**1.2 Chromosomal nomenclature and structure:** large dosage changes:

| Karyotype | FISH | aCGH/array CGH |
|---|---|---|
| • view whole genome<br>• abnormalities **>5Mb**<br>• low resolution<br>• low detection rate<br>• labor intensive → large turn over time<br>• need actively growing cells, no solid tumors of fixed tissues<br>• detects deletions, duplications, translocations, inversions, aneuploidy, polyploidy<br>• doesn't detect microdeletion and micro duplications<br>• cells need to be in metaphase<br>• high false - | • uses cDNA probe for target DNA<br>• fresh/frozen/paraffin/fixed tissues in interphase or metaphase<br>• high resolution<br>• need to know what your fishing for<br>• rapid turnover time<br>• no global genome analysis<br>• limited target per cell<br>• doesn't delineate size or genes involved<br>• detects microdeletion, micro duplications, translocations, gene amplifications<br>• detects chromo. Abnorn.<br>• quickly detects trisomys | • whole genome copy number analysis for detection of cryptic a common chromosomal abnorm.<br>• detects large deletions, microdeletion and micro duplications b comparing two samples<br>• detects common and cryptic aberrations, imbalances relating tc location<br>• don't need cell culture<br>• fast turnaround time<br>• can identify copy # variants of unknown clinical significance<br>• doesn't detect single gene mutation<br>• doesn't detect balanced rearrangements<br>• negative result: no detection of copy # diff = similar amount of patient and control DNA = baseline/0 result on graph<br>• genomic deletion: patient lost DNA = dip in graph<br>• genomic duplication: patient gained DNA = jump in graph |
| • large chromosomal imbalances<br>• suspected chromosomal syndromes (trisomy, turners etc.)<br>• known deletions or duplication syndrome (VCFS)<br>• > maternal age or + maternal screen<br>• known or suspected reciprocal or robertsonian translocation<br>• history of multiple miscarriages | • rapid aneuploidy diagnosis (trisomy 21,18,13,x,y): prenatal or newborn<br>• microdeletion syndromes (velocardiofacial, cri du chat)<br>• translocations<br>• cancer abnormalities<br>• detects cryptic rearrangements or deletions/duplications<br>• only using 3-4 probes at once | • better detection rate (20% vs 3% for karyotype)<br>• can use DNA from non-viable tissue or blood<br>• **can't detect gene mutations or balanced translocations**<br><br>advantages:<br>• performed on isolated DNA<br>• array entire genome for copy # gain or losses; no structura rearrangements<br>• higher resolution that karyotypes or FISH<br>• includes SNP, areas of LOH can be detected<br>disadvantages<br>• can't detect structural rearrangements<br>• normal cell and tumor heterogeneity can complicate analy<br>• many variants of unknown significances |

**1.3 chromosomal syndromes**

| Disease/clinical correlation | Characteristics | Etiology | Recurrence risk |
|---|---|---|---|
| Trisomy 21 (down syndrome) | • **Hypotonia:** muscle tone increases w/age<br>• **Transverse single palmar crease**<br>• **Round flat face w/increased space between eyes**<br>• **Congenital heart defects, septal defects (atrial and ventricular)**<br>• **↑ risk of acute lymphoblastic leukemia and acute myeloid leukemia**<br>• **intellectual disabilities (mild-moderate):** development progress slows with age; reach milestones slower; early development programs help<br>• poor moro reflex<br>• upward slanting palpebral fissures | • nondisjunction (95%): faulty chromosomal segregation in meiosis that's more likely w/ advanced maternal age<br>o age 25:1/1250…45:1/30<br>• **majority of children w/down syndrome are born to women under 35 b/c they have more children than women older than 35**<br><br>• **mosaic trisomy 21:** 2 cell populations (one has 46 and the other has 47) via | nondisjunction: 1% or mothers materna age risk<br><br>translocation: karyotype both parents, looking for balanced translocation<br>• 9% of down babies are born to mothers younger than 30 w/unbalanced translocations<br>• <2% born to mothers >35<br>• ~50% translocation cases are inherited from carrier parent. |

| | | Etiology | Recurrence Risk |
|---|---|---|---|
| | • small abnormal ears<br>• hyper flexible joints<br>• hip dysplasia<br>• clinodactyly: short curved dysplasia 5th finger<br>• nuchal fold: excess skin on back of neck<br>• females can have abnormal mensuration b/v of ovulatory dysfunction<br>• males have low testosterone and low fertility<br>• **no treatment: hearing aids; best outlook= live at home and have normal family life** | **mitotic nondisjunction** → less severe phenotype<br>• **translocation trisomy 21:** part or all of chromosome 21 is attached to another chromosome→ unbalanced→ phenotype is undesignable from trisomy 21; maternal age doesn't affect it | Recurrence depends on type of translocation and sex<br>• balanced translocation offspring's risk: **10-15% if mother is carrier 5% if father is carrier**<br>• **if one parent has balanced 21:21 translocation, 100% affected = isochromosome**<br><br>if parents already have a child w/down, can use CVS or amniocentesis to test future pregnancies |
| Trisomy 18 (Edward's syndrome) | • 2nd most common syndrome<br>• 3:1 females: males<br>• **polyhydramnios, pre/post natal growth retardation, ↓ fetal activity, single umbilical artery**<br>• **clenched fist w/index and little finger overlapping 3rd and 4th finger**<br>• **rocker bottom feet, shortened hypoplastic sternum w/missing 12th rib**<br>• short neck, back of skull is prominent, flexed big toe<br>• hypertonia, microcephaly, low malformed ears, micrognathia, cleft lip/palate, inguinal or umbilical hernia, Meckel's diverticulum, omphalocele, malrotation of bowel, horseshoe kidney, diaphragmatic hernia and cardiac defects | • nondisjunction event that's increases in frequency with maternal age<br>• translocations are rare | • nondisjunction: ≤1%; early embryonic or fetal death or spontaneous abortion<br>• translocation: parental karyotype needed to determine if parent is carrier of balanced translocation→ higher risk in later pregnancies<br>• *mosaicism:* partial expression of typical phenotype pattern w/ longe survival and variable expression |
| Trisomy 13 (Patau syndrome) | • more severe than trisomy 18<br>• **midfacial and forebrain development abnormalities, holoprosencephaly**<br>• **intrauterine growth retardation, cleft lip and/or palate, polydactyly**<br>• micrognathia, small eyes, colobomas, syndactyly, low set ears, broad flat nose, scalp defect, single umbilical artery, microcephaly, cardiac defects (septal wall), severe intellectual disabilities<br>• renal: **polycystic kidney,** hydroneophrosis, horseshoe kidney, ureter duplication<br>• prognosis: 80% die in 1st month; 5% survive 1st 6 months; severe mental retardation w/seizure and failure to thrive | • nondisjunction event that's increases in frequency with maternal age<br>• translocations are rare | • nondisjunction: ≤1%; less that dov b/c of spontaneous abortion<br>• translocation: excluded by chromosomal studies; need paterna karyotype to determine which pare is balanced translocation carrier → higher reoccurrence<br>• *mosaicism:* partial expression of typical phenotype pattern w/ longe survival and variable expression |

