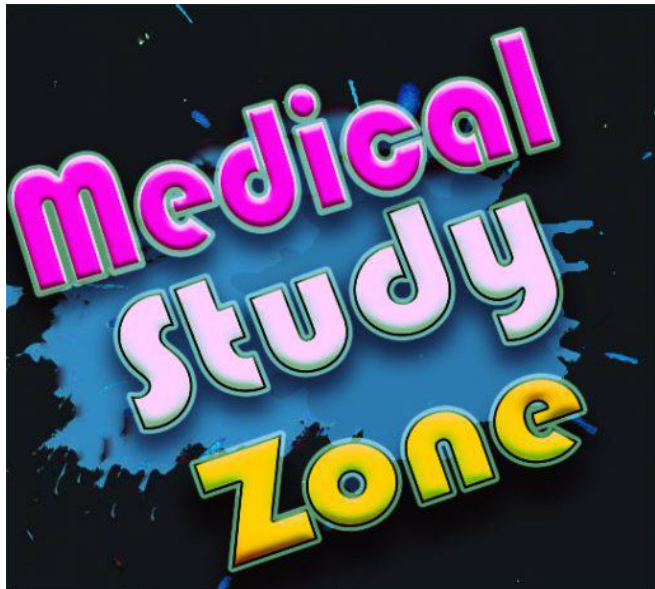
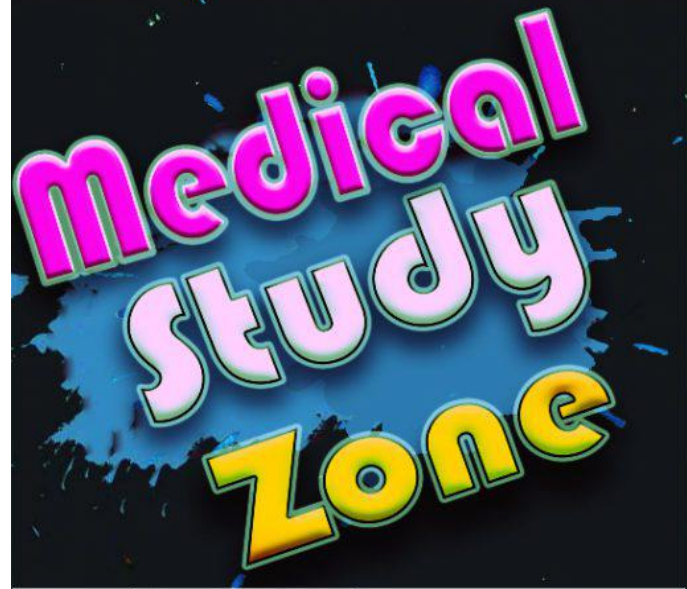


Genetic Principles

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

Genetics

Terminology

- 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**

Chromosomes



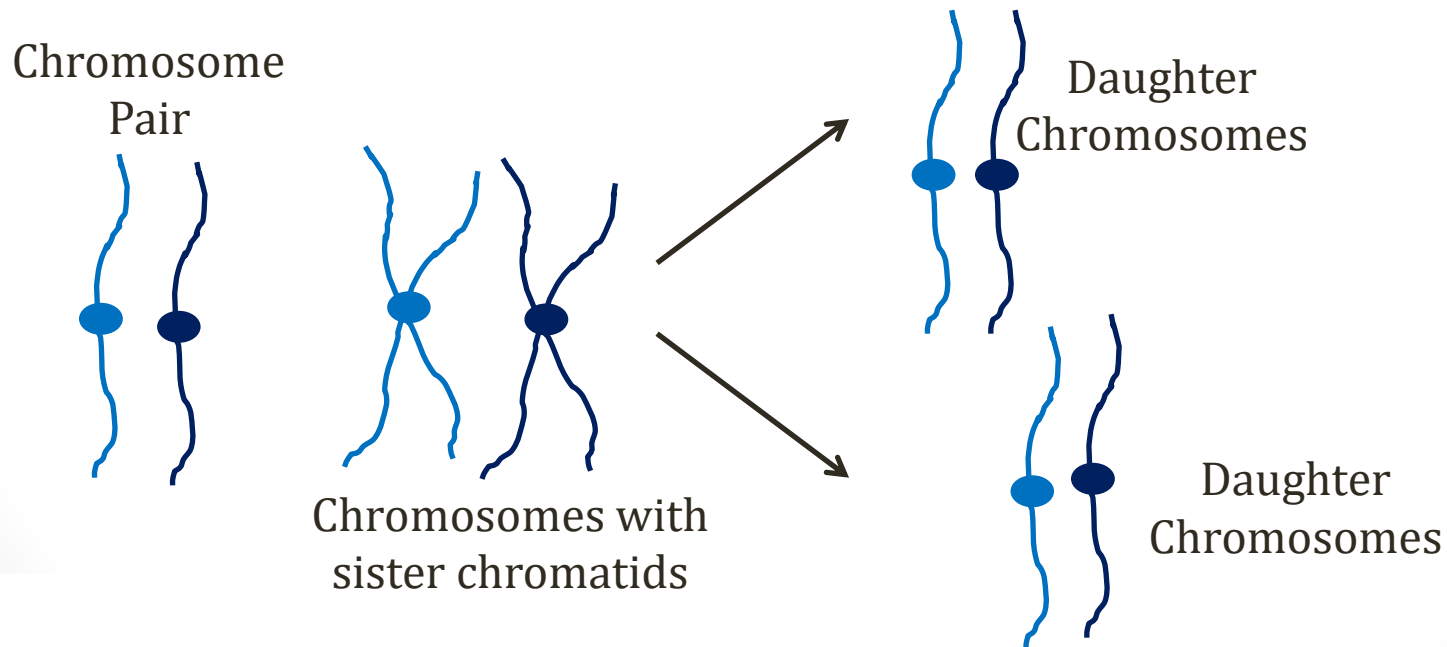
Cell Types

- 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

Genetics

Terminology

- 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

Genetics

Terminology

- 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

Genetics

Terminology

- Homozygous
 - Two identical copies of a gene (i.e. AA)
- Heterozygous
 - Two different copies of a gene (i.e. Aa)

Genetics

Terminology

- **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

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 α 1 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)

