Medical Genetics
GENETIC DISEASES LISTED BY CLASSIFICATION

I. Chromosome Disorders

A. Abnormal Chromosome Number
--aneuploidy (monosomy, trisomy, tetrasomy, double trisomy)
--polyploidy (triploidy, tetraploidy)

*5 numerical chromosomal abnormalities to know are caused primarily by **meiopic non-disjunction** and all show small findings of structural abnormalities (translocation and mixoploidy); **all cause congenital abnormalities**

Trisomy (4 out of 5):
1. Patau's 47,XX (or XY), +13
   - cleft lip/palate
   - polydactly
   - cardiac abnormality
   - mental retardation
   - holoprosencephaly (single small forebrain)
   - poor survival beyond neonatal period
2. Edward's 47,XX (or XY), +18
   - rocker bottom feet
   - cross of fingers
   - cardiac abnormality
   - exomphalus (intestinal contents outside abdomen)
   - micrognathia
   - poor survival beyond one month
3. Down's 47,XX (or XY), +21
   - characteristic faces
   - develop delay
   - congenital heart abnormality
   - single palmar crease
   - **increased maternal age is a risk**
   - possible balanced robertsonian translocation
   - mixoploidy (**mosaicism**)
   - **"triple test"** maternal α-fetoprotein lowered, β-HCG raised, estradiol lowered
4. Klinefelter 47,XXY
   - gynecomastia (breast development)
   - infertility due to axospermia (don't produce sperm)
   - hypogonadism (small testes)
   - long limbs, short trunk
   - learning disability
   - **maternal and paternal age increases risk**

Monosomy (1 out of 5):
5. Turner's 45,X
   - **mosaicism** common in 30%
   - most 45,X conceptions miscarry
   - short stature
   - ovarian dysgenesis (failure to develop)
   - primary amenorrhea
   - infertility
   - webbed neck

- peripheral lymphodema (swollen feet and hands)
- normal IQ
- coarctation of descending aorta

B. Abnormal Chromosome Structure (balanced/unbalanced)

1. Translocation (reciprocal, robertsonian reciprocal)
--Patau's Syndrome

2. Deletion
--Cri Du Chat 46, XX (or XY), **5p-**
- Severe mental retardation
- poor growth
- unusual facial appearance
- congenital HD
- crying like a cat

--DiGeorge/Velocardial Syndrome 46, XX (or XY), **22q11.2**
- complex congenital HD
- cleft palate
- feeding difficulties
- low Ca^{++}, low lymphocyte count
- **FISH**

--Duchenne MD (XR)
- dystrophin gene on Xp21

3. Ring
--Turner's Syndrome X

4. Insertion

5. Inversion

6. Isochromosome
--Turner's Syndrome Xq

C. Mosaicism and chimaerism (mixoploidy)
-- def. of mosaicaism: a mixture of 2 genetically dif cell lines in a person derived from a single embryo
-- def. of chimaerism: presence of 2 genetically dif cell lines in a person, but cell lines are from 2 dif embryos [common reason: after a bone marrow transplant, but very rarely a embryo can form from the fusion of two different (dizygotic) embryos, and give rise to a human chimera]
-- somatic mosaicism: 2 diff cell lines exist in several parts of the body
-- gonadal mosaicism: 2 diff cell lines present in only ovary or testis

1. Turner's Syndrome 45X/46,XX; milder phenotype (less short stature, may ovulate and menstruate, less cardiac disease)
2. Duchenne MD: 2 brothers w/ Duchenne MD but no deletion shown on mother's blood only found in ovaries so gonadal mosaicism

II. Single Gene (monogenic) disorders

A. Autosomal Dominant
-- vertical transfer
-- multiple generations affected
-- male to male transmission occurs
-- males and females affected equally
-- offspring risk is 1 in 2
-- variable expression: clinical effects can vary in severity even in diff members of same family (expression: way in which a genetic disorder is manifest)
-- often age-dependent penetrance (penetrance: the percentage of gene carriers who manifest a disorder)
-- homozygotes are usu much more severely aff than heterozygotes
-- 4 musculoskeletal, 3 brain, 3 Ca , 3 eyes, 1 drug, 1 biochemical