| | | | |
|---|---|---|---|
| Velocardiofacial syndrome (diGeorge syndrome) | • **Velo**pharyngeal incompetence: VPI, cleft palate→ speech and feeding problems (70%)<br>• **Cardi**ac (75%): tetralogy of fallot, interrupter aortic arch, ventricular spetal defect, truncus arteriosus<br>• **Facial** appearance: asymmetric, overfolded ears, small, recessed jaw, bulbous nasal trip, long face<br>• Learning problem (70-90%), hypocalcemia (50%), immunodef (77%) b/c small or no thymus gland<br>• Need help from genetics, plastic surgery, speech pathology, ent, audio, dentist, cardio, psych, neuro, peds, development | > 95% have 22q11 microdeletion<br>• 94% *de novo*<br>• 6% inherited<br>5% small atypical 22q11.2 deletion, rearrangement, or TBX1 gene mutation<br><br>diagnosis: karyotype, FISH, or CSG | • minimal if de novo<br>• 50% if inherited |
| XYY syndrome | • phenotypically normal males, fertile; variable expression;<br>• accelerated mid childhood growth, dull mentality, explosive behavior<br>• facial asymmetry, large teeth, long ears, prominent glabella<br>• ↑length and breadth in skeletal system → narrow heads, long fingers and toes, **tall thin stature** (see at 5-6 years of age)<br>• weak muscle, **poor fine motor coordination**, fine intentional tremor<br>• poor pectoral and shoulder girdle musculature development<br>• behavior problems (easily distracted), hyperactivity, temper tantrums, aggressive behavior, IQ 10-15 points below siblings<br>• severe adolescent nodulocystic acne | | • transmitting to son is rare & unrelated to paternal karyot & most likely due to de novo<br>• extra y chromosome from nondisjunction during male meiosis 2<br>not associated w/advanced maternal age |
| XXY (klinefelter syndrome) | • most common cause of **hypogonadism and infertility** in males<br>• 15-20% have IQs below 80; average IQ is 10-15 points lower than sibling; later onset of speech<br>• 20-50% have fine-moderate intentional tremor<br>• behavior problems: immaturity, insecurity, shyness, unrealistic boastful and assertive activity<br>• long limbs & decreased upper : lower body segment, tall, slim; no testosterone therapy = adult obesity<br>• small testes; testosterone is ½ normal values<br>• infertile; excess gonadotropin → **hyalinization and fibrosis of seminiferous tubules**<br>• virilization is partial and inadequate; 40% have **gynecomastia** | | Karyotype:<br>• 75% have XXY<br>• 22% have XXY/XY mosaics→ better testicular function<br>• meiotic nondisjunction equally occurs in paternal or maternal chromosomes; XXYY and XXXY → more intellectually challenged<br><br>need childhood diagnosis for testosterone supplementation |
| 45X (turner's) syndrome | • **decreased birth weight/short stature, Dysmorphology** (cystic hygroma, webbed neck, low posterior hair line, strabismus, high arched palate, buitus vulugs (outward elbow bend))<br>• **gonadal dysgenesis**<br>• **transient congenital lymphedema (puffy hands/feet, webbed neck)**<br>• **thyroid disease**<br>• **cardiac anomalies (coarctation of arota)**<br>• hearing loss<br>• **hormonal:** ovarian degeneration→ little functioning tissue remaining in adolescence; estrogen replacement→ menstruation; pregnancy via technology<br>• 45X/46XY mosaic: increased **gonadoblastoma** risk→ exploratory laparotomy<br>• **no intellectual disabilities**; delays in visual and spatial organization & math; i**f there are intellectual disabilities, do microarray and look for X autosome translocation (partial duplication/def of autosome)** | | • usually results in embryonic death<br>• **paternal** sex chromosome is missing<br>• no relationship between occurrence and advanced matern age<br>• sporadic w/little recurrence risk |