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

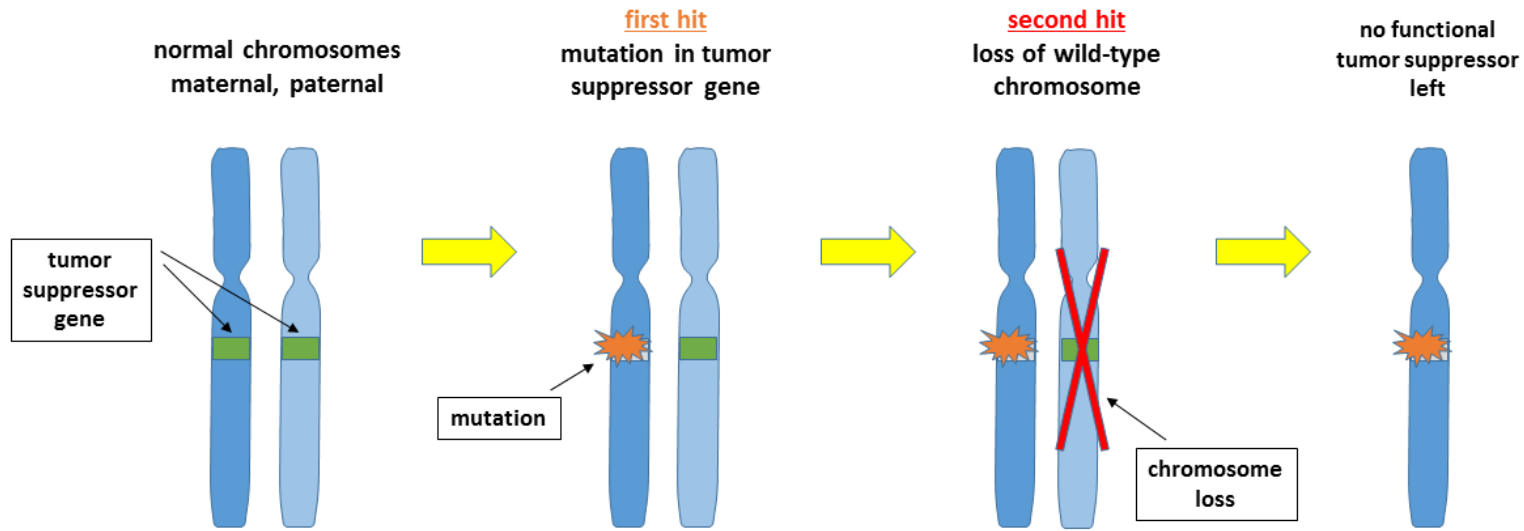
Two-Hit Origin of Cancer

- 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”



Telegram: @eMedicalLibrary

Two-Hit Origin of Cancer



Wpeissner/Wikipedia

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



Wikipedia/Public Domain

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

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

Other Examples

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

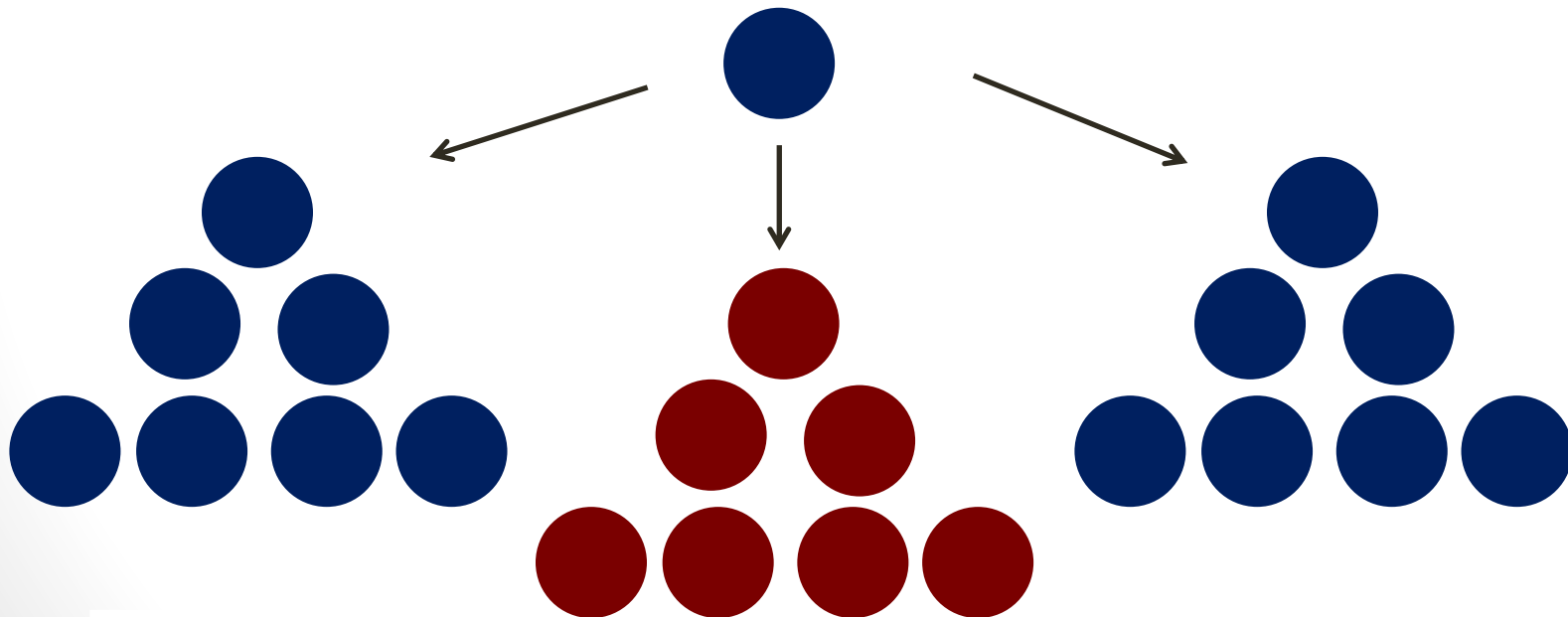
Two-Hit Origin of Cancer

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

Mosaicism

- Gene differences in cells of same individual
- Mutations in cells → 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”)



Alexrk2



Claudia E Dumitrescu, Michael T Collins

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

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

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**

Allelic heterogeneity

- Beta Thalassemia
 - Mutation in beta globin gene
 - Wide spectrum of disease depending on mutation
 - β^0 = no function; β^1 = some function
- Cystic Fibrosis
 - Mutation in CFTR gene
 - Over 1400 different mutations described

Locus heterogeneity

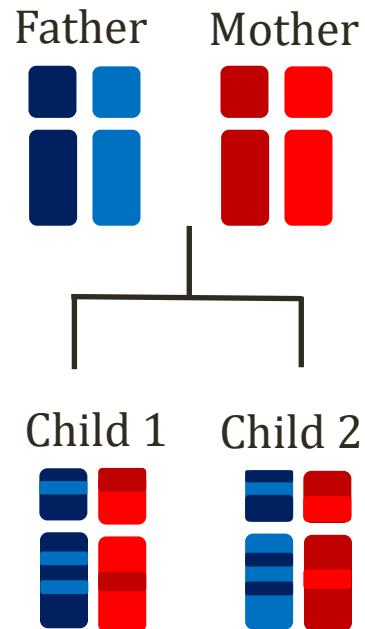
- Mutations in different loci cause same phenotype
- Example: Retinitis Pigmentosa
 - Causes visual impairment
 - Autosomal dominant, recessive, and X-linked forms
 - Mutations at 43 different loci can lead to disease
- **One disease = multiple genes = multiple locations**

