widen anteriorly

## Etiology

-Overall carrier rate: 1:158 and 1:316; high prevalence (1:6184 live births; carrier rate of 1:39) in Quebec, Canada (founder variant GNPTAB, c.3503\_3504delTC)

## Pathogenesis

-Deficiency of GlcNAc-phosphotransferase --> no addition of the common mannose-6-phosphate (M6P) moiety to lysosomal acid hydrolases --> no binding to M6P receptors in trans-Golgi network --> **no receptor-mediated transport of enzymes to lysosomal compartment** --> hydrolases leave cells; appear in excessive amounts in culture media/patient’s body fluid

## Genetic testing/diagnosis

-**Activity of nearly all lysosomal hydrolases 5- to 20-x higher in plasma and other body fluids than in normal controls**; M6P cannot be added to the glycan part of glycoproteins

-Nearly complete inactivity (<<1%) of UDP-N-acetylglucosamine confirms the diagnosis

## Others

-Dark and dense granules in cytoplasm of patient fibroblasts --> “**inclusion cells” (I-cells)**

**-elevated levels of Arylsulfatase A and beta-glucuronidase**

# ATP7A-Related Copper Transport Disorders

## Genetics

-Gene: ATP7A (Copper transporting ATPase1, Xq21.1)

-**XLR** (**1/3 de novo**)

## Clinical findings/Dysmorphic features

1) **Menkes disease**: healthy until 2-3 mths; then loss of developmental milestones, hypotonia, seizures, FTT; infants exhibit **typical neurologic and hair changes** (short, sparse, coarse, twisted, light; **steel wool cleaning pads; pili torti**); temp. instability; hypoglycemia; death by age 3y

2) **Occipital horn syndrome** (OHS)/**X-linked cutis laxa**: "occipital horns" (distinctive wedge-shaped calcifications at occipital bone); lax skin and joints; bladder diverticula; inguinal hernias; vascular tortuosity; intellect is normal or slightly reduced

3) **ATP7A-related distal motor neuropathy**: adult-onset disorder; resembling Charcot-Marie-Tooth disease; no clinical or biochemical abnormalities characteristic of Menkes disease or OHS

## Etiology

-Incidence 1:100,000 births

## Pathogenesis

-ATP7A is transmembrane protein that functions in copper transport across membranes --> copper accumulates in some tissues (small intestine and kidney), low in brain and other tissues

-**Reduced activity of numerous copper-containing enzymes** (i.e. structure and function of bone, skin, hair, blood vessels, nervous system)

## Genetic testing/diagnosis

-**Plasma and CSF catecholamine** analysis: catechol concentrations abnl in males with Menkes disease and OHS (normal in ATP7A-related DMN) (abnl levels reflect partial deficiency of the copper-dependent dopamine beta hydroxylase critical for catecholamine biosynthesis

-Serum copper concentration and serum ceruloplasmin concentration low in Menkes disease and OHS (normal in ATP7A-related DMN)

-ATP7A: Seq 80%, InDel 20%

## Others

-ATP7A-related DMN: unique variants within or near the luminal surface of the protein

# WAGR Syndrome (PAX6-Related Aniridia)

## Genetics

-Isolated aniridia: PAX6 (Pair box protein; **11p13**) --> AD; 30% de novo

-**WAGR: PAX6 + WT1** (Pair box protein + Wilms Tumor 1; **11p13**; **~700kb heterozygous deletion**) --> **AD; usually de novo** (rarely, asymptomatic parent may be mosaic)

## Clinical findings/Dysmorphic features

-**WAGR= Wilms Tumor-Aniridia-Genital Anomalies-Retardation**

-Aniridia: pan ocular disorder: cornea, iris, intraocular pressure (resulting in glaucoma), lens (cataract and subluxation), fovea (hypoplasia), optic nerve (optic nerve coloboma/hypoplasia)

-WAGR:

--> Risk for **Wilms tumor** is 42.5%-77% (of those: 90% by age four; 98% by age seven)

--> **Genital anomalies** (males: cryptorchidism, hypospadias, ambiguous genitalia, ureteric abnormalities, gonadoblastoma; females: normal external genitalia, may have uterine abnormalities and streak ovaries)

--> **ID** in 70%, behavioral abnormalities (ADHD, ASD, anxiety, depression, OCD)