## 1.4 Autosomal Dominant Inheritance

| Disease | Clinical | prevalence | Gene products | Genetic counseling |
|---|---|---|---|---|
| Hypercholest-erolemia | • Caused by **locus heterogeneity**<br>• **LDLR on chromosome 19**<br>• **APOB on chromosome 2**<br>• **PCSK9 on chromosome 1**<br>• **↑in total and LDL cholesterol**<br>• **xanthomas:** yellow/orange lipid nodule on skin<br>• **atheromas:** lipid plaques on artery wall<br>• **arcus cornealis:** white/gray opaque ring in corneal margin; fat deposit<br>• **premature cardiovascular disease** | • **1/500**<br>• **variable expressivity and >90% penetrance**<br>• **penetrance reduced w/ modifier genes:**<br>• Single nucleotide polymorphism in APOA2, EPHX2, or GHR gene alters phenotype<br>• **Genotype/phenotype correlation:** association between certain mutation (genotype) and expression (phenotype)<br>**incomplete dominate:**<br>• **heterozygote: adult ldl >190, child >160; lesions @30-40 years of age; early coronary artery disease**<br>• **homozygote: adult ldl>500; lesions @6-17 years of age; myocardial infarction/heart attack starting @18months, death starting @20 years** | • *LDLR*→LDL receptor<br>• **Primary defect in LDL receptor (most LDL uptake is in liver) →** elevated plasma LDL→ stored in scavengers, xanthomas, atheromas | • **↑ prevalence: Afrikaners in south Africa, French Canadi Lebanese, Finns**<br>• **need to distinguish between homo and hetero before givi recurrence risk**<br>• rule out other causes<br>• **cascade screening:** test 1st deg relative; if + , test those 1st deg relatives<br><br>Treatment:<br>• **statins;** statins don't treat APOB mutations |
| Polycystic kidney disease (PKD) | • **bilateral renal cysts, cysts in other organs** (liver, seminal vesicles, pancreas, arachnoid membrane), **berry aneurysms** (intracranial aneurysms), aortic root dilation, thoracic aorta dissection, mitral valve prolapse, abdominal wall hernia<br>• **hypertension, renal pain and insufficiency →** end stage renal disease | • 1/400-1/1000<br>• *PKD1* mutations that are more 5' are more common in families w/ vascular complications | • ***PKD1*→**Polycystin 1<br>• ***PKD2*→** polycystin 2<br>• Polycystin 1&2 interact w/primary cilia (ciliopathy)<br>• Polycystin 1expressed in medial & cardiac myocytes of elastic, large distributive arteries, valvular myofibroblasts<br>• 10% of individuals with PKD1 or PKD2 mutations doesn't show symptoms | treatment:<br>• **hypertension: ACE inhibitor angiotensin 2 receptor block and diet modification**<br>• **berry aneurysms: surgical clipping**<br>counseling:<br>• 95% have affected parent<br>• **5% de novo; can't rule out gonadal mosaicism**<br>• **later age of onset**<br>• predictive (presymptomatic) testing |
| Neurofibromatosis type 1 (NF1) | • **café au lait spots**<br>• **axillary and inguinal freckling**<br>• **multiple cutaneous neurofibromas**<br>• **iris Lisch nodules**<br>• **learning disabilities (50%)**<br>• less common: plexiform neurofibromas, optic nerve and CNS gliomas, malignant PN | • 1/3000<br>**variable expressivity:**<br>• combination of factors<br>• normal and germline mutation<br>• modifier genes<br>• *NF1* deletion→more severe | • ***NF1*→**neurofibronin >500 mutations → **loss of function mutation**<br>treatment:<br>• surgical removal of cutaneous neurofibromas<br>• **surveillance: annual exam** for complication development | **diagnosis: family tree, don't need genetic testing**<br>counseling:<br>• **50% de novo: test parents**<br>• **gonadal mosaicism**<br>• **somatic mosaicism→ segmen NF1:**<br>• **somatic mutation** in postzygo cell→ daughter cells have |

| | | | | |
|---|---|---|---|---|
| | sheath tumors, scoliosis, tibial dysplasia, vasculopathy | | | mutations. Their offspring has increased chance of gonadal ce being affected |
| Marfan syndrome | • **connective tissue →multiple systems affected**<br>• **pleiotropy: single gene cause ≥2 unrelated effects**<br>• **ectopic lentis** (lens dislocation)<br>• **retinal detachment**<br>• myopia, glaucoma<br>• **bone overgrowth, joint laxity, arachnodactyly** (long fingers), dolichostenomelia (extremities long for trunk), scoliosis<br>• pectus excavatum: rib overgrowth, chest inward → concave<br>• pectus carinatum: chest outward→ convex | • 1/5000-1/10000<br>• **100% penetrance**<br>• **Variable expressivity**<br>• **Normal life expectancy if managed properly** | • ***FBN1*** **→ fibrillin 1 (dominant neg:** interferes w/other normal protein)<br>• **>1000 mutations (allelic heterogeneity)** | **Diagnosis: family history and clin diagnostic criteria; need to rule o other conditions**<br>Treatment**:**<br>• skeletal: orthopedist<br>• **ocular:** optho, surgery<br>• **cardiac: echocardiogram for aortic root dilation**<br>• **beta blocker= ↓hemodynami stress on aortic wall**<br>• **losartan: BP drug to stop aor root dilation**<br>• **avoid: contact sports, coffee, Lasik, decongestants, activiti that cause joint injury**<br>counseling:<br>• 75% have affected parent<br>• **25% de novo**<br>• **test parents for condition** |
| Achondroplasia | • **disproportionate small stature**<br>• **Phizomelic (proximal) shortening of arms and legs w/ skin folds on limbs**<br>• **Large head w/ frontal bossing (protruding forehead)**<br>• **Midfacial retrusion and depressed nasal bridge (flat midface)**<br>• **Life exp. And intelligence normal**<br>• Genu varum (bow legs)<br>• Thoracolumbar kyphosis (hunch back in infancy)<br>• Lumbar lordosis | • 1/26000-1/28000<br>• **incomplete dominant** | • ***FGFR3*** **on chromosome 4: 99% of affected have 1 of 2 mutations** | Management:<br>• **Craniocervical junction constriction (life threatening may need decompression surgery)**<br>• Bone lengthening<br>• Avoid contact sports → limit spinal cord injury @ craniocervical junction<br>Counseling:<br>• **80% de novo b/c of advanced paternal age**<br>• 20% have parent w/it<br>**homo. Achondroplasia:** severe, ea death<br>• double hetero: phenotype is distinct from parent & poor outcome |

