Boards & Beyond: Genetics Slides

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Genetic Principles

Somatic Cell Replication

Mitosis

- S phase of cell cycle
- Chromosomes replicate → two sister chromatids
- M phase (mitosis): Cell divides
- Daughter cells will contain copies of chromosomes

Genetics

Termology

- Genome
  - DNA contained in nucleus of cells
  - "Hereditary material"
  - Passed to successive generations of cells
- Genes
  - Portions of DNA/genome
  - Code for proteins that carry out specific functions

Chromosomes

- Somatic cells (most body cells)
  - Diploid: two sets of chromosomes (23 pairs)
- Gametes (reproductive cells)
  - "Haploid": one set of chromosomes

Genetics

Chromosome

- Rod-shaped, cellular organelles
- Single, continuous DNA double helix strand
- Contains a collection of genes (DNA)
- 46 chromosomes arranged in 23 pairs
  - Chromosomes 1 through 22 plus X/Y (sex)
  - Two copies each chromosome 1 through 22 (homologous)
- Key point: Two copies of any gene of a chromosome

Cell Types

- Somatic cells (most body cells)
- Diploid: two sets of chromosomes (23 pairs)
- Gametes (reproductive cells)
  - "Haploid": one set of chromosomes

Genetic

Principles

Jason Ryan, MD, MPH
Meiosis

- Gametes (reproductive cells)
  - “Haploid”: one set of chromosomes
  - Produced by meiosis of germ line cells
  - Male and female gametes merge in fertilization
  - New “diploid” organism formed
- Key point: one gene from mother, one from father

Genetics

Terminology

- Allele
  - Alternative forms of gene
  - Often represented by letter (A, a)
  - Genetic polymorphism
    - Genes exist in multiple forms (alleles)
    - Locus (plural loci)
      - Location of allele on chromosome
- Wild type gene/allele
  - Common in most individuals
  - Example: A = wild type
  - Mutant gene/allele
    - Different from wild type
    - Caused by a mutation
    - Example: a = mutant
    - Individual: AA, Aa, aa
- Homozygous
  - Two identical copies of a gene (i.e. AA)
- Heterozygous
  - Two different copies of a gene (i.e. Aa)
- Somatic mutations
  - Acquired during lifespan of cell
  - Not transmitted to offspring
- Germ line mutations
  - DNA of sperm/eggs
  - Transmitted to offspring
  - Found in every cell in body
- Genotype
  - Genetic makeup of a cell or individual
  - Often refers to names of two copies of a gene
  - Example: Gene A from father, Gene B from mother
  - Genotype: AB
  - Or two alleles of gene A (A and a): AA, Aa, aa
- Phenotype
  - Physical characteristics that result from genotype
  - Example: AB = blue eyes; BB = green eyes
- Locus (plural loci)
  - Location of allele on chromosome
- DNA →gene →allele →locus →chromosome
- Meiosis
  - Gametes (reproductive cells)
    - “Haploid”: one set of chromosomes
    - Produced by meiosis of germ line cells
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- Key point: one gene from mother, one from father
Genetics

Terminology
- **Dominant gene/allele**
  - Determines phenotype even in individuals with single copy
  - Often denoted with capital letters
  - Example: Gene has two alleles: A, a
  - Aa, AA all have A phenotype
- **Recessive gene/allele**
  - Requires two copies to produce phenotype
  - Often denoted with lower case letters
  - Example: aa = a phenotype; Aa and AA = A phenotype

Codominance
- Both alleles contribute to phenotype
- **Classic example: ABO Blood Groups**
  - A gene = A antigen on blood cells
  - B gene = B antigen
  - O gene = No A or B antigen
  - AB individuals
    - Express A and B antigens

α-1 Antitrypsin Deficiency
- May cause early COPD and liver disease
- **Mutations in AAT gene (produces α1 antitrypsin)**
  - M = normal allele
  - S = moderately low levels protein
  - Z = severely reduced protein levels
- **Combination of alleles determines protein levels**
  - MM = normal
  - ZZ = severe deficiency
  - Other combinations = variable risk of disease

Penetrance
- Proportion with allele that express phenotype
- **Incomplete penetrance**
  - Not all individuals with disease mutation develop disease
  - Commonly applied to autosomal dominant disorders
  - Not all patients with AD disease gene develop disease
  - Example BRCA1 and BRCA2 gene mutations

BRCA1 and BRCA2
- Genetic mutations that lead to cancer
- Germline gene mutations
- Autosomal dominant
- Not all women with mutations develop cancer
- Implications:
  - Variable cancer risk reduction from prophylactic surgery

Expressivity
- **Variations in phenotype** of gene
- Different from penetrance
- **Classic case: Neurofibromatosis type (NF1)**
  - Neurocutaneous disorder
  - Brain tumors, skin findings
  - Autosomal dominant disorder
  - 100% penetrance (all individuals have disease)
  - Variable disease severity (tumors, skin findings)
Two-Hit Origin of Cancer

- Mutations in **tumor suppressor genes**
  - Genes with many roles
  - Gatekeepers that regulate cell cycle progression
  - DNA repair genes
  - Heterozygous mutation = no disease
  - Mutation of both alleles \( \rightarrow \) cancer
  - Cancer requires "two hits"
  - "Loss of heterozygosity"

**Pleiotropy**

- One gene = multiple phenotypic effects and traits
  - Example: single gene mutation affects skin, brain, eyes
  - Clinical examples:
    - Phenylketonuria (PKU): skin, body odor, mental disability
    - Marfan syndrome: Limbs, eyes, blood vessels
    - Cystic fibrosis: Lungs, pancreas
    - Osteogenesis imperfecta: Bones, eyes, hearing

**Other Examples**

- **HNPCC (Lynch syndrome)**
- **Hereditary nonpolyposis colorectal cancer**
- **Inherited colorectal cancer syndrome**
- Germline mutation in DNA mismatch repair genes
- Second allele is inactivated by mutation

**Two-Hit Origin of Cancer**

- **Classic example:** Retinoblastoma
  - Rare childhood eye malignancy
  - Hereditary form (40% of cases)
    - One gene mutated in all cells at birth (germline mutation)
    - Second somatic mutation "hit"
    - Cancer requires only one somatic mutation
    - Frequent, multiple tumors
    - Tumors at younger age

**Two-Hit Origin of Cancer**

- **Retinoblastoma:** Sporadic form (non-familial)
  - Requires two somatic "hits"
  - Two mutations in same cell = rare
  - Often a single tumor
  - Occurs at a later age