## Etiology

-Prevalence of aniridia 1:40,000 to 1:100,000; prevalence of WAGR is 1:500,000

## Pathogenesis

-PAX6 important for ocular devel. during embryogenesis: proliferation, differentiation, migration, adhesion

-PAX6 expression continues in adult retina, lens, cornea (maintains ocular health) --> het mut disturb ocular morphogenesis --> aniridia and related ocular phenotypes; mild CNS defects; hom or comhet mut --> anophthalmia and CNS defects; often fatal (**incomplete dominance**)

-WAGR caused by cryptic or cytogenetically visible deletions (11p that include band 11p13) --> loss of WT1 --> genitourinary + renal abnormalities --> predisposes to Wilms tumor

## Genetic testing/diagnosis

-Isolated aniridia: PAX6 --> Seq 85%, In/Del 15%; WAGR: PAX6 and WT1 --> CMA/FISH 100%

## Others

-Het variant in PAX6 regulatory element (150kb from PAX6 in ELP4 gene) --> isolated aniridia

-Screen children with abdominal US every 3 month until age 8 years

-**Wilms tumor (=Nephroblastoma) = childhood kidney cancer**

# Glucose-6-phosphate dehydrogenase deficiency

## Genetics

-Gene: **G6PD** (glucose-6-phosphate dehydrogenase; Xq28)

-XLR

## Clinical findings/Dysmorphic features

-**Hemolytic anemia** (red blood cells destroyed faster than they get replaced) --> paleness, **jaundice**, **dark urine**, fatigue, shortness of breath, rapid heart rate

-Significant cause of mild to severe jaundice in newborns

-Many people never experience signs/symptoms and are unaware that they have the condition

-Some carrier females with symptoms

## Etiology

-**Most common enzymopathy**; 400 million people worldwide affected; most frequent in parts of Africa, Asia, Mediterranean, Middle East; affects ~ 1 in 10 African American males in US

## Pathogenesis

-**Impaired ability of erythrocytes to form NADPH** --> not enough to regenerate glutathione (natural antioxidant) --> **toxic ROS accumulate** --> hemolysis

## Genetic testing/diagnosis

-G6PD enzyme activity level below 5 units per gram of hemoglobin constitutes deficiency

## Others

-Triggers:

1) Food: **Fava beans**/inhaled pollen with high amounts of chemicals that are highly oxidative

2) Infections: **immune system incites inflammatory response** that generates oxidative species

3) Specific drugs: **antibiotics** and malaria medications

# Pallister-Killian mosaic syndrome

## Genetics

-**Isochromosome 12p or i(12p)**

-**100% de novo**

## Clinical findings/Dysmorphic features

-Hypotonia in infancy and early childhood; ID

-Sparse scalp hair; high forehead; coarse face; widely spaced eyes; broad nasal bridge; highly arched palate; epicanthal fold; large, low-set ears with thick and outwards-protrude lobes

-**Hypopigmented streaks of skin**; **extra nipples**; seizures; droopy upper eyelids, crossed eyes (strabismus); joint contractures; cognitive delays; heart defects; rounded cheeks; wide mouth with thin upper lip and a large tongue

## Etiology

-150 cases reported

## Pathogenesis

-Some cells with isochromosome 12p --> four copies of all genes on p arm of chromosome 12

## Genetic testing/diagnosis

-Karyotype/FISH

# Long QT syndrome

## Genetics

-**15 genes**; most common: KCNH2 (LQT2), KCNQ1 (LQT1), SCN5A (LQT3)

-AD; **mostly inherited; de novo is rare;** exception: **Jervell and Lange-Nielsen syndrome (AR)**

-20% with LQTS without variant in known genes

## Clinical findings/Dysmorphic features

-Cardiac electrophysiologic disorder; QT prolongation and T-wave abnormalities on ECG

-Associated with **tachyarrhythmias** (ventricular tachycardia **torsade de pointes [TdP]**)

-TdP is usually self-terminating --> **syncopal event** (fainting, most common symptom in LQTS)

-Events during exercise/emotional stress, less common during sleep, usually without warning

-In some instances, TdP degenerates to ventricular fibrillation and causes aborted cardiac arrest (if the individual is defibrillated) or sudden death

-50% of untreated individuals with a pathogenic variant in one of the genes have symptoms (one to a few syncopal events); most common from preteen years through the 20s

## Etiology

-Prevalence of LQTS has been estimated at 1:2,500

## Pathogenesis

-LQTS genes encode for **potassium or sodium cardiac ion channels or interacting proteins**