1. Myotonic dystrophy
    - maternal **anticipation** (triplet repeat)
    - Steiner's disease
    - mild late onset form – mild muscle weakness, cataracts
    - typical form – muscle weakness, cardiomyopathy, cataracts, frontal hair loss
    - childhood/infantile form – profound muscle weakness, global developmental delays
    - neonatal death from muscle weakness
    - predictive testing
2. Huntington's disease
    - paternal **anticipation** (triplet repeat)
    - progressive neurological disorder – onset in middle age
    - **fully penetrant**, but age-dependent
    - incurable, death in about 10 yrs from onset
    - predictive testing
3. Familial Adenomatous Polyposis
    - **fully penetrant**
    - development of multiple initially benign colonic polyps usually in teenage yrs
    - untreated, polyps will progress to **colon ca**
    - tx: panproctocolectomy
    - mutations in **APC gene on chromosome 5 (tumor suppressor gene)**
4. Achondroplasia
    - mutation in **signal transduction gene** that encodes fibroblast growth factor receptors (**FGFR**)
    - 80-90% are born to normal parents so often **new mutation**
    - long torso, short limbs, dwarf
    - double dose is lethal
    - only AD disorder w/ **consistent expression**
    - **cause of congenital abnormality**
    - **dysplasia**
5. Neurofibromatosis
    - multiple benign skin tumors
    - **fully penetrant, variable expression**
6. Osteogenesis imperfecta
7. Marfan's
    - tall, long limbs, dilation of aorta
    - **fully penetrant, variable expression**
    - **clinical testing**
8. Familial hypercholeserolemia
    - **most common single gene disorder in western world**
    - **biochemical disorder**

- heterogeneous mutations in LDL receptor gene
- premature CAD, xanthomas
- Tx: statins

9. Waardenburg's syndrome (type 1)
   - mutation in **PAX3 gene** (paired box gene that encode DNA binding proteins which act as transcription control factors)
   - deafness, diff colored irises, white hair patches
10. Multiple Endocrine Neoplasia (MEN)
   - **gain of fcn mutation in RET gene (oncogene, signal transduction gene)**
   - cause thyroid ca
11. Hereditary non-polypotic coli (HNPCC)
   - **error in DNA mismatch repair**: MSH1 and MLH2; microsatellite instability in tumor is indicator of DNA mismatch repair defect
   - mutation analysis and predictive genetic testing in high risk families
   - more common than familial
   - cause colorectal, endometrial, ovarian, gastric, breast ca
12. Malignant Hyperthermia
   - mutations in ryanodine receptor
   - **pharmacogenetic disease**
   - those affected are usually healthy
   - but **halothane anesthetic** induces muscle necrosis and profound hyperthermia
   - can be fatal
13. Heritable Retinoblastoma
   - most common eye tumor in children (under 5 yo)
   - occurs in heritable and non-heritable forms
   - IDing at-risk infants substantially reduces morbidity and mortality
   - **RB1 gene on 13 (first tumor suppressor gene discovered)**
   - **high penetrance**
   - prototype for **"two-hit" hypothesis**: individuals w/ familial Rb inherited a 1st germ-line mutation and developed Rb through the occurrence of a second somatic mutation, while individuals who developed sporadic Rb had 2 somatic mutations; reduced likelihood of 2 events occurring accounted for later age of occurrence and greater likelihood of unilateral rather than bilateral tumors
14. Holoprosencephaly
   - AD inherited holoprosencephaly can occur w/ mutations in SHH on chr 7 (human equivalent of a **segment-polarity gene**)
   - other cause is trisomy 13 (Patau's)
15. Aniridia
   - **loss of fcn/deletions of PAX6 gene**
   - absent iris; glaucoma; visual impairment

B. Autosomal Recessive
-- 1 in 4 offspring will be affected if both parents are carriers
-- once a child is diagnosed with an autosomal recessive disorder, then their parents are obligate carriers
-- males and females equally likely to be affected
-- certain AR recessive conditions are more common in spec ethnic groups
-- consanguineous
-- horizontal inheritance: only members of a single sibship are affected
-- risk that the sibling of an affected child will also be affected equals 1 in 4
-- risk to offspring of an affected individual is very low
-- 5 biochemical, 2 Hb, 1 drug, 1 CF