Genetic Mapping

Jason Ryan, MD, MPH

Genetic Recombination

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

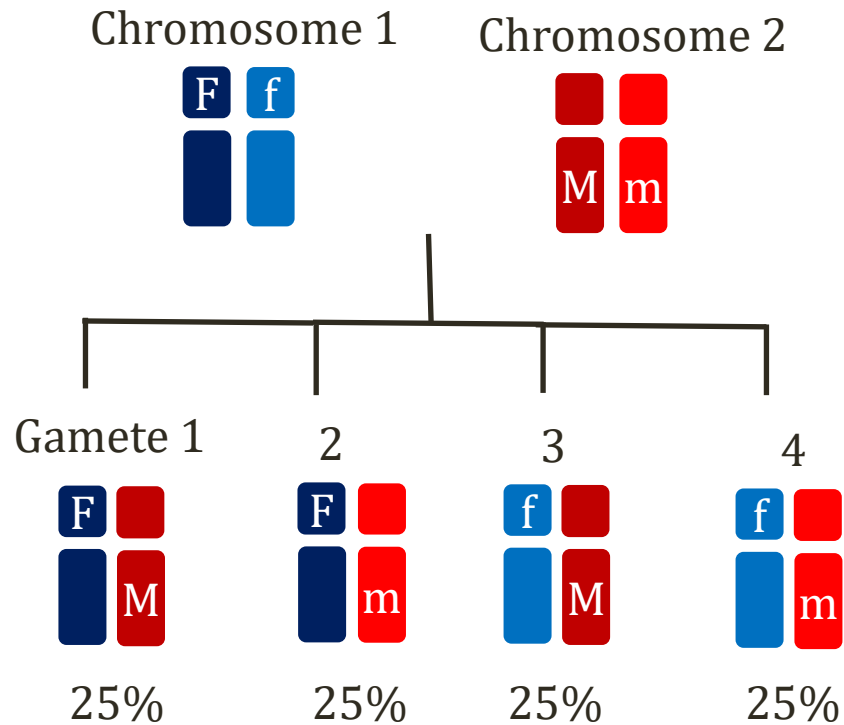


Independent Assortment

- 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

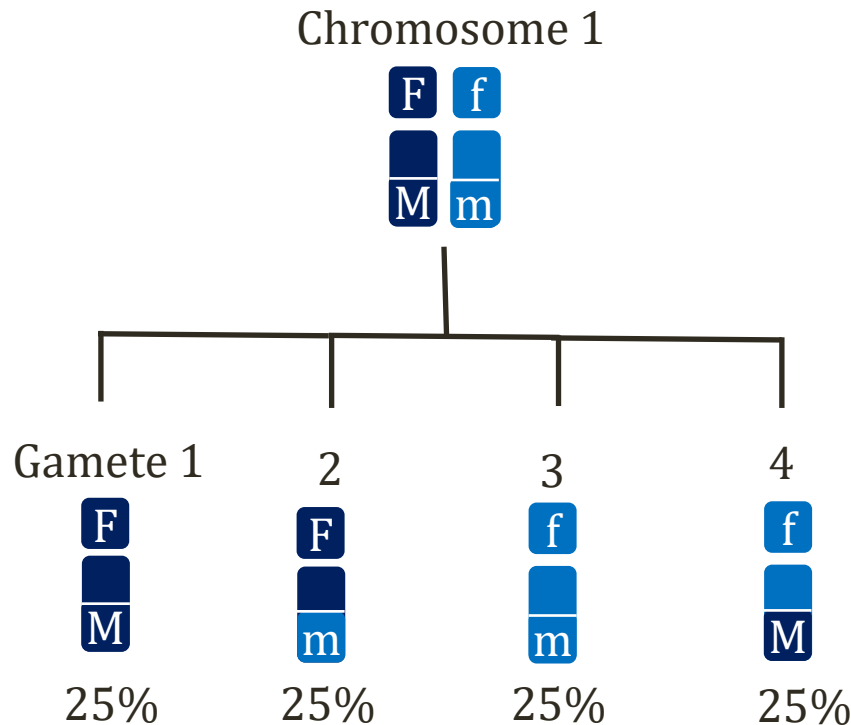
Independent Assortment

Father



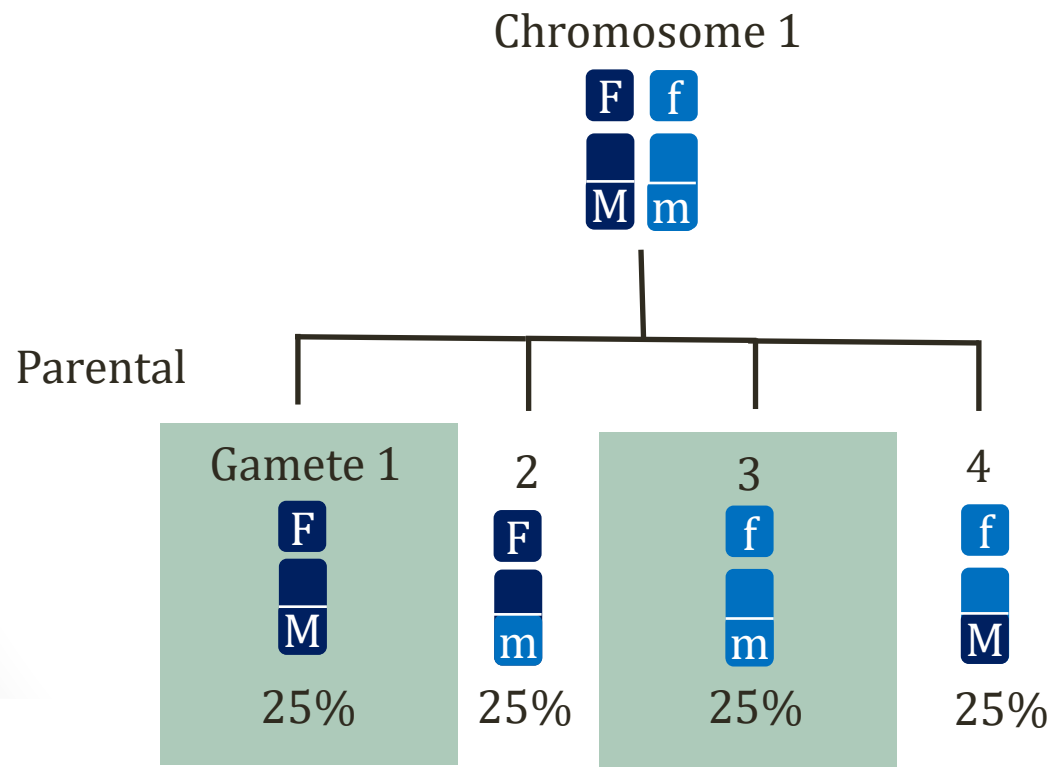
Independent Assortment

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



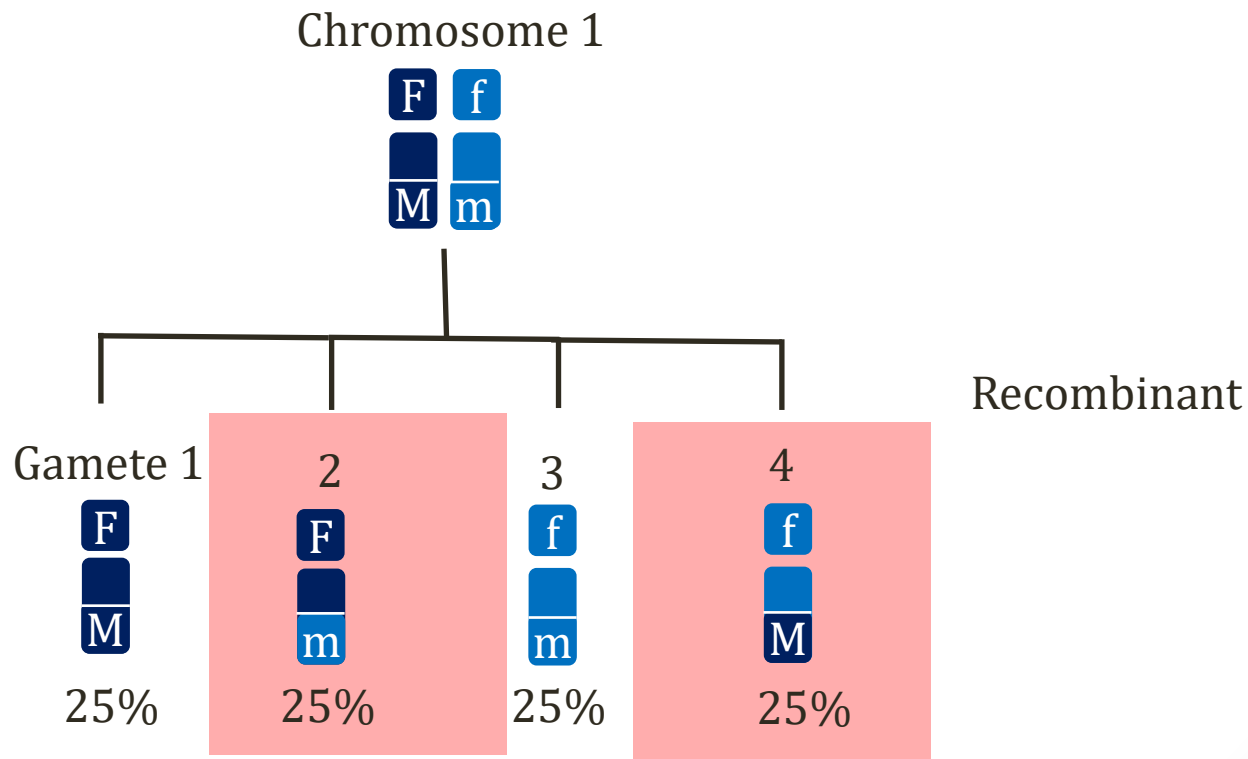
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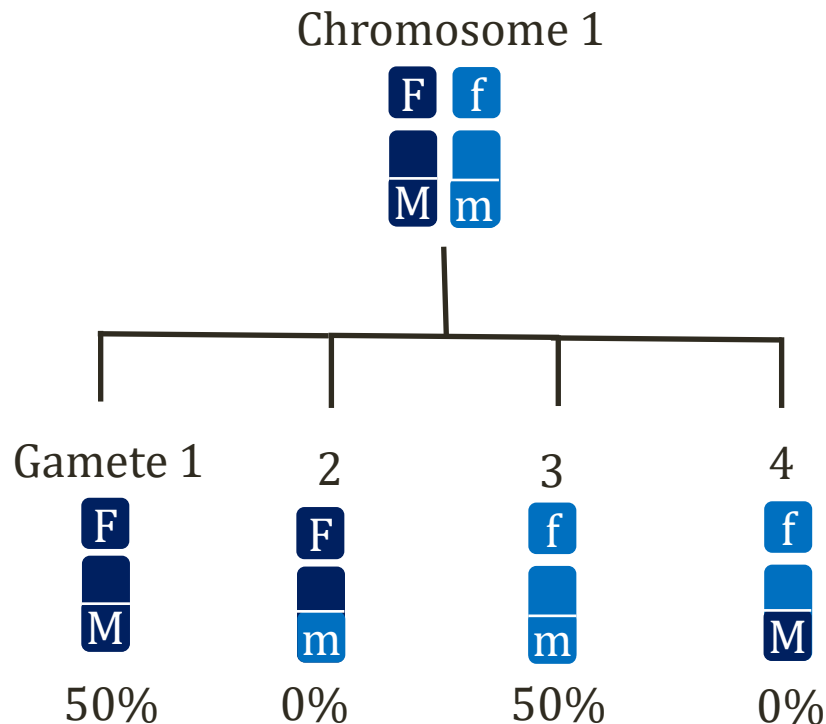
Independent Assortment

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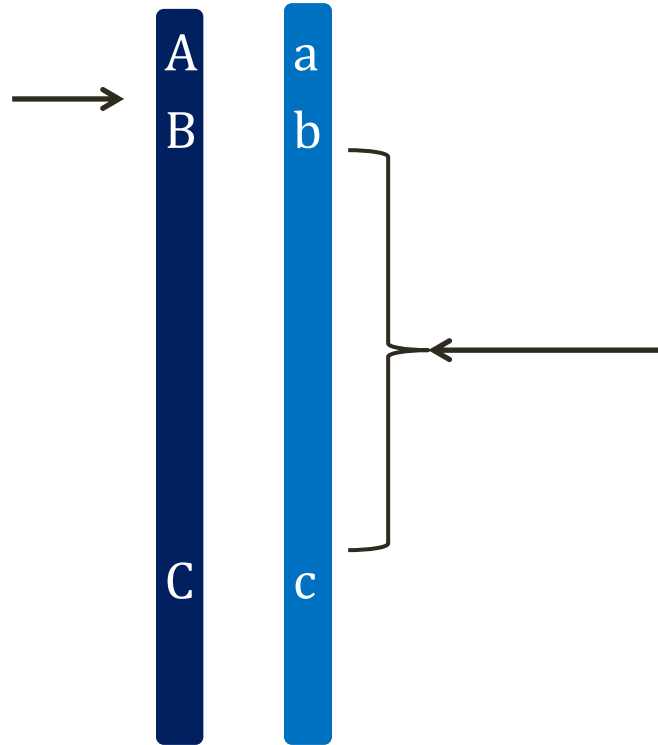
Independent Assortment

- If alleles close together: little crossover
- Low occurrence of recombination (Fm or fM)



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 \propto distance**
 - Close together: $\theta = 0$
 - Far apart: $\theta = 0.5$
 - 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

Combination	Frequency
A-B	0.16
A-C	0.08
C-B	0.08



Linkage

- Tendency of alleles to transmit together
 - More linkage = less independent assortment
 - Close together ($\theta = 0$) = tightly linked
 - Far apart ($\theta = 0.5$) = 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

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

- 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 Equilibrium

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

- Population frequencies should be:
 - $AB = (0.5) \times (0.9) = 0.45$
 - $aB = (0.5) \times (0.9) = 0.45$
 - $Ab = (0.5) \times (0.1) = 0.05$
 - $ab = (0.5) \times (0.1) = 0.05$
- 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