**Two-Hit Origin of Cancer**

- **HNPCC (Lynch syndrome)**
  - Hereditary nonpolyposis colorectal cancer
  - Inherited colorectal cancer syndrome
  - Germline mutation in DNA mismatch repair genes
  - Second allele is inactivated by mutation

**Pleiotropy**

- One gene = multiple phenotypic effects and traits
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**Other Examples**

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**Two-Hit Origin of Cancer**

- **Classic example:** Retinoblastoma
  - Rare childhood eye malignancy
  - Hereditary form (40% of cases)
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    - Second somatic mutation "hit"
    - Cancer requires only one somatic mutation
    - Frequent, multiple tumors
    - Tumors at younger age
McCune-Albright Syndrome

- Rare disorder
- Affects many endocrine organs
- Precocious puberty
  - Menstruation may occur at 2 years old
- Fibrous growth in bones
  - Fractures, deformity
- Skin pigmentation
  - Café-au-lait spots
  - Irregular borders ("Coast of Maine")

Mosaicism

- **Germline mosaicism**
  - Can be passed to offspring
  - Pure germline mosaicism difficult to detect
  - Not present in blood/tissue samples used for analysis
  - Offspring disease may appear sporadic
  - Can present as recurrent "sporadic" disease in offspring

- **Somatic mosaicism**
  - Gene differences in tissues/organs
  - Mutations in cells → genetic changes
  - Individual will be a mixture of cells

Two-Hit Origin of Cancer

**Other Examples**

- **Li-Fraumeni syndrome**
  - Syndrome of multiple malignancies at an early age
  - Sarcoma, Breast, Leukemia, Adrenal Gland (SBLA) cancer syndrome
  - Germline mutation in tumor suppressor gene TP53
  - Codes for tumor protein p53
  - Delays cell cycle progression to allow for DNA repair

- **Familial Adenomatous Polyposis (FAP)**
  - Germline mutation of APC gene (tumor suppressor gene)
  - Always (100%) progresses to colon cancer
  - Treatment: Colon removal (colectomy)

- **45X/46XX mosaic Turner syndrome** (milder form)
- Rare forms of Down syndrome

- **Germline** mosaicism
  - Can be passed to offspring
  - Pure germline mosaicism difficult to detect
  - Not present in blood/tissue samples used for analysis
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- **Somatic** mosaicism
  - Gene differences in tissues/organs
  - Mutations in cells → genetic changes
  - Individual will be a mixture of cells

- **53X/46XX mosaic Turner syndrome** (milder form)
- Rare forms of Down syndrome

Two-Hit Origin of Cancer

**Other Examples**

- **Li-Fraumeni syndrome**
  - Syndrome of multiple malignancies at an early age
  - Sarcoma, Breast, Leukemia, Adrenal Gland (SBLA) cancer syndrome
  - Germline mutation in tumor suppressor gene TP53
  - Codes for tumor protein p53
  - Delays cell cycle progression to allow for DNA repair

- **Familial Adenomatous Polyposis (FAP)**
  - Germline mutation of APC gene (tumor suppressor gene)
  - Always (100%) progresses to colon cancer
  - Treatment: Colon removal (colectomy)
Allelic heterogeneity

- Allele = Alternative form of gene
- Allele 1 = mutation X
- Allele 2 = mutation Y
- Both X and Y cause same disease
- X and Y found at same chromosomal locus (position)
- Many alleles possess multiple mutant forms
- One disease = multiple genes = single location

McCune-Albright Syndrome

- “Postzygotic” mutation
- Occurs after fertilization
- Only some tissues/organs affected (mosaicism)
- Clinical phenotype varies depending on which tissues affected
- Germline occurrences of mutation are lethal
- Entire body effected
- Cells with mutation survive only if mixed with normal cells

Genetic Heterogeneity

- Same phenotype from different genes/mutations
- Different mutations of same allele → same disease
- Different gene (loci) mutations → same disease
- Multiple gene mutations often cause same disease
- Many diseases have multiple genotypes

McCune-Albright Syndrome

- Caused by sporadic mutation in development
- Not inherited
- Somatic mutation of GNAS gene
- Codes for alpha subunit of G3 protein
- Activates adenylyl cyclase
- Continued stimulation of cAMP signalling

Allelic heterogeneity

- Beta Thalassemia
  - Mutation in beta globin gene
  - Wide spectrum of disease depending on mutation
  - $\beta^0 = \text{no function}; \beta^+ = \text{some function}$
- Cystic Fibrosis
  - Mutation in CFTR gene
  - Over 1400 different mutations described
Locus heterogeneity

- Mutations in different loci cause same phenotype
- Example: Retinitis Pigmentosa
  - Causes visual impairment
  - Autosomal dominant, recessive, and X-linked forms
  - Mutations at 43 different loci can lead to disease
- One disease = multiple genes = multiple locations
Gene Mapping

Independent Assortment
- Suppose father has two alleles of F and M genes
  - F and f
  - M and m
  - F and M found on different chromosomes
  - Independent assortment
    - Occurs if F and M genes can independently recombine
    - 25% chance of each combination in gamete

Genetic Recombination
- During meiosis chromosomes exchange segments
- Child inherits “patchwork” of parental chromosomes
- Never exact copy of parental chromosomes

Genetic Mapping

Father Mother
Child 1 Child 2

Independent Assortment
- What if genes on same chromosome?
- If very far apart, crossover may occur in meiosis
- Result: Same combinations as separate chromosomes

Genetic Mapping

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Father
Chromosome 1
F M
Chromosome 2
2 3
f m
Gamete 1
M f
m m
M
25% 25% 25% 25%

Independent Assortment
- What if genes on same chromosome?
- If very far apart, crossover may occur in meiosis
- Result: Same combinations as separate chromosomes

Genetic Mapping

Father
Chromosome 1
F M
Chromosome 2
2 3
f m
Gamete 1
M f
m m
M
25% 25% 25% 25%
**Linkage**
- Tendency of alleles to transmit together
  - More linkage = less independent assortment
  - Close together ($\theta = 0$) = tightly linked
  - Far apart ($\theta = 0.5$) = unlinked

**Genetic Mapping**
- **Linkage Mapping**
  - Done by studying families
  - Track frequency of genetic recombination
  - Use frequency to determine relative gene location
  
<table>
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<tr>
<th>Combination</th>
<th>Frequency</th>
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<tr>
<td>A-B</td>
<td>0.15</td>
</tr>
<tr>
<td>A-C</td>
<td>0.08</td>
</tr>
<tr>
<td>C-B</td>
<td>0.08</td>
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**Independent Assortment**
- What if genes on same chromosome?
  - If very far apart, crossover may occur in meiosis
  - Result: Same combinations as separate chromosomes