1. Tay Sach's
2. Thalassemia: **hemoglobinapathy** (disorder of **Hb synthesis**); **neonatal screening**
   a) α-thalassemia (4 types; usu found in southeast asia)

i) α-thalassemia major (hydrops fetalis): deletion of all 4 α globin genes; both parents heterozygous carriers of 2 α globin gene deletion in cis; only Hb is tetramer of 4 γ globins; usu lethal

ii) α-thalassemia major (Hb H disease): deletion of 3 α genes; one parent heterozygous carrier of 2 α globin gene deletion in cis, other parent carrier of single α globin gene deletion; most Hb is tetramer of 4 β globins; baby w/ severe microcytic anemia, transfusion dependent, no crises

iii) α-thalassemia trait: deletion of 2 α globin genes; heterozygous carrier of 2 α globin gene deletion in cis; homozygous for 2 single α globin gene deletions; mild asymptomatic microcytic anemia; no indication for transfusion

iv) silent carrier: deletion of 1 α globin gene; heterozygous for a single α gene deletion; normal hematology studies, usu diagnosed by deduction when a 'normal' indiv has a child w/ either Hb H disease or microcytic anemia

b) β-thalassemia: anemia due to reduced production of β globin protein due to a variety of mutations in the β globin gene

i) β_o thalassemia: severe transfusion-dependent hemolytic anemia, assoc w/ little β globin; repeated transfusions result in premature death due to complications of iron overload despite iron chelation therapy

ii) β thalassemia trait: heterozygous for β globin mutation; mild microcytosis; raised HbF in infants

iii) β thalassemia major: Cooley's anemia; homozygous or compound heterozygous for β globin mutation; severe anemia; high HbF in infants; transfusion dependent; iron overload; often death in teens

3. Sickle Cell (HbS)
   - **hemoglobinapathy** (disorder of Hb structure)
   - common in West Africa
   - Glu6Val mutation in both copies of β-globin gene on chromosome 11
   - RBCs more fragile and break up (hemolyse)
   - **chronic anemia**
   - sickling crises due to blockage of small blood vessels w/ **fragmented RBCs**
   - sickling → increased viscosity and clumping of cells → ischemia, thrombosis, infarction → abd pain, splenic infarction, limb pain, bone tenderness, rheumatism, osteomyelitis, cerebrovascular accident, hematuria, renal failure, pneumonia, heart failure
   - sickling → destruction of sickle cells → anemia → splenomegaly, weakness, abnormal skull radiographs, heart failure
   - **neonatal screening**
   - Tx: acute crises-pain relief, hydration; chronic mngmt-vaccination, prophylactic antibiotics, blood transfusion
4. Cystic Fibrosis
   - common in Western Europe
   - CFTR gene on **7q** (can be due to **UPD** for chr 7 from a carrier parent)
   - chronic lung disease, pancreatic insufficiency, sometimes diabetes
   - chronic sinusitis
   - infertility in males
   - previously fatal in childhood, lifespan may now be into 40s
   - neonatal screening (biochemical or genetic)
5. Oculocutaneous albinism
   - **inborn error of metabolism**
   - tyrosine hydroxylase deficiency no melanin is made
   - lack of pigment in skin, and in the iris and pigmentary layer of the eye
6. Galactosemia
   - **inborn error of metabolism**: carbohydrates
   - gal-1P uridyl transferase deficiency
   - toxic xs of galactose

- neonatal cataracts, hypotonia, dev delay, liver
- effectively treated by galactose (including lactose) free diet
- **neonatal screening** for galactosemia in many countries

7. Congenital adrenal hypoplasia
   - **inborn error of metabolism**: steroids
   - self-wasting and virilization
   - 21-hydroxylase enz def
   - androgens overproduced; glucocorticoids (cortisol) and aldosterone underproduced
   - cause collapse, low BP, low blood Na
   - Tx: lifelong corticosteroid replacement
8. Phenylketonuria (PKU)
   - **inborn error of metabolism**: amino acid
   - **most common AR metabolic disorder**
   - phenylalanine hydroxylase deficiency causes tyrosine def and xs toxic phenylalanine and metabolites
   - mental handicap, seizures if untreated
   - Tx: restricted diet of phenylalanine gives normal IQ
   - newborn metabolic screening
   - neonatal screening
9. Succinylcholine sensitivity
   - low activity of enz pseudocholinesterase
   - those affected are usually healthy
   - slowly metabolize **muscle relaxant succinylcholine**
   - unable to move after reversal of anesthetic muscle paralysis