**1.5 Autosomal Recessive Inheritance**

| Disease | Clinical finding | Gene/protein | Treatment | Counseling |
|---|---|---|---|---|
| Alpha 1 antitrypsin deficiency (AATD) | • **causes chronic obstructive pulmonary disease (COPD)**<br>• **emphysema, asthma,** airflow obstruction, bronchitis | • AAT: protease inhibitor protein made by liver<br>• **AAT protects lung from neutrophil elastase (produced when there's an** | • **No smoking, avoid air pollutants**<br>• **Inhaled purified AAT** | • **If child has AAT (usually liv disease), both parents are obligate carrier; can't rule o possibility they could be** |

| | | | | |
|---|---|---|---|---|
| | • **liver disease,** infant jaundice, **variable expression**<br>• **smoking amplifies symptoms; lung disease starts at 40-50 vs 60 (nonsmoker)**<br>• diagnosis confirmation: ↓ alpha 1 antitrypsin **and** confirmed AAT protein variant **or** ***SERPINA1*** mutations in both alleles | **infection or lung irritant to digest damaged tissue in lungs)**<br>• **Protease inhibitor (PI) typing: M is normal allele, S & Z common deficient alleles**<br>• **PI MM: normal**<br>• **PI MZ: ↑ risk for ↓ lung function (2-5% of most populations, smokers have more risk)**<br>• **PI SZ: ↑ risk of COPD in smokers; no liver effect**<br>• **PI ZZ: COPD and liver effected; plasma AAT ~18% of normal** | • **Lung transplant, liver transplant**<br>• Inhaled steroids, bronchodilators<br>• Many clinical trial treatment options | **homozygous affects due to hi incidence of disease** |
| AR congenital deafness (DFNB1) | • **Non-progressive, mild profound sensorineural hearing loss; no other problems**<br>• Developed countries: hearing loss is the most common birth defect; bilateral permanent sensorineural hearing loss<br>• Ashkenazi Jews at increased disease and carrier frequency | Mutations in ***GJB2*** **→connexin 26 and *GJB6* →connexin 30**; both mapped to 13q12 but **different loci**<br>• **Connexin 26 &30: gap junction proteins→** cell adhesion & recycling K+<br>• Diagnosis: genetic testing<br>• ~98%:2 identifiable *GJB2* mutations (**homo or compound hetero (two mutant alleles at same locus but mutations on each allele are different ie. ab))**<br>• ~2%: 1 *GJB2* mutation and 1 of 2 large deletions in part of *GJB6* **(double hetero); digenic inheritance: 2 genes at different loci interacting together** | • hearing aid, appropriate educational programs, cochlear implants | • skilled interpreter<br>• medical, educational, social services<br>• preferred terms: probability, chance, deaf and hard of heari |
| Spinal muscular atrophy (SMA) | • **progressive muscle weakness** b/c degeneration and loss of anterior horn cells (lower motor neurons) in spinal cord and brain stem nuclei<br>• onset: adolescence-young adulthood **→five different types**<br>• poor weight gain, sleep diff., pneumonia, scoliosis, joint contractures | • *SMN1* & *SMN2* on chromosome 5<br>• ***SMN1*** **→ survival motor neuron protein:** survival and health of motor neurons; ↓ levels = nerve cell shrinks & dies = muscle weakness = skeletal system changes = breathing problems = more loss of function<br>• ***SMN2***: 2nd gene to **code for SMN; single nucleotide change in exon 7 → decreased transcription & deficiency of normal stable SMN protein**<br>• **Ppl w/out SMA will have one copy of *SMN1* on each chromosome and 0-5 copies of *SMN2* on each chromosome**<br>• Carrier testing complications: 2 copy of SMN1 on 1 chromosome vs the | **Gene modifiers:**<br>• ***SMN2* acts as gene modifier**<br>• **Mutated *SMN1*, SMA occurs b/c *SMN2* can't fully compensate for lack of functional SMN protein**<br>• **↑ *SMN2* copy number = small amounts of full length transcripts generated by *SMN2* function → milder *SMA2* or 3 phenotypes** | • ~98% of parents w/affected ch are hetero → carrier<br>• 2% **de novo;** paternal in origi<br>• |

| | | | | |
|---|---|---|---|---|
| | | typical 1 copy on each chromosome; dosage analysis→ false – carrier test<br>• **SMA 1 phenotype: 9% of normal amount of full length SMN**<br>• **SMA 2 phenotype: 14%**<br>• **SMA 3 phenotype: 18%**<br>• **Once full length SMN levels approach 23% of normal levels, motor neuron function appears to be normal**; carriers: 45-55% of normal | • **milder phenotype if more than 3 copies of *SMN2*** | |

**1.6 Dysmorphology**

| Disease/clinical correlation | Characteristics | causes |
|---|---|---|
| Pierre Robin Sequence | - restriction of mandibular growth before 9th week → tongue is more posterior (glossopteris)→ palate shelves don't close<br>-U shaped cleft palate and small mandible (micrognathia) | Micrognathia causes:<br>- deformation (uterine constraint)<br>- malformation (single gene- stickler syndrome)<br>-isolated birth defect |
| thalidomide | - 1950s drug to treat morning sickness<br>-limb defects<br>day 30 exposure: upper and lower limb defects<br>day 35 exposure: lower limb defect | |
| holoprosencephaly | -1/10-15,000<br>- midface & forebrain development<br>- forebrain fails to separate into 2 hemispheres<br>-ranges: intellectual disabilities or not, early mortality<br>craniofacial anomalies: cleft, hypotelorism, cyclopia<br>-seizures, pituitary dysfunction, developmental delay | Causes:<br>Single gene: losing SHH<br>- 30-40% AD<br>-non syndromic<br>-variable phenotype<br>Chromosome abnormalities: numerical, micro deletion, micro duplication, trisom<br>Maternal diabetes |

**1.7 X and Y linked Inheritance**

| Disease | Characteristics | gene | Treatment |
|---|---|---|---|
| Hemophilia A | • joint & muscle & prolonged and potentially fatal post op hemorrhages, easy bruising<br>• hemarthroses: bleeding in joints → chronic arthritis<br>• hematomas in muscles and intracranial bleeding | X linked recessive<br><br>Most common mutation: large inversions; portion of gene is inverted<br>• def in clotting factors 8<br>• cofactors of factor 9a (converts 10 to activated 10a)<br>• 1/5000 males<br>• 100% male penetrance, 10% female<br>• F8 molecular testing (50% of severe form have intronic inversion)<br>• ~ ½ don't have family history; de novo or passed through carrier female | • Hemophilia A: desmopressin (synthetic vasopressin)<br>o Cell releases unused factor 8<br>• Intravenous factor replacement<br>• Before 1984, blood clotting factor via HIV untested unpurified plasma →90% + in heav treated patients<br>• Now, recombinant factor or highly purified factor free of viral hazards<br>Hemophilia B:<br>• def in clotting factor 9<br>• activated by factor 11a<br>• 1/30000 males<br>• 100% penetrance in males, 10% females<br>• F9 molecular testing (>1500 mutations) |