**Recombination**
- Any break here allows A and B to recombine
- Any break here allows B and C to recombine
- Two copies of parental chromosome

**Recombination Frequency**
- Frequency of recombined genes ($F_m$ or $f_M$)
  - Denoted by Greek letter theta ($\theta$)
  - Ranges from zero to 0.5
  - Key point: recombination frequency $\alpha$ distance
    - Close together: $\theta = 0$
    - Far apart: $\theta = 0.5$
    - Used for genetic mapping of genes
Linkage Disequilibrium
- Used to study genes that are very close together
  - Recombination very rare
  - Family studies impractical
- Done by studying large populations

Linkage Equilibrium
- Gene A has two polymorphisms: A and a
  - A found in 50% of individuals
  - a in 50%
- Gene B has two polymorphisms: B and b
  - B found in 90% of individuals
  - b in 10%

Linkage Disequilibrium
- Population frequencies higher/lower than expected
  - AB = 0.75 (higher than expected 0.45)
  - aB = 0.45
  - Ab = 0.05
  - ab = 0.05
- This is linkage equilibrium

Linkage Disequilibrium
- Used to study genes that are very close together
  - Recombination very rare
  - Family studies impractical
- Done by studying large populations

Linkage Disequilibrium
- Consider new gene mutation A
  - Initially close to gene B
  - AB transmitted together in a population
  - Eventually A and B genes may recombine
  - Depends on distance apart and size of population
  - LD greatest when gene first enters population (i.e. mutation)
  - Fades with successive generations (i.e. population size)
  - Fades if distance between genes is greater

Linkage Disequilibrium
- Linkage disequilibrium affected by:
  - Genetic distance
  - Time alleles have been present in population
  - Different populations: different degrees of linkage disequilibrium

A = 0.5
a = 0.5
B = 0.9
b = 0.1
**Meiosis**

Meiosis begins at puberty.

Meiosis

- Diploid cells give rise to haploid cells (gametes)
- Unique to "germ cells"
  - Spermatocytes
  - Oocytes
- Two steps: Meiosis I and Meiosis II

**Meiosis I**

- Diploid → Haploid ("reductive division")
- Separates homologous chromosomes

**Meiosis II**

- Chromatids separate
- Four daughter cells

**Spermatogenesis**

Begins at puberty
Oogenesis
- "Primary oocytes" form in utero
  - Diploid cells
  - Just beginning meiosis I
  - Arrested in prophase of meiosis I until puberty
- At puberty
  - A few primary oocytes complete meiosis I each cycle
  - Some form polar bodies → degenerate
  - Some form secondary oocytes (haploid)
  - Meiosis II begins → arrests in metaphase
  - Fertilization → completion of meiosis II

Aneuploidy
- Abnormal chromosome number
  - Extra or missing chromosome
- Disomy = two copies of a chromosome (normal)
  - Monosomy = one copy
  - Trisomy = three copies

Meiotic Nondisjunction
- Failure of chromosome pairs to separate
- Most common mechanism of aneuploidy
- Can occur in meiosis I or II

Meiosis I Nondisjunction
- Blue = Paternal
  - Red = Maternal
  - Homologous Chromosomes Fail to Separate
  - Meiosis I
  - Meiosis II begins → arrests in metaphase
  - Meiosis II NDJ
  - Normally no chromosomes

Meiosis II Nondisjunction
- Blue = Paternal
  - Red = Maternal
  - Meiosis I
  - Meiosis II
  - Haploid
  - Diploid Mixture Genes

Nondisjunction
- Blue = Paternal
  - Red = Maternal
  - Meiosis I NDJ
  - Normally no chromosomes
  - Meiosis II NDJ
  - Normally no chromosomes
**Monosomy**
- Fertilization of 1n (normal) and 0n gamete
- Usually not viable
- **Turner syndrome (45,X)**
  - Only one sex chromosome

**Trisomy**
- Fertilization of 1n (normal) and 2n gametes
- Not compatible with life for most chromosomes
- Exceptions:
  - Trisomy 21 = Down syndrome (95% cases due to NDJ)
  - Trisomy 18 = Edward syndrome
  - Trisomy 13 = Patau syndrome

**Trisomy**
- Maternal meiosis I NDJ errors are a common cause
  - Meiosis I protracted in females
  - Begins prenatally, completed at ovulation years later
  - Advanced maternal age → ↑ risk trisomy

**Monosomy**
- Fertilization of 1n (normal) and 0n gamete
- Usually not viable
- **Turner syndrome (45,X)**
  - Only one sex chromosome

**Trisomy**
- Maternal meiosis I NDJ errors are a common cause
  - Meiosis I protracted in females
  - Begins prenatally, completed at ovulation years later
  - Advanced maternal age → ↑ risk trisomy

**Uniparental Disomy**
- Child has two copies of one parent’s chromosomes
- No copies of other parent's chromosomes
- Father = 21A and 21B; Mother = 21C and 21D
- Child AA (isodisomy) = Meiosis II error (father)
- Child CD (heterodisomy) = Meiosis I error (mother)
**Robertsonian Translocation**
- Fusion of long arms of two chromosomes
- Occurs in acrocentric chromosomes
  - Chromosomes with centromere near end (13, 14, 21, 22)

**Karyotype**
- Can be done in couples with **recurrent fetal losses**
- Used to diagnose chromosomal imbalances

**Robertsonian Translocation**
- Carrier has only 45 chromosomes (one translocated)
- Loss of short arms → normal phenotype (no disease)
- 13-14 and 14-21 are most common
- Main clinical consequences
  - Many monosomy and trisomy gametes
  - Frequent **spontaneous abortions**
  - Carrier may have child with **Down syndrome** (trisomy 21)
Hardy-Weinberg Law

Hardy-Weinberg Law

• Large population
• Completely random mating
• No mutations
• No migration in/out of population
• No natural selection

Example
• Given gene has two possible alleles: A and a
• Allele A found in 40% of genes (p = 0.40)
• Allele a found in 60% of genes (q = 0.60)
• What is frequency of genotypes AA, Aa, and aa?

\[ p + q = 1 \]

\[ p^2 + 2pq + q^2 = 1 \]

\[ p^2 = 0.16 \]  → 16% of individuals in population are AA
\[ 2pq = 0.48 \]  → 48% of individuals in population are Aa
\[ q^2 = 0.36 \]  → 36% of individuals in population are aa