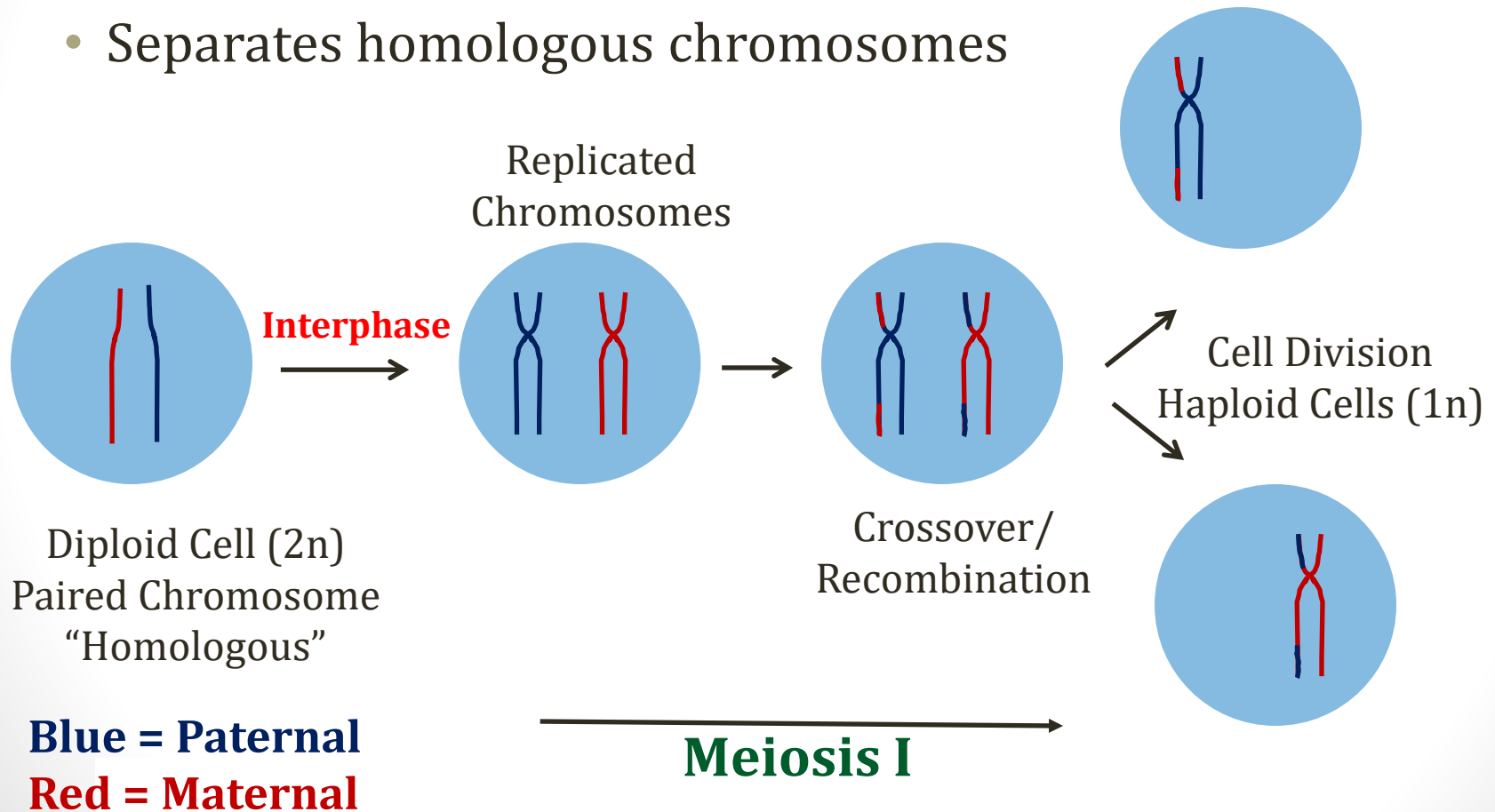
Jason Ryan, MD, MPH

Meiosis

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

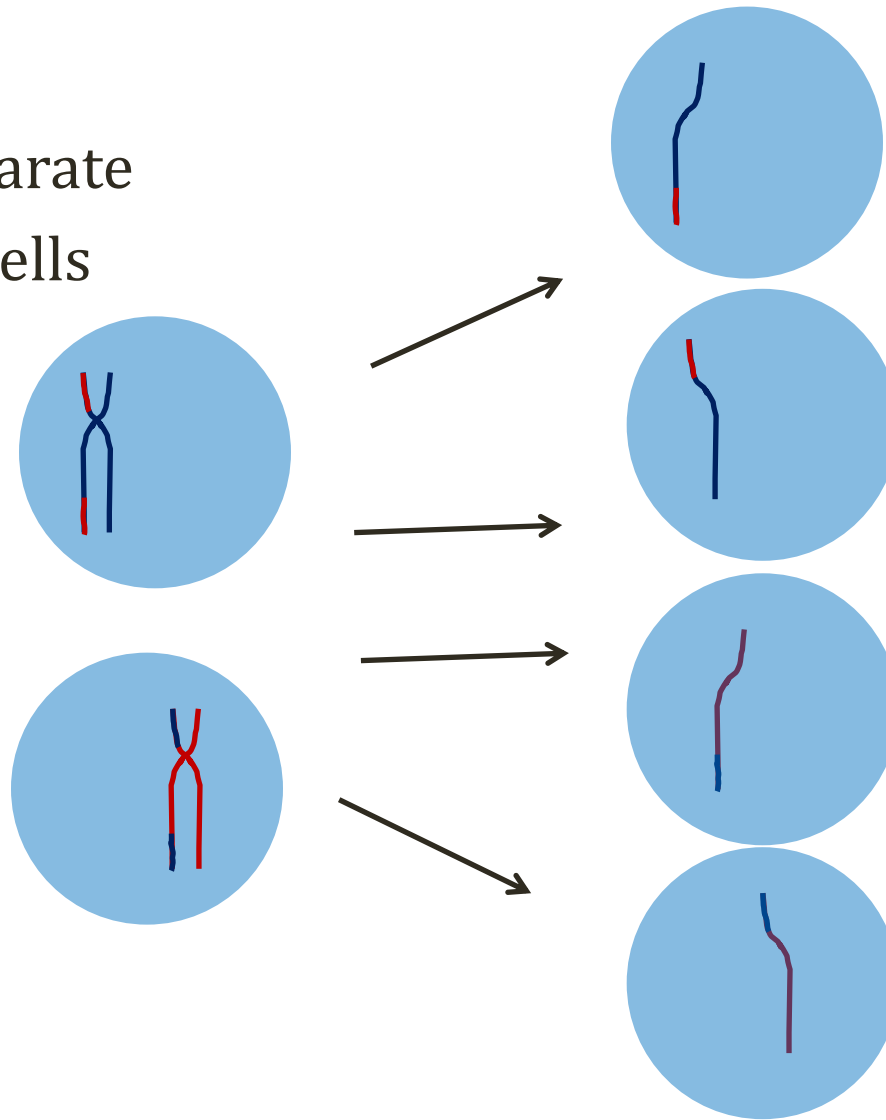
Meiosis I

- Diploid \rightarrow Haploid (“reductive division”)
- Separates homologous chromosomes