-**LOF variants in potassium channels (K+)** and **gain of function in sodium channel (Na+)**

-Abnormal ion function --> prolongation of cardiac AP and susceptibility of cardiac myocytes to early afterdepolarizations (EADs) --> ventricular arrhythmia, TdP

## Genetic testing/diagnosis

-Multigene panel: **KCNQ1 (30-35% of cases**; Seq 98%, In/Del 2-3%); **KCNH2 (25-30%** of cases; Seq 98%, In/Del 2-3%); **SCN5A (5-10%** of cases; Seq 100%)

# Smith - Lemli- Opitz

## Genetics

-Gene: **DHCR7** (7-dehydrocholesterol reductase; 11q13.4)

-AR

## Clinical findings/Dysmorphic features

-Facial features: microcephaly, narrow forehead, **epicanthal folds**, **ptosis**, short mandible with preservation of jaw width, cleft palate, short nose, **anteverted nares**, low-set ears

-**2-3 syndactyly of the toes** (minimal to Y-shaped); postaxial polydactyly

-Growth delay; ID; hypospadias in males

## Etiology

-Prevalence approximately 1:20,000 to 1:40,000 live births

## Pathogenesis

-**Deficiency of 7-DHC reductase** --> **failure to convert 7-DHC to cholesterol**

## Genetic testing/diagnosis

-Diagnostic test: **elevated serum conc. of 7-DHC;** most affected ind. with **hypocholesterolemia**

-Seq. of DHCR7 (96% of known variants): seq. of ex 4-9; targeted analysis of variants; In/Del

-**84% of pathogenic variants are missense** variants distributed among all coding exons

**-Woman pregnant with SLOS fetus have low serum estriol levels**

# PAFAH1B1-Associated Lissencephaly

## Genetics

-**Miller-Dieker syndrome** (MDS): small cytogenetically visible deletions/FISH-detectable microdeletions of **17p13.3** (**include PAFAH1B1 (former LIS1) and YWHAE + intervening genes**)

-80% with MDS have de novo deletion involving 17p13.3; 20% have inherited a deletion from a parent who carries a balanced chromosome rearrangement

-Isolated lissencephaly sequence (ILS): smaller submicroscopic deletions, intragenic in/del or sequence variants of PAFAH1B1 (all PAFAH1B1 intragenic pathogenic variants are de novo)

## Clinical findings/Dysmorphic features

-PAFAH1B1-associated lissencephaly includes MDS and ILS

-Lissencephaly: cortical malformations caused by deficient neuronal migration during embryogenesis (agyria or pachygyria)

-MDS is characterized by lissencephaly, typical facial features, severe neurologic abnormalities

-ILS is characterized by lissencephaly; DD; ID; seizures

## Etiology

-Prevalence 12 to 40 in 1,000,000 births

## Pathogenesis

-Central role in organization of cytoskeleton --> interaction with proteins including tubulin, centrosomes and microtubule dynamics --> **role in neuronal proliferation and migration**

-Pathogenic variants in PAFAH1B1 --> reduction in amount of correctly folded protein

## Genetic testing/diagnosis

-High-res chromosome (> 450-band level) identify cytogenetically visible deletions/structural rearrangements of 17p13.3 in ~ 70% of individuals with MDS but not in individuals with ILS

# MUTYH-Associated polyposis

## Genetics

-Gene: MUTYH (Adenine DNA glycosylase; 1p34.1)

-**AR**

## Clinical findings/Dysmorphic features

-Increased lifetime risk of CRC (almost 100% in absence of timely surveillance)

-10-100s **colonic adenomatous** at 50 years (CRC can develop in absence of polyposis)

-**Duodenal adenomas** in 17%-25% of individuals with MAP (lifetime risk: 4%)

-**Serrated adenomas**, hyperplastic/sessile serrated polyps, and mixed (hyperplastic and adenomatous) polyps can occur

-Modestly inc. risk for late-onset malignancies of **ovary, bladder, skin, breast, endometrial**

-Some ind. develop **sebaceous gland tumors** (recently, thyroid abnormalities were reported)

## Etiology

-1-2% are carriers --> prevalence of 1:40,000 to 1:20,000 for biallelic germline variants

## Pathogenesis

-**Adenine DNA glycosylase** plays role in DNA damage repair (**base excision repair**, caused by ionizing radiation, chemical oxidants, ROS) --> lack of MUTYH leads to accumulation of G:C>T:A transversions in daughter DNA strands post-replication

## Genetic testing/diagnosis

-MUTYH: Seq 99%. In/del ?