Hardy-Weinberg Law

• Frequency of AA = \( p^2 = 0.16 \)
• Frequency Aa = \( 2pq = 0.48 \)
• Frequency aa = \( q^2 = 0.36 \)

\[ p + q = 1 \]

\[ p^2 + 2pq + q^2 = 1 \]

\[ p = 0.4 \]
\[ q = 0.6 \]

\[ p^2 = 0.16 \]
\[ 2pq = 0.48 \]
\[ q^2 = 0.36 \]
Hardy-Weinberg Law

- If assumptions met, allele frequencies do not change from one generation to the next
- "Hardy-Weinberg equilibrium"

Very useful in autosomal recessive diseases
- Disease (aa) frequency often known
  - Example: 1/5000 individuals have disease
  - Carrier (Aa) frequency often unknown

Disease X caused by recessive gene
- Disease X occurs in 1/4500 children
  - \( q^2 = \frac{1}{4500} = 0.0002 \)
  - \( q = \sqrt{0.0002} = 0.015 \)
  - \( p + q = 1 \)
  - \( p = 1 - 0.015 = 0.985 \)
  - Carrier frequency = 2pq
    - \( 2 \times (0.985) \times (0.015) = 0.029 \approx 3\% \)
  - Very rare diseases p close to 1.0
  - Carrier frequency \( \approx 2q \)

Very useful in autosomal recessive diseases
- Disease (aa) frequency often known
  - Example: 1/5000 individuals have disease
  - Carrier (Aa) frequency often unknown

X-linked disease
- Two male genotypes (X^-Y or XY)
- Three female genotypes (XX or X^-X or X^-Y)

If assumptions met, allele frequencies do not change from one generation to the next
- "Hardy-Weinberg equilibrium"
Pedigrees

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Pedigree

- Visual representation of a family
- Often used to study single gene disorders
  - Gene passed down through generations
  - Some members have disease
  - Some members are carriers
- Several typical patterns
  - Autosomal recessive genes
  - Autosomal dominant genes
  - X-linked genes

Pedigree Symbols

- Unaffected Male
- Affected Male
- Unaffected Female
- Affected Female
- Marriage
- Children

Autosomal Recessive

- Two alleles for a gene (i.e. A = normal; a = disease)
- Only homozygotes (aa) have disease

<table>
<thead>
<tr>
<th>Father</th>
<th>Mother</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>a</td>
<td>aA</td>
</tr>
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</table>

- If both parents are carriers (Aa)
  - Child can have disease (aa)
  - Only 1 in 4 chance of child with disease
  - 2 of 4 children will be carriers (Aa)
  - 1 of 4 children NOT carriers (AA)

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- If both parents are carriers (Aa)
  - 50% chance mother gives a to child
  - 50% chance father gives a to child
  - (0.5) x (0.5) = 0.25 chance child has disease
Autosomal Dominant
- Familial hypercholesterolemia
- Huntington’s disease
- Marfan syndrome
- Hereditary spherocytosis
- Achondroplasia
- Many others

Autosomal Recessive
- Cystic fibrosis
- Sickle cell anemia
- Hemochromatosis
- Wilson’s disease
- Many others

Autosomal Dominant
- Males and females affected equally
- One affected parent → 50% offspring with disease
- Male-to-male transmission occurs

Autosomal Recessive
- Males and females affected equally
- Few family members with disease
- Often many generations without disease
- Increased risk: Consanguinity
  - Parents are related
  - Share common ancestors

Autosomal Dominant
- Two alleles for a gene (i.e. A = disease; a = no disease)
- Heterozygotes (Aa) and homozygotes (AA) have disease
**Incomplete Dominance**

Semidominant

- Heterozygote phenotype different from homozygote
  - Heterozygotes: less severe form of disease
  - Homozygotes: more severe

**X-linked Disorders**

- Disease gene on X chromosome (X_d)
  - Always affects males (X_dY)
    - Females (X_dX) variable
    - X-linked recessive = females usually NOT affected
    - X-linked dominant = females can be affected

**X-linked Recessive**

- No male-to-male transmission
  - All fathers pass Y chromosome to sons
  - Sons of heterozygous mothers: 50% affected
  - Classic examples: Hemophilia A and B

**Familial hypercholesterolemia**

- Heterozygotes: total cholesterol 350–550mg/dL
  - Homozygotes: 650–1000mg/dL

**Incomplete Dominance**

Semidominant

- Classic example: Achondroplasia
  - Autosomal dominant disorder of bone growth
  - Heterozygotes (Dd): Dwarfism
  - Homozygotes (dd): Fatal

**X-linked Recessive**

- All males with disease gene have disease
  - Most females with disease gene are carriers

**Familial hypercholesterolemia**

- Heterozygotes: total cholesterol 350–550mg/dL
  - Homozygotes: 650–1000mg/dL

**X-linked Recessive**

- Females very rarely develop disease
  - Usually only occurs if homozygous for gene
  - Father must have disease and mother must be carrier
  - Females can develop disease with skewed lyonization
Mitochondrial Genes

- Each mitochondria contains DNA (mtDNA)
- Code for mitochondrial proteins
- Organs most affected by gene mutations:
  - CNS
  - Skeletal muscle
  - Rely heavily on aerobic metabolism

X-linked Dominant

- Occur in both sexes
- Every daughter of affected male has disease
  - All daughters get an X chromosome from father
  - Affected father MUST give disease X chromosome to daughter

Lyonization

- Random process
- Different inactive X chromosomes in different cells
- Occurs early in development (embryo <100 cells)
- Results in X mosaicism in females
- May cause symptoms in females X-recessive disorders
  - "Skewed lyonization"

X-linked Dominant

- Can mimic autosomal dominant pattern
- Key difference: No male-to-male transmission
  - Fathers always pass Y chromosome to sons

X-linked Dominant

- More severe among males (absence of normal X)
- Classic example: Fragile X syndrome
  - 2nd most common genetic cause of intellectual disability (Down)
  - More severe in males
  - Often features of autism
  - Long, narrow face, large ears and jaw

X-linked Dominant

- Results in inactivated X chromosome in females
  - One X chromosome undergoes "Lyonization"
  - Condensed into heterochromatin with methylated DNA
  - Creates a Barr body in female cells

Lyonization

- Occur in both sexes
- Every daughter of affected male has disease
  - All daughters get an X chromosome from father
  - Affected father MUST give disease X chromosome to daughter

