Boards and Beyond: Genetics

A Companion Book to the Boards and Beyond Website

Jason Ryan, MD, MPH

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Genetics
Terminology

- **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

Genetic Principles

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

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

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
  - Many genes have several forms
  - Often represented by letter (A, a)

- **Genetic polymorphism**
  - Genes exist in multiple forms (alleles)
  - Locus (plural loci)
    - Location of allele on chromosome
  - DNA → gene → allele → locus → 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

- **Germ line mutations**
  - DNA of sperm/eggs
  - Transmitted to offspring
  - Found in every cell in body

- **Somatic mutations**
  - Acquired during lifespan of cell
  - Not transmitted to offspring

- **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

- **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

- **Homozygous**
  - Two identical copies of a gene (i.e. AA)

- **Heterozygous**
  - Two different copies of a gene (i.e. Aa)
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

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

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)

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
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 → cancer
• Cancer requires "two hits"
  • "Loss of heterozygosity"

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

Two-Hit Origin of Cancer

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

Two-Hit Origin of Cancer

• 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
Mosaicism

- Gene differences in cells of same individual
- Mutations in cells \(\rightarrow\) genetic changes
- Individual will be a mixture of cells

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

Mosaicism

- **Somatic mosaicism**
  - Gene differences in tissues/organs
  - 45X/46XX mosaic Turner syndrome (milder form)
  - Rare forms of Down syndrome

McCune-Albright Syndrome

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

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 affected
  - Cells with mutation survive only if mixed with normal cells

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

- 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

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

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
Genetic Recombination

- During meiosis chromosomes exchange segments
- Child inherits "patchwork" of parental chromosomes
- Never exact copy of parental chromosomes

Genetic Mapping

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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

Independent Assortment

- What if genes on same chromosome?
  - If very far apart, crossover may occur in meiosis
  - Result: Same combinations as separate chromosomes
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 (Fm or fM)
• Denoted by Greek letter theta (θ)
• Ranges from zero to 0.5
• Key point: recombination frequency α distance
  • Close together: θ = 0
  • Far apart: θ = 0.5
  • Used for genetic mapping of genes

Genetic Mapping

Linkage Mapping

• Done by studying families
• Track frequency of genetic recombination
• Use frequency to determine relative gene location

<table>
<thead>
<tr>
<th>Combination</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>A-B</td>
<td>0.76</td>
</tr>
<tr>
<td>A-C</td>
<td>0.09</td>
</tr>
<tr>
<td>C-B</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Linkage

• Tendency of alleles to transmit together
  • More linkage = less independent assortment
  • Close together (θ = 0) = tightly linked
  • Far apart (θ = 0.5) = unlinked
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%

\[
\begin{align*}
A &= 0.5 \\
a &= 0.5 \\
B &= 0.9 \\
b &= 0.1
\end{align*}
\]

Linkage Disequilibrium

- Population frequencies should be:
  - AB = (0.5) x (0.9) = 0.45
  - Ab = (0.5) x (0.1) = 0.05
  - aB = (0.5) x (0.9) = 0.45
  - Ab = (0.5) x (0.1) = 0.05
  - This is linkage equilibrium

Linkage Disequilibrium

- Population frequencies higher/lower than expected
  - AB = 0.75 (higher than expected 0.45)
  - This haplotype (AB) is in linkage disequilibrium

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
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 $\rightarrow$ Haploid ("reductive division")
- Separates homologous chromosomes

Meiosis II
- Chromatids separate
- Four daughter cells

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 $\rightarrow$ degenerate
  - Some form secondary oocytes (haploid)
  - Meiosis II begins $\rightarrow$ arrests in metaphase
  - Fertilization $\rightarrow$ 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
- Diploid Mixture Genes
- Meiosis I NDJ
- Normal

Meiosis II Nondisjunction
- Blue = Paternal
- Red = Maternal
- Sister Chromatids Fail to Separate
- Diploid No mixture genes
- No genes
- Meiosis II NDJ
- Normal

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

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

Trisomy

- Cause of NDJ suggested by trisomy genotype
  - Father = 21A and 21B; Mother = 21C and 21D
  - Trisomy 21 ACD = Meiosis I nondisjunction in mother
  - Trisomy 21 ACC = Meiosis II nondisjunction in mother

Uniparental Disomy

- Child is euploid
  - Normal number of chromosomes
  - No aneuploidy
  - Usually normal phenotype
- Can lead to phenotype of recessive disease
  - Father = Aa (recessive gene for disease)
  - Child = aa (two copies of a from father)