| | | | |
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| | | | • 97% sequence variant and 3% are exonic and large gene alterations<br>~ ½ don't have family history |
| Duchenne and Becker muscular Dystrophy | • progressive muscle weakening via deterioration of muscle cells<br>• cardiomyopathy, skeletal deformities, +/- mental retardation<br>• ↑ creatine kinase<br>• onset: early childhood<br>• death: 3rd decade via cardiac or respiratory complications<br>• **becker muscular dystrophy**: milder form, later onset, longer lifespan; caused by mutation in gystrophin gene (allelic heterogeneity)<br>• hard to rise from siting position → **gower maneuver** (walk up to thigh, then raise body)<br>• boys: enlarged calves, b/c of destruction and inflammation of muscle → pseudohypertrophic; eventually affects other muscle groups ie heart | • x linked recessive; 2.5% of hetereo are symptomatic<br>• mutation (mostly deletions, 1/3 are new) in ***DMD*** or dystrophin gene (largest gene); nature of mutation determines severity<br>• dystrophin: structural protein in myofibrillar membrane & structurally links membrane to contractile protein | Diagnosis:<br>creatine kinase: 10X in DMD and 5X in BMD<br>electromyography, muscle biopsy, immunohistochemistry, molecular<br>• deletion in 1 or more exons → 60-70% on D |
| Spinal and bulbar muscular atrophy (Kennedy's disease)<br>CAG repeats | • progressive neuromuscular → proximal muscle weakness<br>• only males; onset: 20-50years<br>• difficulty w/ walking, speech and swallowing →aspiration<br>• gynecomastia, testicular atrophy, reduced fertility b/c of mild androgen insensitivity | • mutation in trinucleotide repeat (20 CAG to 40 CAG repeats) → expansion of polyglutamine receptor protein → gain of function | • physical therapy, ambulatory assistance and endocrine issue management |
| Androgen insensitivity (testicular feminization) syndrome | • **allelic heterogeneity:** diff mutations within same gene → different conditions<br>• normal appearing tall, thin females<br>• primary amenorrhea<br>• normal female external genitalia<br>• absent uterus/fallopian tubes<br>• bilateral internal testes → risk of gonadoblastoma | Y linked heritance<br>• mutation in steroid binding region of androgen receptor gene (30% de novo; premature termination of protein)<br>• normal androgen secretion; end organ unresponsive<br>  ○ excess testosterone → estriol→ feminization (breast development, blind vagina, absent/spar pubic/axillary hair)<br>• 46XY<br>• **SRY:** sex determining region on Y (testis determining factor); initiates male gonad development<br>• **SOX9:** up regulated by SRY in sertoli cells<br>**DAX1:** regulated formation of testicular cords; down regulated by SRY | |
| Fragile X syndrome | • primarily affects males, females can be affected; intellectual disabilities in males (moderate – severe) | X linked dominant; trinucleotide repeats<br>• Normal (5-44): no meiotic or mitotic instability, no changes in repeat number | |

| | | |
|---|---|---|
| | • prominent square jaw, large ears, macroorchidism, ADHD, macrocephaly, behaviorally problems (tactile defensiveness, autism) | • Intermediate (45-54): doesn't cause fragile x, can expand into pre mutation when transmitted, offsprir not at increased risk<br>• Permutation (55-200): no associated w/ fragile x, increased risk of FXTAS and POI, repeat instability when maternal transmitted & can expand to full mutation<br>  ○ **Fragile X tremor ataxia syndrome:** late onset, progressive cerebellar ataxia<br>  ○ **Premature ovarian insufficiency:** cessation of menses in ~20% of permutation carriers<br>• Full (>200): affected, meiotic or post meiotic |
| Y linked inheritance | • SRY/testis determining factor<br>• Azoospermia factor regions including the deleted in azoospermia (DAZ) genes<br>RNA binding proteins are essential for normal spermatogenesis | |

**1.8 molecular genetic diagnosis**

small dosage change:

| Single nucleotide polymorphism array | Dosage by inactivation (methylation) | Multiplex ligation dependent probe amplification (MLI |
|---|---|---|
| • targets SNP at many sites at the same time<br>• **identifies:**<br>  ○ **copy number (1 vs 2)**<br>  ○ **consanguinity and incest**<br>  ○ **uniparental disomy**<br>  ○ **loss of heterozygosity in tumor specimens**<br>  ○ **deletions/duplication syndromes** | | |

Sequence variant testing:

| Sanger sequencing: | Next generation sequencing: |
|---|---|
| • dideoxy bases terminate newly synthesizing fragment→ size separated and DNA can be read<br>• PCR amplication, then sequencing<br>• Detects point mutations, small duplications, insertions, deletions<br>• Diagnosis tumor of unknown origin, evaluations of prognostic markers and establishing treatment | • process millions of sequences read at the same time → can read any number of genes<br>• limitations:<br>  ○ long turnaround time<br>  ○ lots of computer analysis and storage, expensive<br>  ○ will find multiple sequence variants of unknown pathogenicity<br>  ○ need to filter out benign vs pathogenic mutations (can't manually annotate all variants)<br>• parallel, high throughput sequencing<br>• ideal for patients w/little tumor available for testing<br>• detects point mutations, small insertions or deletions<br>• sensitivity <<1%<br>• |

| Targeted mutation analysis | Comprehensive gene sequencing | Targeted gene panel | Whole exome sequencing | Whole genome sequencing |
|---|---|---|---|---|
| • testing targeted to known condition<br>• CF panel of known pathogenic variant<br>• Sickle cell/hemo c disease | • Sequence entire gene looking for variant<br>• Single gene<br>• Difficult to use when looking at more than 1 gene that causes disease→ less effective | • Includes all genes that could cause a disease<br>• Good for diagnostic and expanded carrier testing<br>• Answers patient's phenotype and preconception info | • 1% of genome<br>• base subs and small insertions and deletions; 85% of mutations are in coding region→ won't identify all mutations | • Entire genome (coding and noncoding)<br>• Can detect deletions/ insertion combines whole exome sequencing and comparative genomic hybrid |

| | | | |
|---|---|---|---|
| **Carrier Screening** | • IDs couples at risk for passing on genetic conditions | Recommended:<br>• If test is straightforward, inexpensive and accurate | Ex: *Cystic fibrosis* (heterogeneous & autosomal recessive) |