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Polygenic Inheritance
- Many traits/diseases depend on multiple genes
  - Height
  - Heart disease
  - Cancer
  - "Run in families"
  - Do not follow a classic Mendelian pattern

Mitochondrial Myopathies
- Rare disorders
- Weakness (myopathy), confusion, lactic acidosis
- Wide range of clinical disease expression
- Classic hallmark: Red, ragged fibers
  - Seen on muscle biopsy with special stains
  - Caused by compensatory proliferation of mitochondria
  - Accumulation of mitochondria in muscle fibers visualized
  - Mitochondria appear bright red against blue background

Mitochondrial Disorders
- Mitochondrial DNA inherited from mother
  - Sperm mitochondria eliminated from embryos
- Homoplasmic mothers → all children have mutation
- Heteroplasmic mothers → variable

Mitochondrial Genes
- Heteroplasmy
  - Multiple copies of mtDNA in each mitochondrion
  - Multiple mitochondria in each cell
  - All normal or abnormal: Homoplasmy
  - Mixture: Heteroplasmy
  - Mutant gene expression highly variable
    - Depends on amount of normal versus abnormal genes
    - Also number of mutant mitochondria in each cell/tissue

Ragged Red Fibers
- Mitochondrial Myopathies
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Mitochondrial Disorders
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- Homoplasmic mothers → all children have mutation
- Heteroplasmic mothers → variable
Multifactorial Inheritance

- Genes, lifestyle, environment → disease
- Seen in many diseases
  - Diabetes
  - Coronary artery disease
  - Hypertension
Imprinting

Jason Ryan, MD, MPH

Imprinting Syndromes

- Prader-Willi and Angelman syndromes
- Both involve abnormal chromosome 15q11-q13
- Paternal copy abnormal: Prader-Willi
- Maternal copy abnormal: Angelman
- Differences due to imprinting

Imprinting Syndromes

- PWS genes
  - Normally expressed on paternal chromosome 15
  - NOT normally expressed on maternal copy
- UBE3A
  - Normally expressed on maternal chromosome 15
  - NOT normally expressed on paternal copy

Imprinting

- Occurs during gametogenesis (before fertilization)
  - Genes “marked” as being parental/maternal in origin
  - Often by methylation of cytosine in DNA

Imprinting

- Epigenetic phenomenon
  - Alteration in gene expression
  - Different expression in maternal/paternal genes

Imprinting

- After conception, imprinting controls gene expression
  - “Imprinted genes”: Only one allele expressed
  - Non-imprinted genes: Both alleles expressed

Cytosine Methylcytosine

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Imprinting

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**Prader-Willi Syndrome**

- **PWS**
  - Loss of function of *paternal copy* of PWS gene

**Angelman Syndrome**

- **Frequent laughter/smiling**
  - “Happy puppet”
- **Seizures (80% patients)**
- **Ataxia**
- **Severe intellectual disability**

**Prader-Willi Syndrome**

- Majority of cases caused by deletions
- Only about 3-5% from uniparental disomy
  - Paternal disomy much less common than maternal
  - Non-disjunction less common

**Angelman Syndrome**

- Abnormal *maternal* chromosome 15q11-q13
  - Lack of expression of UBE3A

**Prader-Willi Syndrome**

- ~75% cases from deletion of paternal gene
  - Most cases due to sporadic mutation
- ~25% from maternal *uniparental disomy*
  - Two copies of maternal gene inherited
  - No copies of paternal gene

**Angelman Syndrome**

- ~75% cases from deletion of paternal gene
  - Most cases due to sporadic mutation
- ~25% from maternal *uniparental disomy*
  - Two copies of maternal gene inherited
  - No copies of paternal gene

- Loss of function of paternal copy of PWS gene

- Most common “syndromic” cause of obesity
  - Hypotonia
  - Newborn feeding problems
  - Poor suck reflex
  - Delayed milestones
  - Hyperphagia and obesity
    - Begins in early childhood
  - Intellectual disability (mild)
    - Contrast with AS (severe)
  - Hypogonadism
    - Delayed puberty

- Abnormal maternal chromosome 15q11-q13
  - Lack of expression of UBE3A
Down Syndrome

Jason Ryan, MD, MPH

Dysmorphic Features

- Most common liveborn chromosome abnormality
- Most common form intellectual disability
- Other key features
  - "Dysmorphic" features (face, hands, stature)
  - Congenital malformations (heart, GI tract)
  - Early Alzheimer’s disease
  - Increased risk of malignancy
- Clinical phenotype variable
  - Range of features from mild to severe

Down Syndrome

- Prominent epicanthal folds
  - Skin of the upper eyelid
  - Covers the inner corner of the eye
- Upslanting palpebral fissures
  - Separation upper/lower eyelids
  - Outer corners higher than inner

Trisomy Disorders

- Down syndrome (21)
- Edward syndrome (18)
- Patau syndrome (13)

Brushfield Spots

- White spots on iris
**Gastrointestinal Anomalies**

- Occur in 5% of patients
- Duodenal atresia or stenosis (most common)
- Hirschsprung disease
- More common than in general population

**Intestinal Disability**

- Almost all patients affected
- Wide range of cognitive impairment
- Normal IQ ~100
- Mild Down syndrome: 50 to 70
- Severe Down syndrome: 20 to 35

**Other Physical Features**

- Hypotonia
  - Often identified at birth
  - Short stature

**Congenital Heart Disease**

- Occurs in 50% of patients
- Most commonly endocardial cushion defects
  - Involves atrioventricular septum
  - Forms base of interatrial septum
  - Forms upper interventricular septum

**Dysmorphic Features**

- Short, broad hands
- Transverse palmar crease
- "Sandal gap"
  - Space between 1st/2nd toes

**Congenital Heart Disease**

- Common defects:
  - Primum ASD
  - VSD (holosystolic murmur)

**Other Physical Features**

- Hypotonia
- Often identified at birth
- Short stature
Down Syndrome

Genetics

- Rarely (<2% cases) caused by mitotic error
- Error in mitosis of somatic cells after fertilization
- May result in somatic mosaicism
- Some cells trisomy 21, others normal
- Can lead to milder features of DS
- No association with advanced maternal age

Prenatal Screening

- Definitive test: Fetal karyotype
- Chorionic villus sampling (placental tissue)
- Amniocentesis (amniotic fluid)

Genetics

- Rarely caused by Robertsonian translocation
- 2-3% of cases
- Chromosome 21 fused with another chromosome
- Most commonly chromosome 14 or 10
- Two copies 21 passed to fetus from one parent
- No increased risk with advanced maternal age
- High recurrence risk within families