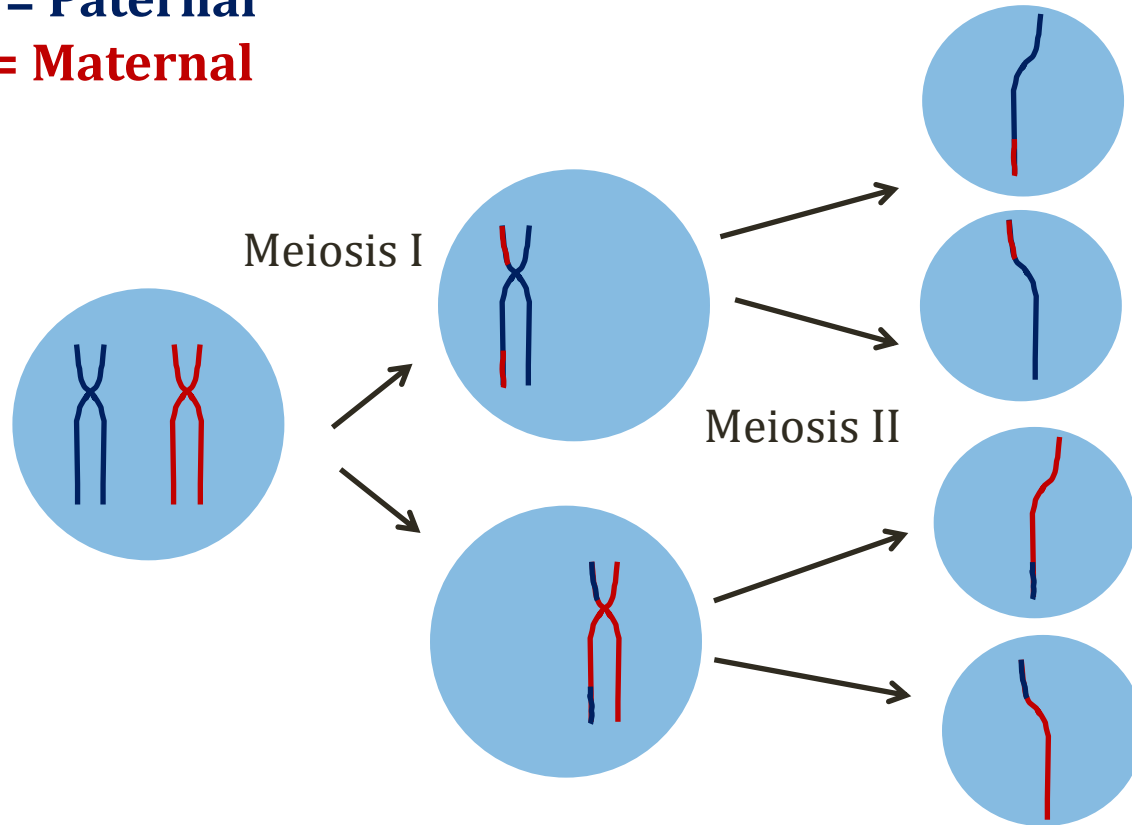
Meiosis II

- Chromatids separate
- Four daughter cells



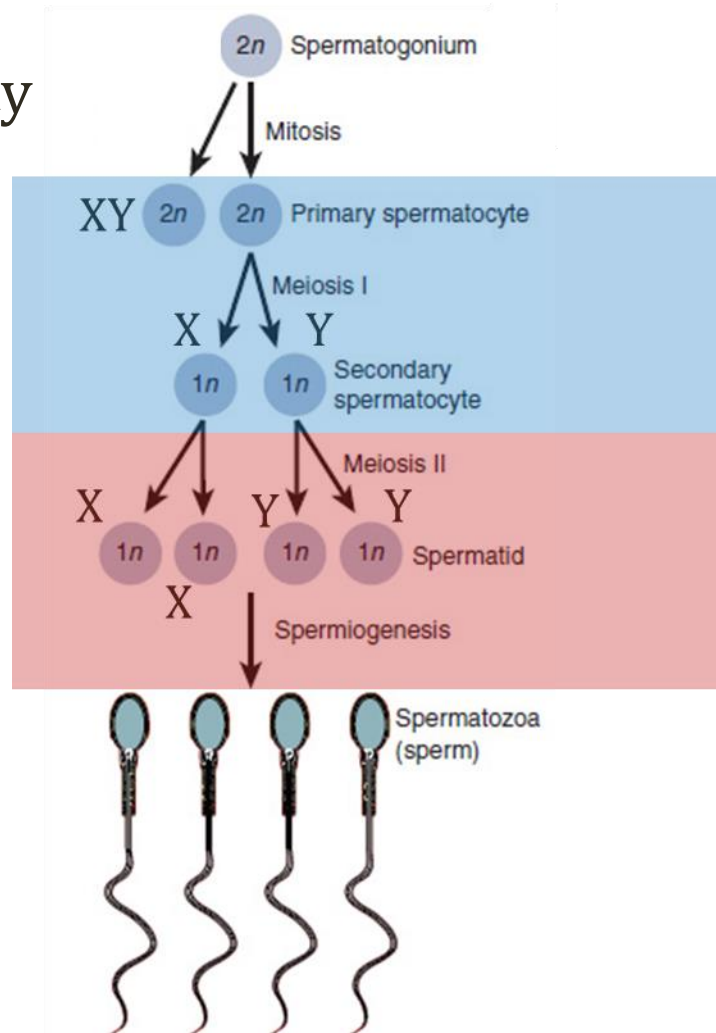
Meiosis

Blue = Paternal
Red = Maternal



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 1 each cycle
 - Some form polar bodies → degenerate
 - Some form secondary oocytes (haploid)
 - **Meiosis II begins → arrests in metaphase**
- Fertilization → completion of meiosis II

Aneuploidy

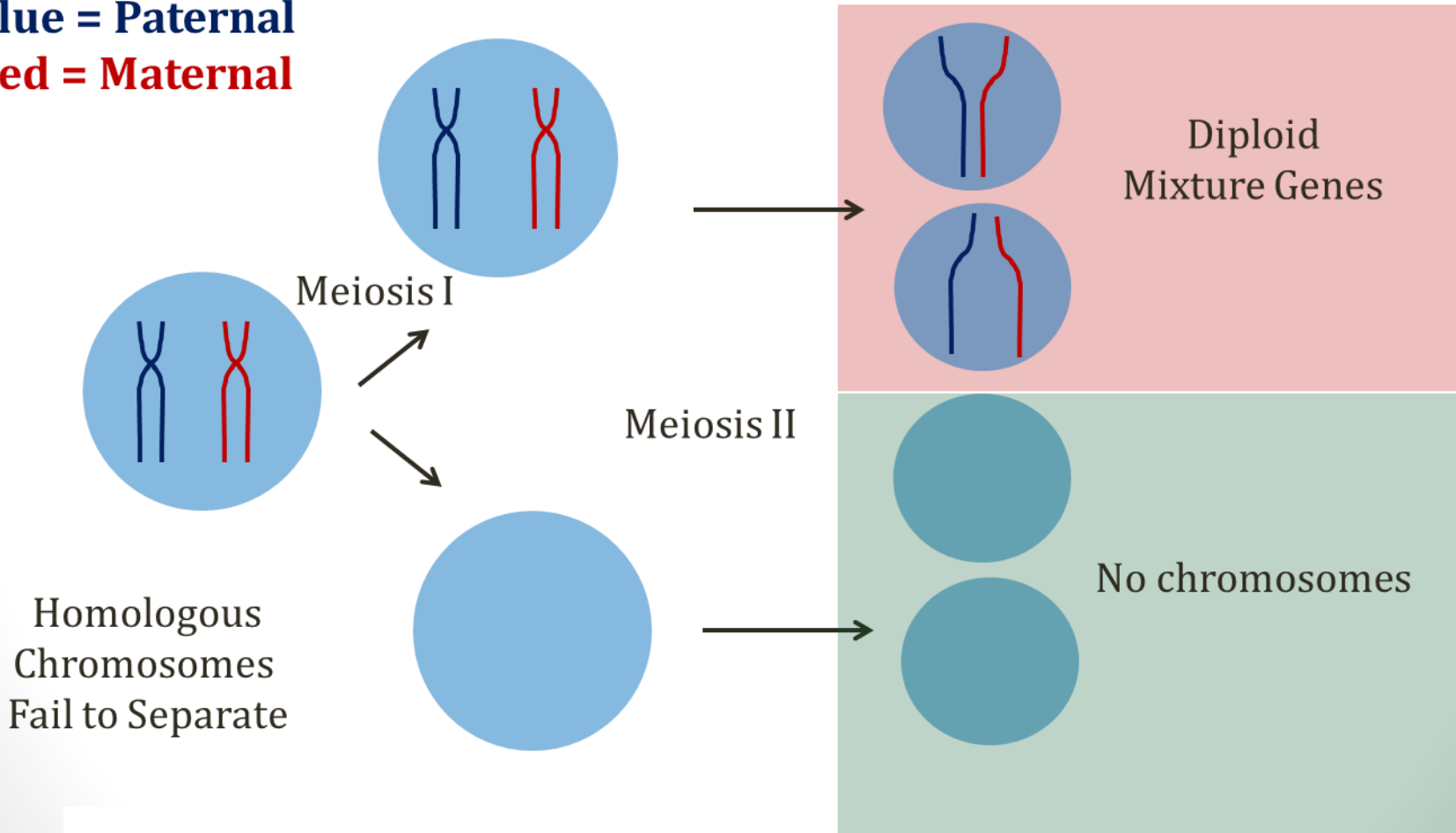
- Abnormal chromosome number
 - Extra or missing chromosome
- Disomy = two copies of a chromosome (normal)
- Monosomy = one copy
- Trisomy = three copies