C. X-Linked Recessive
-- diagonal transfer
-- 1 in 2 for sons of a carrier female; 1 in 2 that each daughter will be a carrier
-- affected male transmits allele to all daughters (obligate carriers); transmits none to sons
-- therefore no male to male transmission
-- female can be affected rarely if:
   a) she is homozygous having inherited a mutant allele from both parents
   b) Turner's syndrome
   c) 46, XY w/ androgen insenstitivity
   d) non-random X inactivation (poss due to X-autosome translocation)

1. Duchenne & Becker Muscular Dystrophy
   - mutation of the dystrophin gene on Xp21 (dystrophin gene is largest known human genome)
   - progressive muscle weakness and wasting from early childhood, become wheelchair bound in early teens, and die in late teens or early twenties
   - biochemical testing (raised creatine kinase levels)
   - DNA linkage testing
2. Glucose 6P Dehydrogenase deficiency
   - those w/ mutated allele are normally healthy
   - **pharmacogenetic disease**
   - given **antimalarials, sulphonamides or eat fava beans** they experience acute hemolysis
   - G6PD is involved w/ red cell metabolism
   - 2 alleles are found in diff areas of world
3. Hemophilia A and B
   - treatable
4. Non-specific mental retardation
5. Red-green color blindness
6. Ornithine transcarbamyl deficiency (OTC)
   - **inborn error of metabolism**: urea cycle
   - xs protein load, illness, stress

- triggers hyperammonemia: acute and chronic brain damage, coma, death
- **variable expression**
- some females can also be affected

7. Lesh-Nyhan
   - **inborn error of metabolism**
8. Fragile X syndrome
   - **anticipation** (triplet repeat) maternal
   - fragile site on Xq
   - 2nd most common genetic cause of learning disability after Down's syndrome
   - behavior disturbances; tall, large ears, long face, loose jts, macroocrhidism
   - Dx w/ molecular methods via an intermediate permutation not seen in other triplet repeats
   - intermediate state of a **premutation**: a person is unaffected, but the unstable premutation triple repeat may expand to a full mutation in meiosis
   - only mothers who carry premutations will have children with full mutations, who could be affected
   - premutation males with have premutation carrier daughters
9. Androgen Insensitivity Syndrome
   - 46, XY female
   - female w/ normal ext genitalia and secondary sex charact
   - no internal female genitalia
   - gonads found in inguinal region - histological testes w/ high testosterone levels
   - mutation in androgen receptor gene blocks response to usu effect of testosterone
   - lack of testosterone effect, despite high circulating levels, means no external male genitalia form
   - Tx: excision of gonads, female hormone replacement
   - female carriers and females affected

D. X-Linked Dominant Inheritance (XD)
-- both males and females are affected (females are usually less severely affected
-- affected females can show a mosaic pattern of involvement in tissues like skin
-- 1 in 2 chance that any son or daughter born to an affected female will be affected
-- all daughters and none of sons of an affected male will be affected
-- therefore no male to male transmission
-- 2 types

1. XD disorder which affects both males and females but females may be less affected
   a) Rickets
2. XD disorder which affects females only b/c mutation is lethal in hemizygous male pregnancies
   a) Rett syndrome
   b) Incontinentia pigmenti

III. Polygenic Disorders (multifactorial inheritance: several genes + environment)
*Hirschsprung's Disease (illustrates consequences of **liability/threshold model**)
   -- absent autonomic innervation of colon: stomach distends, cannot digest food
   -- polygenic inheritance: mild-short segment aff; severe-long segment aff; commoner in boys
   -- rare familial forms can be caused by inactivating mutation (loss of fcn) in the **RET oncogene**

**Approaches to identify heritability:
   -- family studies: increased prevalence in 1st/2nd degree relatives
   -- twin studies: concordance in MZ and DZ twins 'reared apart' studies
   -- adoption studies: "adopted in/out"
   -- population/migration studies: diff in prevalence w/ migration

A. Congenital Anomalies
1. Deformation: abnormal form or position caused by a non-disruptive mechanical force
   -- talipes
2. Disruption: morphological defect resulting from a breakdown of, or interference w/, an originally normal developmental process