Alzheimer’s Disease

- Occurs early
- Average age of onset in 50s
- Amyloid Precursor Protein (APP)
  - Found on chromosome 21
  - Breakdown forms beta amyloid
  - Amyloid plaques form in AD

Malignancy

- Lifetime risk of leukemia about 1 to 1.5%
- Often occurs in childhood
- Acute lymphoblastic leukemia
  - Risk 10 to 20 times higher in DS
- Acute myeloid leukemia
  - M7 subtype
  - Megakaryoblastic leukemia

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VashiDonsk/Wikipedia

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  - M7 subtype
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VashiDonsk/Wikipedia
Down Syndrome
First Trimester Screening
- Maternal blood testing
  - Pregnancy-associated plasma protein-A (PAPP-A)
    - Glycoprotein produced by placenta
    - Lower levels in pregnancies with fetal Down syndrome
  - Free or total β-hCG
    - Hormone produced by placenta
    - Levels are higher in pregnancies with fetal Down syndrome
- Fetal ultrasound
  - Small, poorly-formed nasal bones
  - Nuchal translucency
    - Fluid under at back of neck

Down Syndrome
Second Trimester Screening
- α-fetoprotein and estriol (uE3)
  - Reduced in pregnancies with fetal Down syndrome
  - NOTE: Increased AFP associated with neural tube defects
  - β-hCG and inhibin A
    - Increased in pregnancies with fetal Down syndrome
    - Inhibin A synthesized by placenta
    - “Quad screen”
Edward Syndrome
Trisomy 18
• Congenital heart disease (50% babies)
• Ventricular septal defects
• Patent ductus arteriosus
• Gastrointestinal defects (75% cases)
• Meckel’s diverticulum
• Malrotation
• Omphalocele

Trisomy Disorders
• All associated with advanced maternal age
• All most commonly due to meiotic nondisjunction
• Common features
  • Intellectual disability
  • Physical deformities
  • Congenital heart defects

Edward Syndrome
Trisomy 18
• 2nd most common trisomy in live births
• Severe intellectual disability
• Often female (3:1 female to male ratio)

Edward Syndrome
Trisomy 18
• Poor intrauterine growth – low birth weight
• Abnormally shaped head
  • Very small
  • Prominent back of skull (occiput)
• Low set ears
• Small jaw and mouth
• Clenched fists with overlapping fingers
• “Rockerbottom” (curved) feet

Edward Syndrome
Trisomy 18
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Edward Syndrome
Trisomy 18
- Many cases die in utero
- 50% affected infants die in first two weeks
- Only 5 to 10% survive first year

Edward Syndrome
Screening
- Physical features often diagnosed by fetal ultrasound
  - Limb deformities, congenital heart defects

First Trimester
<table>
<thead>
<tr>
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Edward Syndrome
Trisomy 18
- Many cases die in utero
- 50% affected infants die in first two weeks
- Only 5 to 10% survive first year

Edward Syndrome
Trisomy 13
- Rare
- Severe intellectual disability
- Severe structural malformations
- Detected by fetal ultrasound >90% of cases

Edward Syndrome
Screening
- Physical features often diagnosed by fetal ultrasound
  - Limb deformities, congenital heart defects

Edward Syndrome
Trisomy 13
- Many cases die in utero
- 50% affected infants die in first two weeks
- Only 5 to 10% survive first year

Patau Syndrome
Trisomy 13
- Eye abnormalities
  - Microphthalmia: abnormally small eyes
  - Anophthalmia: absence of one or both eyes
  - Cleft lip and palate
  - Post-axial polydactyly
    - Polydactyly: extra finger or toe
    - Extra digit away from midline (ulnar)

Patau Syndrome
Trisomy 13
- Holoprosencephaly
  - CNS malformation
  - Failure of cleavage of prosencephalon
  - Left/right hemispheres fail to separate
  - May result in “alobar” brain

Patau Syndrome
Trisomy 13
- Rare
- Severe intellectual disability
- Severe structural malformations
- Detected by fetal ultrasound >90% of cases
Patau Syndrome
Trisomy 13

- Congenital heart disease (80% cases)
  - Ventricular septal defect (VSD)
  - Patent ductus arteriosus (PDA)
  - Atrial septal defect (ASD)

Most cases die in utero
Median survival 7 days
91% die within 1st year of life

Patau Syndrome
Trisomy 13

- Usually diagnosed by fetal ultrasound

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Muscular Dystrophy

Jason Ryan, MD, MPH

Muscular Dystrophies

- Group of genetic disorders
- More than 30 types
- All result from defects in genes for muscle function
- Main symptom: Progressive muscle weakness

Muscular Dystrophies

- Duchenne: Most common
- Becker: Milder variant of Duchenne
- Myotonic: Trinucleotide repeat disorder

Duchenne and Becker

- Both X-linked
- "X-linked muscular dystrophies"
- Both involve DMD gene and dystrophin protein
- Myotonic dystrophy
- Different gene
- Different protein
- Not X-linked (autosomal dominant)

DMD

Duchenne Muscular Dystrophy

- X-linked recessive disorder
  - All male carriers affected
  - 1/3 cases new mutations in fertilized egg (no parental carrier)
  - 2/3 inherited from carrier mothers

DMD

Duchenne Muscular Dystrophy

- Abnormal DMD gene
  - Massive gene (2300kb)
  - 1.5% of the X chromosome
  - Among largest known genes
  - High mutation rate
  - Codes for dystrophin
Dystrophin

- Maintains muscle membranes
- Connects intracellular actin to transmembrane proteins
- Binds α- and β-dystroglycan in membrane
- Connected to the extracellular matrix (laminin)

Dystrophin

- Also found in cardiac and smooth muscle
- Also found in some brain neurons

Dystrophin Gene Mutations

- Most mutations are deletions
- Duchenne: Frameshift mutation
  - Deletion disrupts reading frame
  - Early stop codon
  - Truncated or absent dystrophin protein
- Becker: Non-frameshift mutation
  - Some functioning protein
  - Less severe disease

DMD

Duchenne Muscular Dystrophy

- Loss of dystrophin → myonecrosis
- Creatine kinase elevation
  - Common in early stages
  - Released from diseased muscle
- Other muscle enzymes also elevated
  - Aldolase
  - Aspartate transaminase (AST)
  - Alanine transaminase (ALT)