-Two mutations account for 75% (c.536A>G (p.Tyr179Cys) and c.1187G>A (p.Gly396Asp))

## Others

-Hallmark of MUTYH carcinomas: **KRAS c.34G>T in codon 12 in 64% of MAP** CRCs cancers

-MUTYH tumors are mainly MSI-stable

-Colonoscopy every 1-2 years starting age 20-25

# DICER1-Related Disorders

## Genetics

-Gene: DICER1 (Endoribonuclease Dicer; 14q32.13)

-AD; 80% inherited

## Clinical findings/Dysmorphic features

-Familial tumor susceptibility syndrome --> increased risk for **pulmonary pleuroblastoma** (PPB; neoplasm that arises during lung development or shortly after birth); **ovarian sex cord-stromal tumors**; cystic nephroma; **thyroid gland neoplasia**

-Less common: ciliary body medulloepithelioma; botryoid-type embryonal **rhabdomyosarcoma** of the cervix; nasal chondromesenchymal hamartoma; renal sarcoma; pituitary blastoma

-Majority of tumors in individuals < 40 years

## Etiology

-unknown

## Pathogenesis

-DICER1 encodes RNase III enzyme --> **miRNA and siRNA biogenesis** --> cleaves precursor double stranded RNAs into active forms

-LoF germline pathogenic variants in DICER1 + somatic pathogenic variants --> production of defective mature miRNAs from the 5' (5p) end of the miRNA hairpin

## Genetic testing/diagnosis

-Dicer sequencing: 65%

# Nevoid basal cell carcinoma syndrome (Gorlin syndrome)

## Genetics

-**PTCH1** (Protein patched homolog 1; 9q22.32); SUFU (Suppressor of fused homolog; 10q24.32)

-AD; 70-80% inherited

## Clinical findings/Dysmorphic features

-Formation of **multiple jaw keratocysts** (2nd decade) and/or **basal cell carcinomas** (3rd decade)

-60% with **macrocephaly**, frontal bossing, coarse facial features, facial milia (keratin-filled cysts)

-Most with skeletal anomalies (e.g., **bifid ribs**, **wedge-shaped vertebrae**)

-**Ectopic calcification** (falx cerebri) in > 90% of affected individuals by 20 years

-Cardiac (2%) and ovarian (20%) fibromas; ~5% of affected children develop medulloblastoma (primitive neuroectodermal tumor; risk higher in ind. with SUFU variant (33%) vs. PTCH1 (<2%)).

## Etiology

-Prevalence approx. 1:57,000

## Pathogenesis

-**PTCH1** is membrane protein with 12 transmembrane regions, 2 extracellular loops, and putative sterol-sensing domain --> functions as **SHH receptor** --> represses signaling activity of the co-receptor smoothened --> in complex with SHH, protein patched homolog 1 is not a repressor --> signaling happens

-Pathogenic variants result in a truncated protein and missense variants --> LoF

-**SUFU** protein --> negative regulator in SHH pathway --> heterozygous LoF variants cause NBCCS

## Genetic testing/diagnosis

-PTCH1: Seq 50-85%; InDel 6-21%; SUFU: Seq 5%; InDel 1%; Unknown: 15-27%

## Others

-Life expectancy in NBCCS is not significantly different from average

# Retinoblastoma

## Genetics

-Genes: RB1 (Retinoblastoma-associated protein; 13q14.2); MYCN

## Clinical findings/Dysmorphic features

-AD susceptibility for retinoblastoma; from cells with cancer-predisposing mut in 2 RB1 copies

-**Malignant tumor of developing retina** in children < 5y; may be unifocal or multifocal;

-~60%: unilateral RB (age of diagnosis 24 mths); ~ 40%: bilateral RB (age of diagnosis 15 mths)

-Individuals are also at increased risk of developing non-ocular tumors; sarcomas

## Etiology

-Incidence between 1:15,000 and 1:20,000 live births

## Pathogenesis

-RB1 encodes ubiquitously expressed **nuclear protein involved in cell cycle regulation (G1 to S transition)** --> RB is **phosphorylated** by members of the cyclin-dependent kinase system prior to the entry into S-phase --> binding activity of pocket domain is lost --> release of cellular proteins