-- amniotic bands

3. Malformation: morph defect resulting from an intrinsically abnormal dev process

*major: causes significant medical or cosmetic problems (e.g. spina bifida)

*minor: no medical significance (e.g. accessory nipple, single palmar crease)

a) sequence: multiple anomalies derived from a single known or presumed structural defect

i) Potter's sequence: arises from any cause of lack of amniotic fluid surrounding a fetus

b) syndrome: mult abnormalities thought to be pathogenetically related b/c happen more requently than chance and not explained by a sequence

i) chromosomal: Down's (trisomy 21)

ii) monogenic: achondroplasia (AD)

iii) teratogenic

-- congenital infection: CMV, Rubella, Toxoplasmosis

-- maternal diabetes/epilepsy

-- maternal medication/drugs: phenytoin, alcohol

iv) polygenic/multifactorial

-- neural tube defects: failure of closure of dev neural tube during first 4 wks of embryonic life leads to anencephaly, encephalocoele, lumbo-sacral myelocoele, meningocoele, spina bifida; screening for maternal serum α-fetoprotein and fetal ultrasound scanning; folic acid supplementaion

-- cleft lip/palate

-- congenital HD

v) unknown: >50%

B. Common Disorders of Adult Life

1. Diabetes mellitus

- increased concordance in MZ vs DZ twins indicates a significant genetic component
- type I insulin-dependent (IDDM): childhood onset, HLA gene
- type II non-insulin dependent (NIDDM): onset usu > 50 yrs
- maturity-onset diabetes of young (rare) MODY: single gene AD; usu non-ins dep; polymorphisms w/in MODY genes can become candidates for NIDDM and IDDM
- increased risk of diabetes in sibs in both NIDDM and IDDM indicates a genetic effect in both; NIDDM also assoc w/ environmental effects (obesity)

2. Coronary Artery Disease

- major cause of morbidity and mortality accounting for 50% of deaths in developed countries
- polygenic factors and single gene mode of inheritance via familial hypercholesterolemia

3. Schizophrenia

IV. Mitochondrial Disorders

- mitochondrial genome exclusively maternally inherited
- mutations can occur in the mit genome indep of cell mitosis
- mit mutations can accumulate w/ age
- some mit mutations can be inherited
- in any one cell, some mit can have a mutation, and some do not
- heteroplasmy: mixture of normal and mutant mit in a cell
- all offspring of an affected or carrier female are at risk of becoming affected themselves
- all daughters of an affected or carrier female are at risk of transmitting the condition

GENETIC DISEASES LISTED BY LECTURE TOPICS:

Pharmacogenetics: genetic basis for drug response
1) hereditary conditions only revealed in presence of a particular medicine
    a) glu-6P dehydrogenase deficiency (XR)
    b) malignant hyperthermia (AD)
    c) succinylcholine sensitivity (AR)
2) genetic variation which controls response or side effects from drugs
    a) Tx for TB
        -- N-acetyltransferase activity of Isoniazid
        -- acetylation inactivates drug
        -- slow acetylators-higher longer levels of drug (more side effects)
        -- fast acetylators-more liver disease
    b) Clozapine
        -- anti-dopaminergic drug used in tx of schizophrenia
        -- responders to drug have higher freq of spec alleles

Anticipation: the manifestation of a genetic disorder at an earlier age or with increasing severity in succeeding generations due to an enlarged meiotically unstable DNA triplet repeat
1. Huntington's disease (CAG) (AD)
2. Myotonic dystrophy (AD)
3. Fragile X syndrome (XR)

Biochemical Genetics: inborn errors of metabolism
1. Lesch-Nyhan syndrome (XR)
2. Familial hypercholesterolemia (AD)
3. Phenylketonuria (AR)
4. Galactosemia (AR)
5. Congenital adrenal hypoplasia (AR)
6. Ornithine transcarbamyl deficiency (XR)
7. Oculocutaneous albinism (AR)

Hemoglobinopathies
1. Disorders of Hb structure
    a) HbS (point mutation: β, 6 glu to val)
    b) Hb Lepore/Anti-Lepore (fusion chain: δ-like residues at N-terminal end, δ-like residues at C-terminal end)
2. Disorders of Hb synthesis
    a) α-thalassemia
    b) β-thalassemia
3. Structure/Developmental Expression
    a) HbF (fetal Hb): $\alpha_2\gamma_2$
    b) HbA (adult Hb): $\alpha_2\beta_2$
    c) HbA_2 (2-3% in adults): $\alpha_2\delta_2$
    d) α-like cluster on chromosome 16
    e) β-like cluster on chromosome 11