DMD

Duchenne Muscular Dystrophy

- Affected boys normal first few years
- Weakness develops age 3-5
- Wheelchair usually by age 12
- Death usually by age 20
- Usually due to respiratory failure
- Sometimes heart failure
DMD
Becker Muscular Dystrophy
- Also X-linked recessive disorder
- 90% cases inherited from carrier mothers
- Less severe disease
- More males pass gene on to female offspring

DMD
Duchenne Muscular Dystrophy
- Diagnosis: Genetic testing
- Usually with variations of polymerase chain reaction
- Identify most common DMD gene abnormalities

DMD
Duchenne Muscular Dystrophy
- Western blot
- Absence of dystrophin in Duchenne
- Altered dystrophin in Becker

DMD
Duchenne Muscular Dystrophy
- Cardiomyopathy
  - Depressed LVEF
  - Systolic heart failure
  - Myocardial fibrosis
  - Conduction abnormalities
    - AV block
    - Arrhythmias

DMD
Duchenne Muscular Dystrophy
- Proximal muscles affected before distal limb muscles
- Lower limbs affected before upper extremities
- A affected children:
  - Difficulty running, jumping, climbing stairs
  - Use hands to push themselves up from chair (Gower’s sign)
  - Waddling gait
- Muscle replaced with fat/connective tissue
  - Calf enlargement
  - "Pseudohypertrophy"

DMD
Duchenne Muscular Dystrophy
- Muscle biopsy (rarely done in modern era)
  - Degeneration of fibers
  - Replacement of muscle by fat and connective tissue

DMD
Duchenne Muscular Dystrophy
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- Depressed LVEF
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DMD
Becker Muscular Dystrophy
- Also X-linked recessive disorder
- 90% cases inherited from carrier mothers
- Less severe disease
- More males pass gene on to female offspring
BMD
Becker Muscular Dystrophy

• Milder form of muscular dystrophy
• Late age of onset
• Some patients remain ambulatory
• Often survive into 30s
Trinucleotide Repeat Disorders

Fragile X Syndrome

- X-linked dominant disorder
- Abnormal FMR1 gene
- Fragile X mental retardation 1 gene
- Found on long arm of X chromosome
- Most commonly an increase in CGG repeats
- Normal <55 repeats
- Full mutation: >200 repeats
- Leads to DNA methylation of FMR1 gene
- Gene silenced by methylation

- More severe among males (absence of normal X)
- 2nd most common genetic cause intellectual disability
- Anxiety, ADHD
- Often has features of autism
- Long, narrow face, large ears and jaw
- Macroorchidism (large testicles)
- Classic feature

- Down syndrome most common
- Anxietey, ADHD
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- Classic feature

- Occur in genes with repeat trinucleotide units
- Example: CAGCAGCAGCAG
- Most disorders involve nervous system
- Key examples
  - Fragile X syndrome
  - Friedreich's ataxia
  - Huntington's disease
  - Myotonic dystrophy

- Disease gene: "Unstable repeat expansions"
- Number of repeats may increase in offspring
- One generation to next: more repeats
- Key point: genetic abnormality changes over time
  - Anticipation
    - Disease severity worse in subsequent generations
    - Earlier onset in subsequent generations
    - Associated with more repeats in abnormal gene

Wild-type (normal) allele
- Found in most individuals
- Polymorphic
- Variable number of repeats from person to person
- Overall number of repeats relatively low

Disease (abnormal) allele
- Found in affected individuals
- Increased ("expanded") number of repeats
- Beyond the normal range
- Likely due to slipped DNA mispairing

Trinucleotide Repeat Disorders

Jason Ryan, MD, MPH
Myotonic Dystrophy

- **Type I** (most common)
  - Abnormal DMPK gene (chromosome 19)
  - Dystrophia myotonica protein kinase
  - CTG expansion
  - Codes for myotonic dystrophy protein kinase
  - Abnormal gene transcribed to mRNA but not translated
- **Type 2**: abnormal CNBP gene
  - Rare type
  - Usually less severe than type I
  - CCTG (tetranucleotide) repeat (not a trinucleotide disorder)

Huntington's Disease

- Degeneration in **basal ganglia** (striatum)
- Leads to chorea, dementia
- Onset of symptoms 30s-40s
- Death after 10-20 years

Friedreich's Ataxia

- **Hereditary ataxia disorder**
- Autosomal dominant
- Mutation of frataxin gene on chromosome 9
  - Needed for normal mitochondrial function
  - Increased number GAA repeats
  - Leads to decreased frataxin levels
- Frataxin: mitochondrial protein
  - High levels in brain, heart, and pancreas
  - Abnormal frataxin → mitochondrial dysfunction

Huntington's Disease

- Movement (CNS) disorder
- Autosomal dominant
- Mutation in the HTT gene
  - Codes for protein huntingtin
- Mutation → Increased CAG repeat
  - CAG codes for glutamine
  - "Polyglutamine disorders:" Huntington’s, other rare CNS diseases
- Normal 10-35 repeats
- Huntington’s 36 to 120 repeats

Friedreich's Ataxia

- Begins in adolescence with progressive symptoms
- Cerebellar and spinal cord degeneration
  - Loss of balance
  - Weakness
- Associated with hypertrophic cardiomyopathy
- Physical deformities:
  - Kyphoscoliosis
  - Foot abnormalities
Myotonic Dystrophy

- Most common MD that **begins in adulthood**
- Often starts in 20s or 30s
- Progressive muscle wasting and weakness
- Prolonged muscle contractions (myotonia)
- Unable to relax muscles after use
- Cannot release grip
- Locking of jaw

Myotonic Dystrophy

- Facial muscles often affected
- Characteristic facial appearance
- Caused by muscle weakness and wasting
- Long and narrow face
- Hollowed cheeks

Myotonic Dystrophy

- **Multisystem disorder**
- Many non-muscle features
- Hypogonadism
- Cataracts
- Cardiac arrhythmia
- Frontal balding

Myotonic Dystrophy

- **Cardiac involvement**
- Arrhythmias and conduction disease common
- First degree atrioventricular block (20 to 30%)
- Bundle branch block (10 to 15%)
- Atrial flutter and atrial fibrillation

Myotonic Dystrophy

- **Endocrine involvement**
- Primary hypogonadism
- Low testosterone
- Elevated FSH
- Oligospermia
- Infertility
- Testicular atrophy
- Insulin resistance

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Myotonic Dystrophy

**Lung Involvement**
- Respiratory complications common
- Weakness/myotonia of respiratory muscles
- Decreased vital capacity
- Alveolar hypoventilation
- Respiratory failure may occur

Myotonic Dystrophy

**Intellectual Disability**
- Common in myotonic dystrophy
- Severity worse with younger age of onset
- Childhood disease → severe cognitive impairment
Deletion Syndromes