-**Pathogenic variants in RB1 --> loss of cell cycle-regulating function**

-Partial active proteins associated with low-penetrance retinoblastoma

## Genetic testing/diagnosis

-Eye exam using indirect ophthalmoscopy; imaging studies: support diagnosis and stage tumor

-Diagnosis: proband with retinoblastoma AND family history of retinoblastoma OR identification of het germline variant in RB1

-Seq and In/Del analysis of RB1 are performed on peripheral blood DNA

-If tumor tissue available: Seq and In/Del analysis of RB1 on tumor DNA

--> if pathogenic variants found --> blood is tested for presence of these variants

--> if no pathogenic variants found: **methylation analysis of RB1 promoter CpG island** --> if no hypermethylation --> **amplification of MYCN** is tested (cause of retinoblastoma in absence of RB1 variants in ~ 1.5% of individuals with isolated unilateral retinoblastoma)

## Others

-Eye examination under anesthesia every 3-4 weeks until 6mths, then less frequently until 3y

-15% of unilateral retinoblastoma patients carry a germline mutation --> 1% recurrence risk for unilateral (it is 5-7% for bilateral, due germline mosaicism, mainly in father)

# Peutz-Jeghers Syndrome

## Genetics

-Gene: **STK11** (95% of PJS; Serine/threonine-protein kinase STK11; 19p13.3)

-AD

## Clinical findings/Dysmorphic features

-**GI polyposis + mucocutaneous pigmentation + cancer predisposition**

-**Hamartomatous polyps**: most common in small intestine but also in stomach, large bowel, extraintestinal sites (renal pelvis, bronchus, gall bladder, nasal passages, urinary bladder, ureters) --> chronic bleeding, anemia, recurrent obstruction, **intussusception**

-Mucocutaneous hyperpigmentation: dark blue/brown macules around mouth, eyes, nostrils, perianal area, buccal mucosa

-Increased risk for epithelial malignancies: colorectal, gastric, pancreatic, breast, ovarian; **Sertoli cell tumors of the testes, sex cord tumors with annular tubules (SCTAT)**

## Etiology

-Estimates range widely from 1:25,000 to 1:280,000

## Pathogenesis

-Dysregulation of mTOR is common molecular pathway for hamartoma syndromes

-**STK11 acts as suppressor for mTOR** pathway by **activating mTOR inhibitor TSC2** through (AMP-dependent protein kinase (AMPK)--> leading to accumulation/activation of mTOR --> protein synthesis and angiogenesis

-STK11 is multi-tasking tumor suppressor with roles in apoptosis, cell cycle arrest, cell proliferation, cell polarity, energy metabolism

## Genetic testing/diagnosis

-STK11: Seq 81%, InDel 15%

## Others

-PTEN also effects TSC2 and mTOR pathway via AKT1

-**Rapamycin is mTOR inhibitor**

# Juvenile Polyposis Syndrome

## Genetics

-Genes: **BMPR1A** (28%; Bone morphogenetic protein receptor type-1A; 10q23.2); **SMAD4** (27%; Mothers against decapentaplegic homolog 4; 18q21.2); 45% unknown cause

-AD; 1/3 inherited

## Clinical findings/Dysmorphic features

-Predisposition to **hamartomatous polyps in GI** tract (stomach, small intestine, colon, rectum)

-Most ind. with some polyps by age 20y; some with only 4-5 over lifetime, some with >100

-If polyps untreated --> bleeding and anemia

-Most juvenile polyps are benign; however, malignant transformation can occur

-Risk for GI cancers: 9% to 50%.

## Etiology

-Incidence between 1:16,000 and 1:100,000

## Pathogenesis

-SMAD4 (tumor suppressor; intracellular mediator of TGF-β signaling); BMPR1A (unclear if tumor suppressor; type I cell surface receptor for BMP pathway --> ligands, such as TGF-β or BMP, bind to receptor and activate signaling pathways --> protein complexes that migrate to nucleus --> bind DNA sequences to regulate transcription

## Genetic testing/diagnosis

-Diagnosis is established in proband with any of the following:

--> more than five juvenile polyps of colorectum;

--> multiple juvenile polyps throughout GI tract;

--> any number of juvenile polyps and a family history of juvenile polyposis

-Identification of a heterozygous pathogenic variant in SMAD4 or BMPR1A confirms diagnosis if clinical features are inconclusive

-BMPR1A: Seq 69-85%; InDel 15%; SMAD4: Seq 83%; InDel 17%

## Others

-Close proximity of BMPR1A to PTEN (both on 10q22-q23), but not members of same pathways