Meiotic Nondisjunction

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

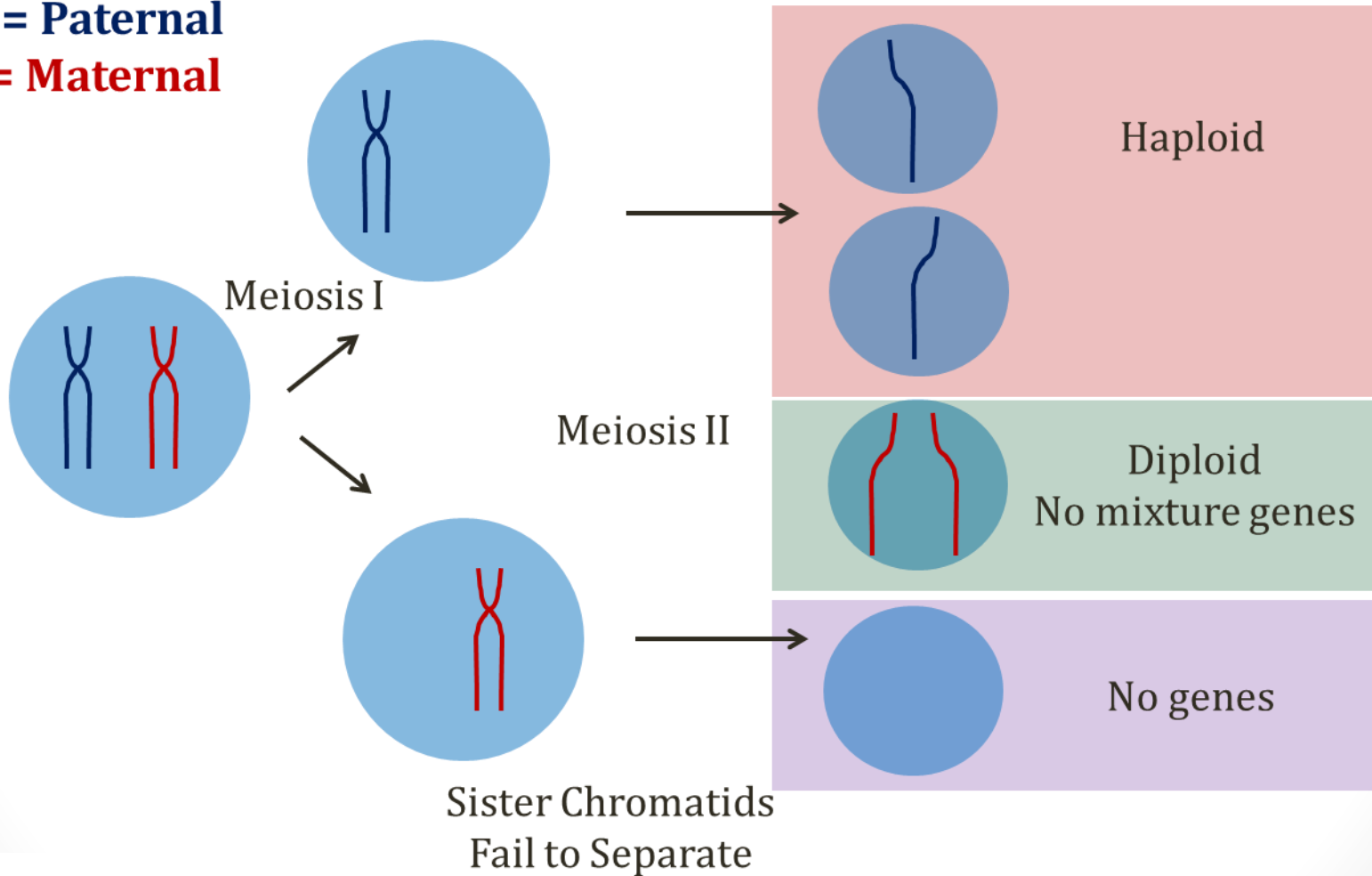
Meiosis I Nondisjunction

Blue = Paternal
Red = Maternal



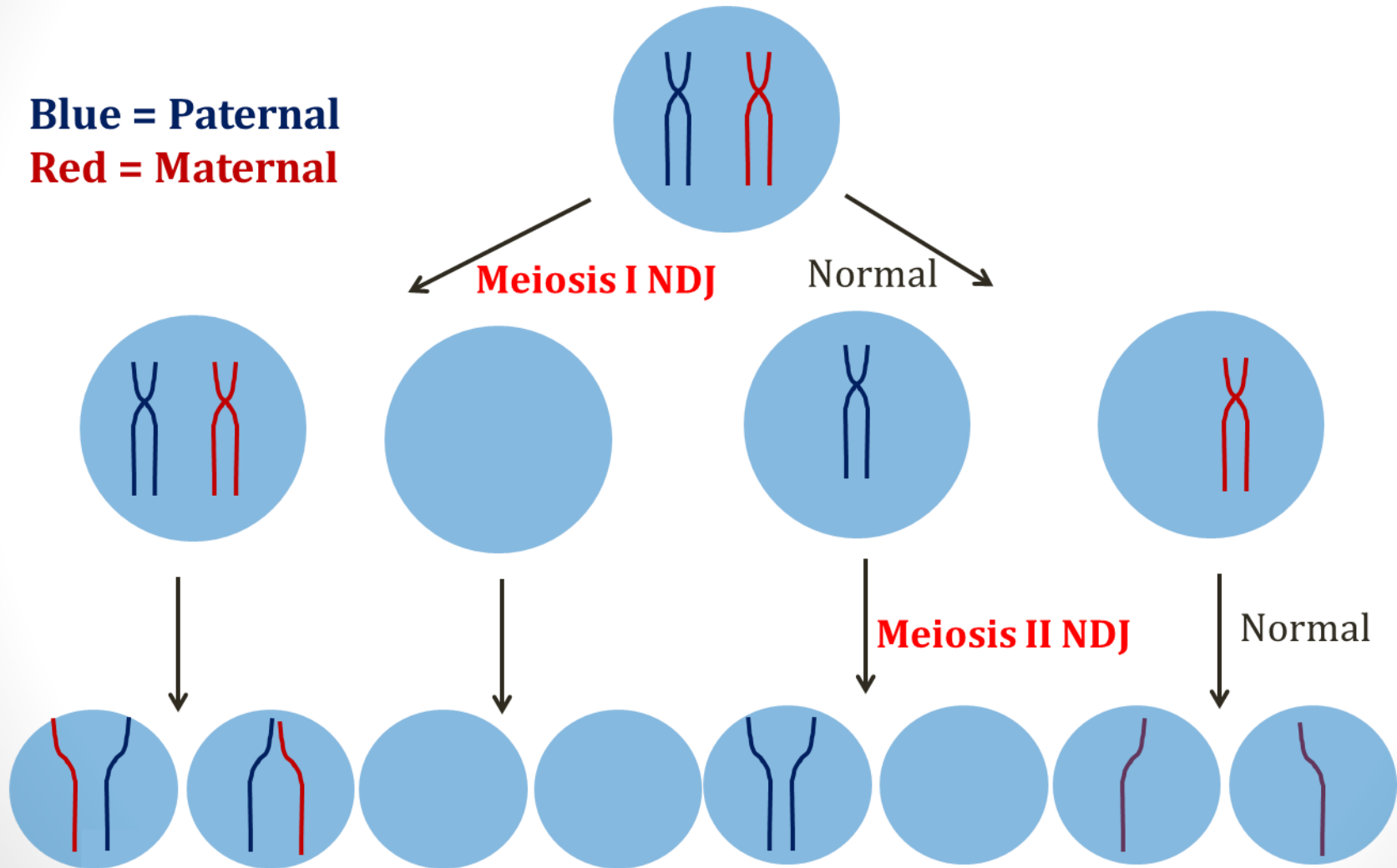
Meiosis II Nondisjunction

Blue = Paternal
Red = Maternal



Nondisjunction

Blue = Paternal
Red = Maternal



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

Trisomy

- Cause of NJD 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

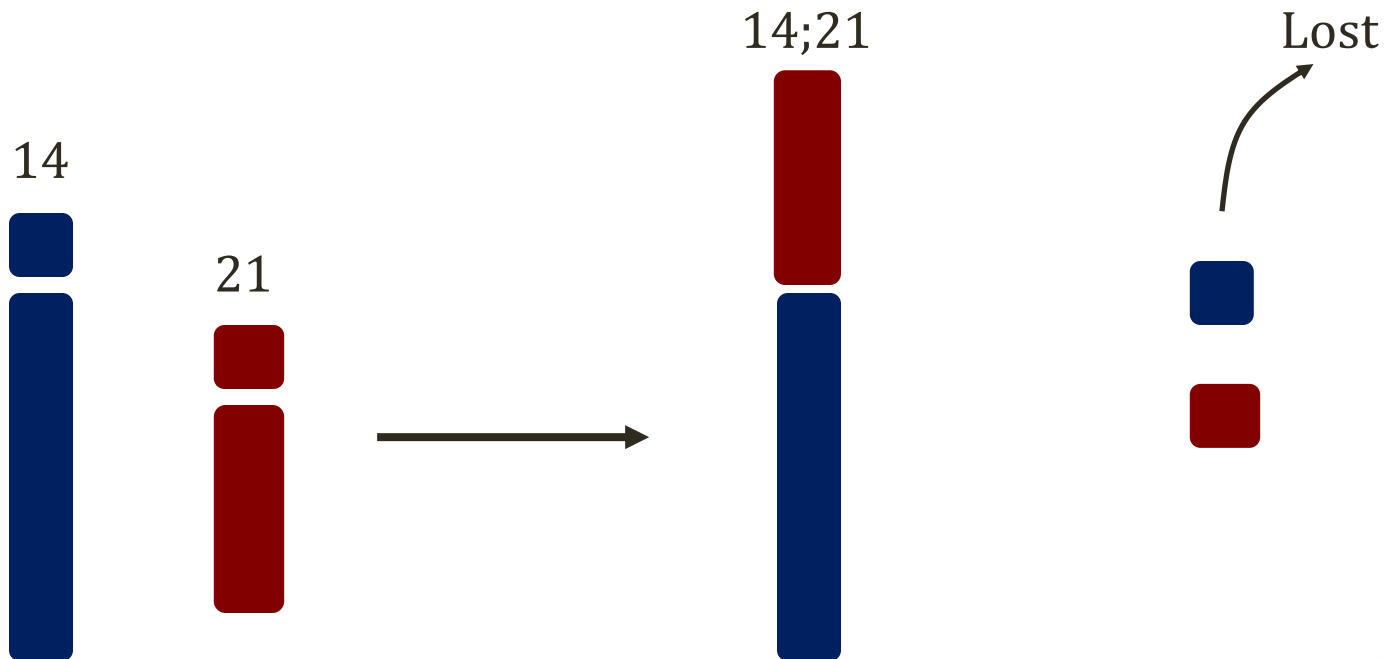
- Child has **two copies** of **one parent's chromosomes**
- No copies of other parent's chromosomes
- Father = **21A** and **21B**; Mother = **21C** and **21D**
- Child **AA** (isodisomy) = Meiosis II error (father)
- Child **CD** (heterodisomy) = Meiosis I error (mother)

Uniparental Disomy

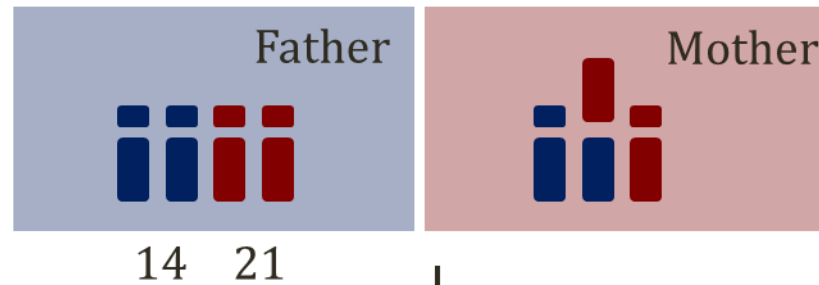
- Child is euploid
 - Normal number of chromosomes
 - No aneuploidy
- Usually normal phenotype
- Can lead to phenotype of **recessive disease**
 - Father = Aa (recessive gene for disease)
 - Child = aa (two copies of a from father)

Robertsonian Translocation

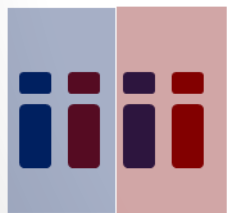
- Fusion of long arms of two chromosomes
- Occurs in **acrocentric** chromosomes
 - Chromosomes with centromere near end (13, 14, 21, 22)



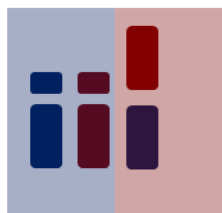
Robertsonian Translocation



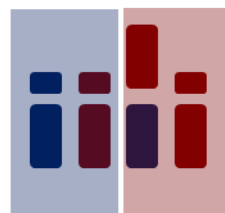
Zygotes



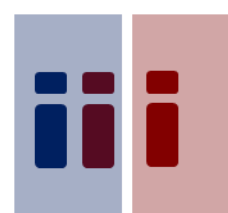
Normal



Carrier



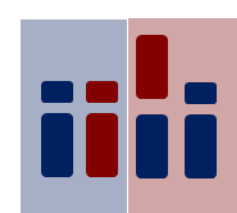
Trisomy 21
(Down)



Monosomy
14



Monosomy
21



Trisomy
14

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



Wikipedia/public domain

Hardy-Weinberg Law

Jason Ryan, MD, MPH

Hardy-Weinberg Law

- Used in studies of populations
- Used to derive **genotypes** from **allele frequencies**