- 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 I 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)
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)

Karyotype

- Can be done in couples with recurrent fetal losses
- Used to diagnose chromosomal imbalances
Hardy-Weinberg Law

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?

\[ p + q = 1 \]

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

\[ p = 0.4, q = 0.6 \]

\[ p^2 = 0.16 \]

\[ 2pq = 0.48 \]

\[ q^2 = 0.36 \]

Hardy-Weinberg Law

Assumptions
• Large population
• Completely random mating
• No mutations
• No migration in/out of population
• No natural selection
Hardy-Weinberg Law

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

Hardy-Weinberg Law

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

Hardy-Weinberg Law

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

Hardy-Weinberg Law

- Special case: X-linked disease
- Two male genotypes (X\(d\)Y or XY)
- Three female genotypes (XX or X\(d\)X or X\(d\)X\(d\))

Hardy-Weinberg Law

X-linked Disease

- Consider males and females separately
  - Among males
    - \( p + q = 1 \) (all males are either X\(d\) or X)
    - \( p = \) frequency healthy males (XY)
    - \( q = \) frequency diseased males (X\(d\)Y)
  - Males/females have same allele frequencies
    - \( p \) males = \( p \) females
    - \( q \) males = \( q \) females
  - Among females
    - \( p^2 = \) frequency healthy females (XX)
    - \( 2pq = \) frequency carrier females (X\(d\)X)
    - \( q^2 = \) frequency diseased females (X\(d\)X\(d\))
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

Autosomal Recessive

- 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)

Autosomal Recessive

- If both parents are carriers (Aa)
  - 50% chance mother gives a to child
  - 50% chance father gives a to child
  - \((0.5 \times 0.5) = 0.25\) chance child has disease
### Autosomal Recessive

**Mother (1/50)**

<table>
<thead>
<tr>
<th>Father (1/100)</th>
<th>A</th>
<th>Aa</th>
<th>aa</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>AA</td>
<td>Aa</td>
<td></td>
</tr>
<tr>
<td>a</td>
<td>Aa</td>
<td></td>
<td>aa</td>
</tr>
</tbody>
</table>

- Mother 1/50 chance of being carrier
- Father 1/100 chance of being carrier
- Chance BOTH carriers = (1/100) * (1/50) = 1/5,000
- Chance child affected = (1/4) * (1/5000) = 1/20,000

### 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 Recessive

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

### Autosomal Dominant

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

### Autosomal Dominant

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

- Familial hypercholesterolemia
- Huntington’s disease
- Marfan syndrome
- Hereditary spherocytosis
- Achondroplasia
- Many others
Incomplete Dominance
Semidominant

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

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

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

X-linked Disorders

- Disease gene on X chromosome (Xα)
- Always affects males (X,Y)
- Females (X,X) variable
  - X-linked recessive = females usually NOT affected
  - X-linked dominant = females can be affected

X-linked Recessive

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

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

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
Lyonization

- 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

- 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

- 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

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

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

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
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

Mitochondrial Disorders

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

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

Polygenic Inheritance

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

Multifactorial Inheritance

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

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Imprinting

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

Cytosine

Methylcytosine

Imprinting Syndromes

- Prader-Willi and Angelman syndromes
  - Both involve abnormal chromosome 15q11-q13
    - “PWS/AS region”
    - 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
Prader-Willi Syndrome

PWS

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

- ~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

Prader-Willi Syndrome

PWS

- 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

Angelman Syndrome

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

- 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

- Frequent laughter/smiling
  - "Happy puppet"
- Seizures (80% patients)
- Ataxia
- Severe intellectual disability
Down Syndrome

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Trisomy Disorders

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

Down Syndrome

- 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

Dysmorphic Features

- "Flat" facial profile
- Flat nasal bridge
- Low-set small ears
- Short neck
- Brachycephaly
  - Posterior skull is flat (not rounded)

Dysmorphic Features

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

Brushfield Spots

- White spots on iris
Dysmorphic Features

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

Other Physical Features

- Hypotonia
  - Often identified at birth
- Short stature

Intellectual 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

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

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

Gastrointestinal Anomalies

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

Down Syndrome
Genetics
- Meiotic nondisjunction
  - Two chromosomes from one parent; one from other
  - Most common cause of Down syndrome (95% cases)
  - Usually meiosis I (90% of cases)
- Extra chromosome from mother in 90% cases
  - Increased risk with advanced maternal age