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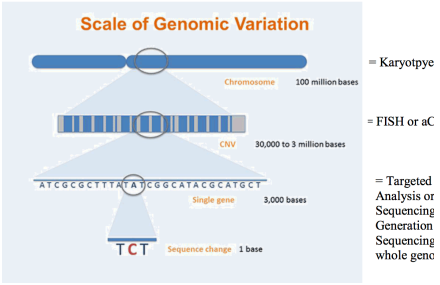
|---|---|---|---|---|
| | (within families or general populations<br>• Usually autosomal recessive conditions are screened for<br>• Usually no defined health benefit to carrier<br>• **Negative screen reduces carrier risk but residual risk remains** | • High level of public health/ population interest<br>• Preconception planning<br>• Early pregnancy counseling | • Chronic obstructive lung disease, colonization of airways by pathog organisms, exocrine pancreatic insufficiency, infertility, ↑ [sweat electrolytes]<br>• *CFTR* on 7q (large, ~2000 diff mutations; F508del is most common; mutations have a drug that opens altered na+ channels)<br>• 23 mutation panel w/90% detection rate in Caucasians (less sensitive other races)<br>• not 100% sensitive → population risk modification<br>• can be caused by isodisomy UPD | |
| **Expanded carrier testing** | • Next gen for >100 disorders (x linked and dominant) | Benefits<br>• Efficient, simultaneously screen for many conditions<br>• Ethnicity info is less important b/c everyone screened for same thing<br>• Info to optimizes pregnancy planning and outcomes<br>• | Challenges<br>• Pre and posttest counseling<br>• Some disorders screened don't affect life quality compared to initial screening programs<br>• Less defined phenotypes<br>• Carrier frequency unknown & pathogenicity of some variants unclear<br>• can't calculate residual risk | Negative result:<br>• **carrier chance reduced, but 0; screening tests cannot dete all mutations**<br>Positive result:<br>• individual is a carrier<br>• counseling and recommended test partner<br>Carrier couple:<br>• 25% risk of affected offspring each pregnancy<br>• counseling and planning optio |
| **Pre symptomatic testing:** test asymptomatic patients at risk of inheriting disease → determine if individual will develop disease | Non carrier advantages: not at risk, no need for medical screening, normal family planning<br>Carrier advantages: increased medical surveillance, treatment?, prenatal testing<br><br>Non carrier disadvantages: survivor guilt, no excuse for behavior, haves vs have notes<br>Carrier disadvantages: confusion, anxiety, depression, insurance/health discrimination | *Huntington's disease*: auto. Dom.<br>• neurodegenerative, adult onset w/choreic movements, cognitive decline and progressive neurologic sequelae<br>• selective neuron loss in caudate and putamen<br>• expansion of CAG trinucleotide repeats<br>  ○ normal: <27 repeats<br>  ○ mutable normal: 27-35 repeats; no symptoms, meiotically unstable<br>  ○ reduced penetrance: 36-39 repeats; meiotically unstable, can have associated phenotype<br>  ○ fully penetrant: >40 repeats<br>• # of CAG repeats ∝1/age of onset | • HD testing:<br>• If inherited mutant gene, will develop disease<br>• Test can determine genetic status before symptoms develop<br>• Significant psychological implication (survivors guilt, risk to offspring, life decisions of education, employment etc |
| **Predisposition (susceptibility) genetic testing:** risk estimate based on genotype, not absolute that disease will develop | *Inherited thrombophilia disorders (Factor V leiden)*<br>• ↑risk of venous thrombosis if hetero or homo; not all carriers develop symptoms<br>• no treatment for asymptomatic carrier<br>• test?: general population, children of known carriers, individuals w/risk factors, prior to surgery | | | |

- targeted mutation testing: known mutations within gene
- sanger sequencing: entire gene (limitations)

- targeted phenotype panels: sequencing multiple genes
- whole exome sequencing: sequencing all exons
- whole genome sequencing: sequence all genes




### 1.9 genetic technologies in clinical practice

| Large dosage change | Uniparental disomy | Single gene pathogenic variant |
|---|---|---|
| • Karyotype<br>• FISH- micro deletions<br>• Comparative genomic hybridization-microarray | • SNP array | • Trinucleotide repeat disorder<br>• Targeted or sanger + deletion/duplication testing<br>• Next gen- gene panels/whole exome sequencing |

### 1.10 multifactorial Inheritance

| | | |
|---|---|---|
| Pyloric stenosis | • Hypertrophy and hyperplasia of smooth muscle narrows that pylorus so its obstructed leading to feeding problems → projectile vomiting → surgically corrected<br>• Multifactorial threshold model<br>• 5x more common in boys; lower male threshold but females have greater genetic liability<br>sons of affected mothers are at highest risk | |
| Neural tube defect | • **most common: spina bifida (myelomeningocele) and anencephaly**<br>• failure of neural tube to fuse during 4th week<br>• **heterogeneous group of disorders**<br>  ○ **multifactorial**<br>  ○ **malformation syndrome** (trisomy 13, 18, Meckel gruber syndrome); autosomal recessive disorder characterized by encephalocele, polydactyly and polycystic kidneys<br>• **teratogenic**: anticovulsant, valproic acid<br>• if only environmental etiologies, **3-5% recurrence risk for 1st degree relatives.** Two siblings affected, 10% and slightly more females than males are affected<br>• **prevention: folic acid reduces recurrence risk** | Environmental factor evidence:<br>• diabetes, obesity, lower socioeconomic status, materna age<br>• seasonal variation<br>• no consumption folic acid; consumption of valproic ac<br><br>Genetic factor evidence:<br>• ↑prevalence in certain ethnic groups<br>• ↑concordance in mono twins than di twins<br>• familial aggregation: 1st degree 3.2%, 2nd degree 0.5% degree 0.17%<br>• recurrence risk if one offspring is affected: 3-5%<br>• recurrence risk if ≥2 offspring is affected: 10% |