-Contiguous gene deletion of PTEN and BMPR1A associated with severe form of early-onset JPS

-"Juvenile" refers to type of polyp rather than to the age of onset

-Combined syndrome of JPS and HHT is present in most individuals with SMAD4 variant

# Dyskeratosis congenita

## Genetics

-Genes: **DKC1** (XL; 20-25%); TINF2 (AD; 12-20%); TERC (AD; 5-10%); RTEL1 (AD/AR; 2-8%); TERT (AD/AR; 1-7%); unknown 20-30%

## Clinical findings/Dysmorphic features

-**1) dysplastic nails; 2) lacy reticular pigmentation of upper chest/neck, 3) oral leukoplakia**

-Increased risk for: pulmonary **fibrosis**, progressive bone marrow failure, myelodysplastic syndrome, acute myelogenous **leukemia**, solid tumors (**squamous cell carcinoma of head/neck** or anogenital cancer); bone marrow failure

## Etiology

-Rare, 2015: 400 families

## Pathogenesis

-**TTAGGG nucleotide repeats** fold back to create a t-loop --> many proteins bind to t-loop and others bind to those proteins to form a stable telomere "cap".

-11 genes (DKC1, TERC, TERT, TINF2, NOP10, NHP2, WRAP53, ACD, RTEL1, PARN, CTC1) encoding critical components of telomere can be mutated in individuals with DC

## Genetic testing/diagnosis

-Individuals with DC have abnormally short telomeres for their age --> multicolor flow cytometry fluorescence in situ hybridization (flow-FISH) on white blood cell subsets

-Serial single-gene testing or multigene panel; in AJ testing for c.3791G> A (p.Arg1264His) in RTEL1 can be considered first

# MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

## Genetics

-Genes: **MT-TL1 (>80%);** MT-ND5 (<10%)

-Maternal inheritance

## Clinical findings/Dysmorphic features

-Multisystem disorder; onset between 2 and 40y

-Manifestations: **stroke-like episodes**; **encephalopathy** with seizures/dementia; muscle weakness; exercise intolerance; headaches; vomiting; hearing impairment; peripheral neuropathy; LD; short stature

-During stroke-like episodes: increased T2-weighted signal areas that do not correspond to the classic vascular distribution (hence: "stroke-like")

-**Lactic acidemia** is very common and muscle biopsies typically show **ragged red fibers**

## Etiology

-Prevalence estimated to be 0.2:100,000 in Japan

-Prevalence of **m.3243A>G** estimated to be 16:100,000–18:100,000 in Finland

## Pathogenesis

-**11 mt-tRNAs** (mainly **MT-TL1**) involved in MELAS --> **impaired mitochondrial protein synthesis**

-**6 protein-encoding genes** also involved in MELAS (i.e. MT-ND1, NADH dehydrogenase subunit 1 and MT-ND5, NADH dehydrogenase subunit 5) --> pathogenic variants in ETC structural subunits result in **impaired ATP synthesis via oxidative phosphorylation**

## Genetic testing/diagnosis

-Diagnosis based on clinical diagnostic criteria and identifying a pathogenic variant

-Blood leukocyte DNA is initially tested for **m.3243A>G in MT-TL1 (**present in ~ 80% of individuals with typical clinical findings) --> if normal, targeted testing for pathogenic variants m.3271T>C and m.3252A>G in MT-TL1 and m.13513G>A in MT-ND5

## Others

-mtDNA encodes 22 **tRNAs**

-During acute stroke-like episode --> intravenous arginine within three hours, followed by intravenous arginine as a continuous infusion over 24 hours for the next three to five days

# Mitochondrial DNA-Associated Leigh Syndrome and NARP

## Genetics

-Genes: **MT-ATP6** (~50% Leigh syndrome; >50% NARP); MT-ND5; MT-ND3; MT-ND6

-If nuclear: mostly AR

## Clinical findings/Dysmorphic features

-Spectrum: progressive neurodegenerative disorders due to anomalies of mt energy generation

-**Leigh syndrome**: onset between 3 and 12mths (often following viral infection); decompensation (often with elevated lactate levels in blood/CSF) during an intercurrent illness --> psychomotor retardation/regression; **neurologic features** include **hypotonia, spasticity, movement disorders** (including chorea), cerebellar ataxia, peripheral neuropathy, **basal ganglia + brainstem MRI abnormalities in Leigh syndrome**; **extraneurologic manifestations** may include **hypertrophic cardiomyopathy;** 50% of affected individuals die by 3 years (respiratory or cardiac failure)