Genetic Imprinting: if region is imprinted (e.g. methylated) copies of that region from both parents are needed to be normal (for non-imprinted regions, inheritance of both copies of that region from only one parent may not be disadvantageous)
1. Prader-Willi syndrome
- deletion of 15q11 from Dad (dad-active SNRPN gene, mom-inactive SNRPN; as long as there is an expressed SNRPN gene, a person will not develop PW)

- poor neonatal muscle tone (hypotonia) and poor infant feeding
- children become hyperphagic, obese; learning disability; cryptorchidism (small genitalia)
- can be detected w/ FISH

2. Angelman syndrome
- deletion of 15q11 from Mom (mom-active UBE3A gene, dad-inactive UBE3A; as long as there is an expressed UBE3A gene, a person will not develop Angelman)
- seizures; abnormal gait w/ jerky arm mvts; no speech; usu blonde hair

Uniparental Disomy: inheritance of both members of a homologous pair of chromosomes from one parent
-- causes of UPD
- meiotic non-dysjcn that causes a disomic gamete
- when fertilized by a normal monosomic gamete, the resultant embryo is trisomic
- an attempt is made to get rid of the xtra chr "trisomic rescue"
- rescue attempt may get rid of the chr derived from the original gamete leaving the embryo w/ UPD

-- 2 types of UPD
- uniparental heterodisomy: non-disjcn in meiosis I; 2 diff chromosomes both from same parent
- uniparental isodisomy: non-disjcn in meiosis II; 2 identical chromosomes both from same parent

--effects of UPD
- can cause disease if isodisomic chrm has an autosomal recessive dis mutation (i.e. Cystic Fibrosis)
- can cause disease if UPD occurs in imprinted chromosomal region
  a) Prader Willi: if baby has UPD for 2 maternal chromosomes 15
  b) Angelman syndrome: if baby has UPD for 2 paternal chromosomes 15

Developmental Genetics

1. Segmentation genes: segment polarity mutants can cause deletion of a segment w/ duplication on the opposite side
   --mut in human Sonic Hedgehog on chr 7 cause holoprosencephaly (incomp cleavage of forebrain)
2. PAX genes: Paired Box genes that encode DNA binding protein which act as transcription control factors
   -- mutations in PAX3 cause Waardenburg's syndrome
   -- mutations in PAX6 cause aniridia
3. Zinc Finger genes: finger-like loop projection formed by a complex of a zinc ion w/ 4 AAs to act as a transcription control factor through binding to DNA
   -- deletions in a zinc finger gene called GLI3 cause Greig syndrome (cephalosynpolydactyly: fusion of skull bones, fingers, and xtra fingers and toes)
4. Signal transduction genes: mutations can cause cancer and/or dev abnormalities
   -- gain-of-fcn mutations in RET cause MEN and thyroid Ca; loss of fcn in RET cause Hirschsprung's disease
   -- mut in genes for fibroblast growth factor receptors (FGFR) can cause achondroplasia
5. Hydatidiform moles: disorganized proliferation of the placenta
   -- partial: triploidy of paternal origin (69,XYY)
   -- complete: 46 chrs which are exclusively paternal; high potential for malignant change (46,YY)

Hereditary Cancer

A. Classification

1. by tumor type
   a) rare hereditary ca syndromes defined by a rare tumor type w/ familial clustering
   b) subset of common cancers which is hereditary (e.g. colon, br, ovarian ca)
2. by type of gene mutated
   a) tumor suppressor genes: cell's brakes for tumor growth; Ca arises when both brakes fail
   -- Rb (13q)
   -- Breast Ca (BRCA1)
   -- Familial Adenomatous Polyposis (APC)
   b) oncogenes: accelerates cell division; Ca arises when stuck in "on" mode
   -- Multiple Endocrine Neoplasia (RET)

c) DNA damage-response genes: repair mechanics for DNA; Ca arises when both genes fail, speeding the accumulation of mutations in other critical areas
-- Hereditary Non-Polypotic Colon Ca (MSH2, MLH1)