### 1.12 Non mendelian Inheritance: Imprinting Disorders:

| Disease | | |
|---|---|---|
| Diandry (90%) | • **Large cystic placenta**<br>• **Two paternal and one maternal** haploid set of chromosomes<br>• Large head, severe intrauterine growth retardation, syndactyly<br>• Maternal genetic info → *fetus* development | |
| Digyny (10%) | • **Small undeveloped placenta**<br>• **Two maternal and one paternal sets**<br>• Paternal genetic into → *placenta* development | |
| Prader willi syndrome | • Maternal silencing<br>• *15q11-13 deletion is **paternal** in origin*<br>• hypotonia, poor infancy feeding, obesity, hyperphagia, hypogonadism, intellectual disability, short stature, small hands and feet, characteristic facies | • maternal UPD (no paternal DN)A seen 30% of the tim |
| Angelman syndrome | • paternal silencing<br>• *15q11-13 deletion is **maternal** in origin* | • paternal UPD (no maternal DNA) in 5-7% |

| | | |
|---|---|---|
| | • intellectual disabilities, microcephaly, laughter, ataxic movements, seizure, characteristic facial appearance<br>• 11% caused by *UBE3A* mutation; paternally imprinted→ maternal mutation inactivation → causing AS; in father → no AS (possible in future generations) | |
| Beckwith-Wiedman syndrome | • paternal silencing; **UPD involving segment of chromosome**<br>• **10-20% have paternal UPD** or imprinting defects, duplication or translocation, mutation in maternal *CDKN1C* in 11p15; all have abnormal regulation of gene transcription in imprinting domain on chromosome 11p15.5<br>• overgrowth, hemihypertrophy, abdominal wall defects, macroglossia, abdominal embryonal tumors | |

**1.12 mitochondrial disease**

| | |
|---|---|
| **Kearns Sayre syndrome (KSS)** | • multisystem disorder affecting skeletal muscle, CNS, heart<br>• progressive external opthalmoplegia before age 20, pigmentary retinopathy, heart block<br>• poor prognosis, death by 3rd or 4th decade |
| **MERRF (myoclonic epilepsy associated w/ragged red fibers)** | • myoclonus, generalized seizures, cerebellar ataxia, ragged red fibers in muscle biopsy w/ modified gomori trichrome stain and hyperactive fibers w/succinate dehydrogenase stain |
| **MELAS (mitochondrial encephalopathy, lactic acidosis, stroke like episodes)** | • stroke like episodes before 40, encephalopathy, seizures, dementia, lactic acidosis, ragged red fibers,<br>• at least two of: normal early development, recurrent headaches, recurrent vomiting |
| **LHON (Leber Hereditary Optic Neuropathy)** | • acute unilateral central vision loss→ loss of vision in other eye within weeks; only affects eyes<br>• onset: 18-30<br>• reduced penetrance: males 4/5X more affected; other genetic and environmental factors plat a role in development of vision loss |

**1.14 Cancer Genetics**

| Disease/clinical correlation | Characteristics |
|---|---|
| chronic myelogenous leukemia (CML) | • **Reciprocal translocation between chromosome 9 and 22**→fusion of BCR and ABL1 genes<br>  • Fusion gene codes for chimeric protein→ increases tyrosine kinase activity<br>  • Fusion protein→ abnormal proliferation → leukemia<br>  • Treatment:<br>  ○ imatinib mesylate (gleevec): Blocks ATP binding pocket → Inhibits BCR-ABL1 kinase activity<br>  ○ resistant to imatinib= ABL1 kinase domain mutation: inhibit binding of fusion protein by the drug → treat w/bone marro transplant or ponatinib |
| acute lymphoblastic leukemia and down syndrome related ALL | • deletion of pseudo autosomal region 1 (PAR1)→ fuses exon 1 of P2RY8 w/ exon 1 of CRLF2→ activates CRLF2 transcription |
| burkitt's lymphoma | • **translocation to an active chromatin domain**<br>  - rare B cell jaw tumor<br>  - translocation between chromosome 8 and 14, 22 or 2 → c-MYC gene under control of immunoglobin heavy or light chain regulatory elements<br>• c-MYC: transcription factor that up regulated expression of genes involved in cellular proliferation |
| Lynch Syndrome | • -four mismatch genes: PMS2, MLH1, MSH2, MSH6 |

| **Allele specific PCR** | **Reverse transcriptase quantitative PCR** | **Gene expression microarrays** |
|---|---|---|
| • pcr using primers specific to wild type or mutant allele<br>• sensitivity: 1-5% mutant<br>• targeted assay | • detect and quantify fusion transcript produced by chromosomal translocations (RNA → DNA)<br>• monitor residual disease in patient undergoing therapy | • compare gene expression in tumor sample to normal<br>  ○ whole genome<br>  ○ targeted |

| | | |
|---|---|---|
| • detect point mutation<br>• or locus specific primers in combination w/fluorescently labels allele specific reported probes<br>  ○ measure fluorescence of report in real time PCR<br>  ○ detect point mutation, small insertions/deletions | ○ sensitivity down to 1/100,000 cells | • profile generated for particular sample<br>• diagnosis of tumor of unknown origin, evaluation of prognostic markers and establishing treatment |