-**NARP (neurogenic muscle weakness, ataxia, and retinitis pigmentosa)**: proximal neurogenic muscle weakness with sensory neuropathy, ataxia, pigmentary retinopathy; onset of symptoms, particularly ataxia and learning difficulties, often in early childhood; can be stable for years, but may suffer episodic deterioration (associated with viral illness)

## Etiology

-Prevalence is likely to be 1:30,000 to 1:40,000; no data on prevalence of NARP

## Pathogenesis

-Caused by mutations in more than **75 different genes**; **most in nuclear DNA, some in mtDNA**

-Pathogenic variants fall into 2 classes: 1) **tRNA** --> decreased mitochondrial protein synthesis; 2) **Protein-coding mtDNA genes** --> decreased activity of respiratory chain complex

-**m.8993T>G, p.Leu156Arg** in subunit 6 of the mt ATP synthase --> ATP synthase (or complex V) uses the proton gradient generated by respiratory chain complexes I to IV to drive ATP synthesis --> impaired proton translocation and inhibition of ATP synthesis

## Genetic testing/diagnosis

-Diagnosis: progressive neurologic disease with motor and intellectual DD, signs of brain stem/basal ganglia disease, raised lactate in blood/CSF, and any one of the following:

--> Characteristic features on brain imaging/typical neuropathologic changes/typical neuropathology in a similarly affected sibling

-Identification of a pathogenic variant in one of 14 mitochondrial genes confirms diagnosis: targeted seq 2 common MT-ATP6 variants, concurrently with del/dup on leukocyte DNA --> mt genome sequencing next

-MT-ATP6: Seq 95%; InDel 5%; most common: m.8993T>G

# MERRF (myoclonic epilepsy with ragged red fibers)

## Genetics

-Genes: **MT-TK** (**90%, encoding tRNALys**; **80% m.8344A>G**); MT-TF, MT-TL1, MT-TI, MT-TP

## Clinical findings/Dysmorphic features

-Multisystem disorder: onset in childhood, after normal early development; **myoclonus** (quick, involuntary muscle jerk, i.e. **hiccups**) often the first symptom --> **generalized epilepsy, ataxia, weakness, dementia**

-Common findings: HL, short stature, optic atrophy, **cardiomyopathy**

## Etiology

-Prevalence of the m.8344A>G: <1:100,000

## Pathogenesis

-MT-TK pathogenic variant directly inhibits protein synthesis --> cell cultures containing >85% mutated mtDNA with **decreased translation** (**mainly proteins with large numbers of lysines**)

-Cells with m.8344A>G contain low levels of tRNALys and aminoacylated tRNALys

## Genetic testing/diagnosis

-Diagnosis: 4 "canonic" features: **myoclonus, generalized epilepsy, ataxia, ragged red fibers**

# Mitochondrial DNA Deletion Syndromes

## Genetics

-**mtDNA large-scale deletion** ranging from 1.1 to 10 kb

## Clinical findings/Dysmorphic features

1) **Kearns-Sayre syndrome (KSS)**: progressive multisystem disorder; onset < 20y; **pigmentary retinopathy; progressive external ophthalmoplegia (paralysis/weakness of the eye muscles)**; additional features: cerebellar ataxia, impaired intellect, SNHL, ptosis, oropharyngeal and esophageal dysfunction, exercise intolerance, muscle weakness, endocrinopathy

2) **Pearson syndrome**: **sideroblastic anemia and exocrine pancreas dysfunction**; may be fatal in infancy without appropriate hematologic management; (pancreatic failure, sideroblastic anemia, and pancytopenia)l typically lethal in infancy

3) **Progressive external ophthalmoplegia (PEO)**: ptosis, ophthalmoplegia, oropharyngeal weakness, variably severe proximal limb weakness with exercise intolerance.

4) Rarely, a mtDNA deletion can manifest as Leigh syndrome

## Etiology

-Adults with single large-scale mtDNA deletions: 1.5:100,000 individuals

## Pathogenesis

-Even smallest mtDNA deletion cover several tRNA genes --> "deleted" mtDNA is normally transcribed --> transcript is not translated because essential tRNAs are missingfor protein syn.