Down Syndrome
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

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

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

Prenatal Screening

- Noninvasive tests
  - Ultrasound
  - Maternal serum testing

Down Syndrome

Second Trimester Screening

- α-fetoprotein and estriol (uE3)
  - Reduced in pregnancies with fetal Down syndrome
  - AFP: protein produced by yolk sac and liver
  - 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
  - "Quadscreen"
Trisomy Disorders

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

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

- Congenital heart disease (50% babies)
  - Ventricular septal defects
  - Patent ductus arteriosus
- Gastrointestinal defects (75% cases)
  - Meckel’s diverticulum
  - Malrotation
  - Omphalocele
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

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<tr>
<th>First Trimester</th>
<th>Down</th>
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Edward Syndrome  
Screening

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

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 "alojar" brain
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

### First Trimester

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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 Dystrophy

Jason Ryan, MD, MPH

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 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 \( \rightarrow \) 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**

Duchenne Muscular Dystrophy

- Proximal muscles affected before distal limb muscles
- Lower limbs affected before upper extremities
- **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

- **Cardiomyopathy**
  - Depressed LVEF
  - Systolic heart failure
  - Myocardial fibrosis
- **Conduction abnormalities**
  - AV block
  - Arrhythmias

**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

- **Western blot**
  - Absence of dystrophin in Duchenne
  - Altered dystrophin in Becker

**BMD**

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
BMD
Becker Muscular Dystrophy

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

- 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

Trinucleotide Repeat Disorders

- 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

- 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

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

Fragile X Syndrome

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

• Hereditary ataxia disorder
• Autosomal recessive
• 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

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

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

Huntington’s Disease

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

Myotonic Dystrophy

• Muscle disorder
• Autosomal dominant

Myotonic Dystrophy

• Type 1 (most common)
  • Abnormal *DMPK* gene (chromosome 19)
  • Dystrophia myotonica protein kinase
  • CUG 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 1
  • CCTG (tetranucleotide) repeat (not a trinucleotide disorder)
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

- 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

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

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

- **Cataracts**
  - High prevalence
  - Occur at younger age
  - Regular slit-lamp exams for screening
Myotonic Dystrophy

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

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

Jason Ryan, MD, MPH

Deletion Syndromes

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

Deletion Syndromes

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

Meiosis
Replication/Crossover

Deletion Syndromes

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

Cri-du-chat Syndrome

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

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
Cri-du-chat Syndrome

- Microcephaly (small head)
- Characteristic facial features
  - Widely set eyes (hypertelorism)
  - Low-set ears
  - Small jaw
  - Rounded face

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

Williams Syndrome

Williams-Beuren syndrome

- Partial deletion on long arm of chromosome 7
- Deleted portion includes gene for elastin
  - Elastic protein in connective tissue
  - Results in elastin "haploinsufficiency"

- Classically an "elfin" facial appearance
  - Small nose
  - Small chin
  - Wide mouth
  - Long philtrum (upper lip length)

- Intellectual disability
  - Delayed developmental milestones
  - Well-developed verbal skills
  - Extremely friendly with strangers
    - Unafraid of strangers
    - Great interest in talking with adults

- Vascular Manifestations
  - Supravalvular aortic stenosis
    - Constriction of ascending aorta above aortic valve
  - High prevalence among children with WS
  - Pulmonary artery stenosis
  - Renal arterystenosis
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
Klinefelter and Turner Syndromes

Klinefelter and Turner

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

Karyotype

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

Klinefelter Syndrome

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

Klinefelter Syndrome

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

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

Klinefelter Syndrome
Genital Abnormalities
• Cryptorchidism (undescended testes)
• Hypospadias
• Micropenis

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

Klinefelter Syndrome
Cognitive Findings
• Learning disabilities
  • Delayed speech/language development
• Quiet personality
  • Quiet, unassertive

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

Turner Syndrome
• Often 45, X0 (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
**Turner Syndrome**

**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

**Turner Syndrome**

**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)

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

**Turner Syndrome**

**General Features**
- Lymphatic obstruction in fetal development
- Webbed neck
- Swollen hands/feet (especially at birth)
**Turner Syndrome**

**Ovarian Function**
- Most women **infertile**
- Some can become pregnant with donated oocytes

**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 of renal disease
  - Often primary

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

**Osteoporosis**
- High incidence of **osteoporosis**
- Low circulating estrogens
- Estrogen treatments often prescribed

**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