**1.15 Inborn Errors of Metabolism 1**

| **Diseases:** | **Enzyme/characteristics** | **Symptoms** | **Diagnosis** | **treatment** |
|---|---|---|---|---|
| Phenylketouria (PKU) | - autosomal recessive<br>-deficiency in phenylalanine hydroxylase<br>- ↑phenylalanine (substrate) = ↑phenylpyruvic acid (toxic alternative product) = ↓tyrosine= ↓ neurotransmitter dopamine and norepinephrine (product deficient)<br>-classic PKU: loss of PAH activity (premature stop→truncated protein)<br>-can have residual PAH activity →less severe phenotypes<br>-BH4 mutation = ↓ PAH activity = ↑ Phe | - intellectual disabilities, dry skin, seizures, autism, fair skin and hair color, musty odor | - ↑phenylalanine levels<br>-↓tyrosine levels<br>- ↑phenylalanin: tyrosine ratio | - early diagnosis via newborn screening<br>- prevent phe build up via phenylalanine restricted diet (dieta restrictions, low protein, extra tyrosine)<br>-some patients respond to BH4 (cofactor for PAH); sapropterin is synthetic form of BH4 |
| Maternal PKU | - women w/PKU having children<br>-elevated maternal Phe causes birth defects→ baby doesn't have PKU but has intellectual disability, microcephaly, heart defects, growth deficiency | | | -past: stop diet in adolescence now: lifelong diet b/c of harm to nervous system |
| Urea cycle disorders: toxic to CNS | -autosomal recessive except **ornithine transcarbamylase deficiency (OTC) that's X linked**<br>- ↑blood NH3 (except w/arginase def)<br>- ↑ metabolites related to affected enzyme | -related to ammonia ↑<br>- vomiting, encephalopathy, tachypnea, **progressive spastic diplegia (arginase def),** episodic encephalopathy in milder forms<br>- appear normal but rapid onset<br>- cerebral edema, lethargy, anorexia, hyperventilation or hypoventilation, hypothermia, speech slurring, blurry vision, seizures, neurological posturing, coma | - enzyme or molecular testing to confirm<br>- plasma AC: ↑in which metabolite? | - depends on pathway<br>- ↓ NH3 via protein restriction<br>-↑ NH3 removal via alternative pathways |
| Maple syrup urine diseases | • branched chain AC defect (leucine, isoleucine, valine) –X-->branched chain keto acids via branched chain ketoacid DH<br>• BCKA DH deficient: buildup of 3 BCAC | • Severe neonatal, intermediate or intermittent presentations<br>• Acute neurologic (irritability, poor feeding, seizures)<br>• Microcephaly/mental retardation<br>• Maple syrup odor in urine | • ↑plasma BCKA and urine organic acids<br>• enzyme and molecular analysis | • restrict BCAA<br>• avoid catabolism and providir cofactors |

| | | | | |
|---|---|---|---|---|
| Galactosemia | • autosomal recessive<br>• **galactose 1 phosphate uridyl transferase** mutations | • after breast or cow's milk feeding<br>• vomiting, diarrhea<br>• lethargy, hypotonia<br>• jaundice, hepatomegaly<br>• gram – bacteria susceptibility<br>• death due to liver failure if untreated<br>• some learning difficulties<br>• premature ovarian failure/infertility common in females | • elevated galactose in blood or urine<br>• measure galactose 1 phosphate in blood<br>• enzyme and/or molecular analysis | • minimize galactose accumula<br>• remove lactose from diet (mil products)<br>• soy based formulas and milk substitutes<br>• good outcomes |
| Medium chain acyl coa dehydrogenase deficiency (MCAD) | • autosomal recessive<br>• | • episodic illness via fasting or infection→ vomiting, lethargy, seizures, coma, death<br>• hypoketotic hypoglycemia<br>• well intervals between illness episodes | • hypoketotic hypoglycemia<br>• dicarboxylic aciduria ← alternative pathway<br>• medium chain acylcarntine elevations<br>• molecular or enzymatic confirmation | • avoid fasting (prevent hypoglycemia) and prompt treatment of intercurrent illne<br>  ○ frequent feedings<br>  ○ intravenous glucose they can't tolerate o feeds<br>  ○ reduction in dietary<br>  ○ carnitine supplemen<br>• good outcomes |
| Tay sachs disease | • autosomal recessive<br>• inability to degrade sphingolipid Gm2 ganglioside<br>• severe def in hexosaminidase A<br>• Ashkenazi Jewish at increased risk<br>• 3 mutant alleles in ^ make 98% of mutations | • impacts brain: neurological degradation<br>• loss of milestones, motor weakness, increased sensitivity to noise, seizures, blindness, spasticity<br>• death by 2-5<br>• **cherry red spot:** GM2 ganglioside build up in retina | • enzyme assay | • no treatment |
| Mucopolysaccharidoses (MPS) | • heterogeneous group of storage diseases: mucopolysaccharides build up in lysosomes<br>• all are autosomal recessive except hurlers | | | |
| Hurler syndrome<br><br>X linked | • x linked recessive<br>• prototypic MPS disorder | • normal at birth, regression by 6-12 months<br>• coarse facial features, large head, frontal bossing, depressed nasal bridge, large tongue, cloudy cornea, hearing | • Mucopolysaccharide in urine<br>• Screening test<br>• Enzyme assay | • Bone marrow transplant<br>• Enzyme replacement: doesn't cross blood brain barrier→ca prevent intellectual disabilitie |

| | | | | |
|---|---|---|---|---|
| | | loss, short stature, stiff joints<br>• death by 5<br>• Hurler Scheie: milder variant: allelic heterogeneity | | |
| Methylmalonic academia | • Organic academia<br>• Can't convert methylmalonyl CoA to succinyl CoA via methylmalonyl CoA mutase<br>• Some have mutations in enzyme code or cofactor (B12) | • Toxic methylmalonic acid accumulation → metabolic acidosis and neurologic symptoms (seizures, poor muscle tone, microcephaly, intellectual disability) | • Elevated methylmalonic acid in urine<br>• Enzyme assay or molecular analysis | • Cofactor defect: large amount B12 given<br>• Non responsive form: Restric dietary protein → still have acidosis |
| Biotinidase deficiency | • Autosomal recessive<br>• Recycling biotin defect; cofactor needed for carboxylase enzymes<br>• Enzymes: activated by covalent enzymatic attachment of biotin by enzyme holocarboxylase synthetase<br>• Biotinidase: cleave biotin from biocytin → recycle biotin | • Metabolic acidosis, neurologic abnormalities (seizures, hearing loss, poor muscle tone, intellectual disability), eczema like skin rash, hair loss (alopecia), coma, death | • Urine organic acids<br>• Enzyme assay or molecular analysis | • Supplement biotin<br>• Treating specific enzyme in h |

**1.17 Clinical Cancer Genetics**