-Larger deletions also remove mRNAs required for synthesizing the mtDNA-encoded subunits of respiratory chain complexes I, III, IV, or V --> impaired mitochondrial energy production.

## Genetic testing/diagnosis

-Deletion/duplication analysis of mtDNA: 100% of KSS; 100% of PEO; <5% of Leigh syndrome

-**Common deletion m.8470\_13446del4977** present in 30% of KSS individuals

## Others

-Almost always de novo: mtDNA deletions in mother's oocytes during germline development or in embryo during embryogenesis  
-Homologous recomb. or slipped mispairing (i.e., unequal crossing over) as origin of deletions

# Hypophosphatasia

## Genetics

-Gene: **ALPL** (Alkaline phosphatase, tissue-nonspecific isozyme; 1p36.12)

-AR; milder forms, i.e. odontohypophosphatasia, may be AR or AD

## Clinical findings/Dysmorphic features

-**Defective mineralization of bone/teeth** due to low activity of **bone alkaline phosphatase**

-Continuum: stillbirth w/o mineralized bone - pathologic fractures of extremities in adulthood

-Six clinical forms: **1) Perinatal (severe)**: respiratory insufficiency and hypercalcemia; **2) Perinatal (benign)**: prenatal skeletal manifestations resolve into milder form; **3) Infantile**: onset between birth and age 3mths of rickets without elevated serum alkaline phosphatase activity; 4) **Childhood (juvenile)**: ranges from low bone mineral density for age with unexplained fractures to rickets and premature loss of primary teeth with intact roots; **5) Adult**: stress fractures/pseudofractures of lower extremities in middle age; **6) Odontohypophosphatasia:** premature exfoliation of primary teeth and/or severe caries without skeletal manifestations

## Etiology

-Prevalence of severe forms has been estimated at 1:300,000 in Europe

## Pathogenesis

-Alkaline phosphatase, tissue-nonspecific isozyme (TNSALP): isozyme present in liver, kidney, bone --> acts as a (lipid) **membrane-bound ectophosphatase** with PPi, PLP, and PEA as natural substrates; pathogenic variants are LoF

## Genetic testing/diagnosis

-All forms with reduced activity of unfractionated serum alkaline phosphatase (ALP)

-Presence of one or two pathogenic variants in ALPL; ALPL-Seq: 95%; In/Del unknown

## Others

-**Biphosphonates contraindicated** --> phosphate motifs in bisphosphonates have similar conformation to inorganic pyrophosphate (PPi), the natural substrate of TNSALP --> treatment with bisphosphonates is thought to be analogous to "adding fuel to the fire”

-Excess vitamin D can exacerbate hypercalcemia/hypercalciuria

-Craniosynostosis is often found in the perinatal or infantile form

# Gaucher Disease

## Genetics

-GBA (**Lysosomal acid glucosylceramidase**; 1q22)

-AR

## Clinical findings/Dysmorphic features

-Continuum: perinatal lethal - asymptomatic type

-**Type 1**: clinical/radiographic evidence of **bone disease** (osteopenia, focal lytic or sclerotic lesions, osteonecrosis, “**Erlenmeyer flask bone**”), **hepatosplenomegaly**, anemia/thrombocytopenia, lung disease, **absence of primary CNS disease**

-Types 2 and 3: **presence of primary neurologic disease**

--> 2: onset <2y; limited psychomotor development; **rapidly progressive** course; **death by 2-4y**

--> 3: onset ~2y; more **slowly progressive course**; survival into 3rd or 4th decade

## Etiology

-GD type1: with prevalence of 1:855 and carrier frequency of 1:18 in AJ

## Pathogenesis

-Defective lysosomal enzyme **glucocerebrosidase** --> accumulation of glucosylceramide (GL1) and other glycolipids --> GL1 is stored in cells of monocyte/macrophage lineage

-CNS: GL1 originates from turnover of membrane gangliosides, although neuronal cell death may be the basis of neuropathic involvement

## Genetic testing/diagnosis

-Diagnosis: deficient glucocerebrosidase activity in peripheral blood leukocytes or identification of biallelic variants in GBA

-Targeted first in AJ: c.84dupG + c.115+1G>A + p.Asn409Ser + Leu483Pro account for 90%

-GBA: Seq >99%, InDel <1%

## Others

-Most common lysosomal storage disorder

-**Severe horizontal gaze palsy (fixed esotropia) and preserved vertical gaze movement**

-Carriers are at an increased risk for developing **Parkinsonism**