Cri-du-chat Syndrome

• Severe intellectual disability
• Cognitive, speech, motor delays
• Infants cry like a cat
• Classically described as “mewing”: high-pitched cry
• Occurs soon after birth then resolves

• Deletion of part of short arm (p) of chromosome 5
  • “5p- syndrome”

• Partial deletion of chromosome
  • Long or short arm
  • Portion of long/short arm

Deletion Syndromes

• Most cases sporadic (congenital)
• Key syndromes:
  • Cri-du-chat
  • Williams
  • Thymic aplasia

Deletion Syndromes

• Usually an error in **crossover** in meiosis
  • Unbalanced exchange of genes
  • One chromosome with duplication; other with deletion

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Williams Syndrome

- Supravalvular aortic stenosis
- Constriction of ascending aorta above aortic valve
- High prevalence among children with WS
- Pulmonary artery stenosis
- Renal artery stenosis

Cri-du-chat Syndrome

- Congenital heart defects
  - Ventricular septal defect (VSD)
  - Patent ductus arteriosus (PDA)
  - Tetralogy of Fallot (TOF)
  - Others

Cri-du-chat Syndrome

- Partial deletion on long arm of chromosome 7
- Deleted portion includes gene for elastin
- Elastic protein in connective tissue
- Results in elastin "haploinsufficiency"
Thymic Aplasia
DiGeorge Syndrome
• Many different names
  • 22q11 deletion syndrome
  • Velocardiofacial syndrome
  • Shprintzen syndrome
  • Conotruncal anomaly face syndrome
• Partial deletion of long arm (q) chromosome 22
• Immune deficiency
• Hypocalcemia
• Congenital heart defects

Williams Syndrome
Hypercalcemia
• Higher calcium than general pediatric population
• Evidence of ↑ vitamin D levels and ↑ vitamin D sensitivity
• Usually mild to moderate
• Does not usually cause symptoms
• May lead to constipation

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**Klinefelter Syndrome**

- Male with primary hypogonadism
- Small, firm testes
- Atrophy of seminiferous tubules
- Low testosterone
- Ratio of estrogens:testosterone determines severity

**Klinefelter and Turner**

- Sex chromosome aneuploidy disorders
- Klinefelter: Male with extra X (XXY)
- Turner: Female with missing X (X0)

**Karyotype**

- Diagnosis of both syndromes
- Often multiple cells to look for mosaicism

**Klinefelter Syndrome**

- Usually 47 XXY (~80% of cases)
- Usually *meiotic nondisjunction* of either parent
- Rarely 48,XXXY (more severe)
- Or 46,XY/47,XXY mosaicism (less severe)
- Nondisjunction during *mitosis* after conception

**Klinefelter Syndrome**

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  - Small, firm testes
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  - Ratio of estrogens:testosterone determines severity
Klinefelter Syndrome

- Increased gonadotropins
  - Loss of inhibin B → ↑FSH
  - ↓ testosterone → ↑ LH

Cognitive Findings
- Learning disabilities
- Delayed speech/language development
- Quiet personality
- Quiet, unassertive

Physical Appearance
- Long legs and arms
- Extra copy of SHOX gene (X-chromosome)
- Important for long bone growth
- “Eunuchoid body shape”

Genital Abnormalities
- Cryptorchidism (undescended testes)
- Hypospadias
- Micropenis

Low Testosterone Features
- Delayed puberty
- Reduced facial/body hair
- Female pubic hair pattern
- Gynecomastia
- Infertility/reduced sperm count

FSH and LH

- Increased gonadotropins
- Loss of inhibin B → ↑FSH
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Klinefelter Syndrome

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Klinefelter Syndrome
**Turner Syndrome**

- Hallmark: female with primary hypogonadism
- Loss of ovarian function
- "Gonadal dysgenesis"
- May have "streak ovaries"
- Streaks of fibrous tissue seen in expected location of ovaries
- No or very few follicles

**General Features**
- Female with short stature
- Loss of one copy of SHOX gene on X-chromosome
- Growth hormone treatment: given in childhood
- Broad chest (shield chest)
- Widely spaced nipples

**Genetic Causes**
- Often 45, XO (45% cases)
- Most cases caused by sperm lacking X chromosome
- Mosaic Turner syndrome (often milder)
  - 45,X/46,XX
  - Mitotic nondisjunction during post-zygotic cell division

**Genetics**
- Barr Body
  - Inactivated X chromosome
  - Normally found in cells of females (XX)
  - One X chromosome undergoes "Lyonization"
  - Condensed into heterochromatin with methylated DNA
  - Seen in cells of patients with Klinefelter's
    - Not normally seen in males

**Cystic Hygroma**
- Congenital lymphatic defect
- Large collection of lymph/cysts
- Often found in head/neck
- Often seen in utero on US

**Turner Syndrome**

- Lymphatic obstruction in fetal development
- Webbed neck
- Swollen hands/feet (especially at birth)

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    - Not normally seen in males

**Ovarian Function**
- Hallmark: female with primary hypogonadism
  - Loss of ovarian function
  - "Gonadal dysgenesis"
  - May have "streak ovaries"
    - Streaks of fibrous tissue seen in expected location of ovaries
    - No or very few follicles
Turner Syndrome

Ovarian Function

- Decreased inhibin B
- Decreased estrogens
- Increased LH/FSH
- Levels can vary during childhood
  - Sometimes within normal range
  - Often abnormal in early childhood (<5) and pre-puberty (>10)

- Most women infertile
- Some can become pregnant with donated oocytes

Turner Syndrome

Cardiovascular

- ~30% of children born with bicuspid aortic valve
- 5-10% of children have coarctation of the aorta
- High blood pressure may occur in childhood
  - Sometimes due to coarctation or renal disease
  - Often primary

- Primary amenorrhea (most common cause)
  - “Menopause before menarche”
  - Some girls menstruate with menopause in teens/20s
  - More common in cases with mosaicism

Turner Syndrome

Renal Manifestations

- Kidney malformations affect ~ 1/3 patients
- Abnormal collecting ducts
- Often a horseshoe kidney

Turner Syndrome

Osteoporosis

- High incidence of osteoporosis
- Low circulating estrogens
- Estrogen treatments often prescribed
Turner Syndrome

Endocrine

- Type II Diabetes
  - Turner syndrome 2x risk of general population
- Thyroid disease
  - ~1/3 have a thyroid disorder
  - Usually hypothyroidism from Hashimoto’s thyroiditis