 - Allele: one of two or more alternative forms of **the same** gene
 - Key point: Used to study **single genes** with multiple forms
 - Not used for different genes at different loci/chromosomes

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?

$$p + q = 1$$

Hardy-Weinberg Law

$$\begin{array}{l} p = 0.4 \\ q = 0.6 \end{array}$$

- Frequency of AA = $p^2 = 0.16$
 - Frequency Aa = $2pq = 0.48$
 - Frequency aa = $q^2 = 0.36$
-
- 1.00

$$p^2 + 2pq + q^2 = 1$$

$$p + q = 1$$

Hardy-Weinberg Law

$$\begin{aligned} p &= 0.4 \\ q &= 0.6 \\ p^2 &= 0.16 \\ 2pq &= 0.48 \\ q^2 &= 0.36 \end{aligned}$$

- **$p + q = 1$**
 - $p = 0.4 \rightarrow 40\%$ of GENES in population are A
 - $q = 0.6 \rightarrow 60\%$ of genes in population are a
- **$p^2 + 2pq + q^2 = 1$**
 - $p^2 = 0.16 \rightarrow 16\%$ of INDIVIDUALS in population are AA
 - $2pq = 0.48 \rightarrow 48\%$ of individuals in population are Aa
 - $q^2 = 0.36 \rightarrow 36\%$ of individuals in population are aa

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
 - $q^2 = 1/4500 = 0.0002$
 - $q = \text{SQRT}(0.0002) = 0.015$
- $p + q = 1$
 - $p = 1 - 0.015 = 0.985$
- Carrier frequency = $2pq$
 - $2(0.985)(0.015) = 0.029 = \mathbf{3\%}$
- Very rare diseases p close to 1.0
- Carrier frequency $\approx 2q$

Hardy-Weinberg Law

- Special case: **X linked disease**
- Two male genotypes (X_dY or XY)
- Three female genotypes (XX or X_dX_d or X_dX)

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_dY)
- Males/females have same allele frequencies
 - p males = p females
 - q males = q females

Hardy-Weinberg Law

X-linked Disease

- Among females
 - p^2 = frequency healthy females (XX)
 - $2pq$ = frequency carrier females (X_dX)
 - q^2 = frequency diseased females (X_dX_d)

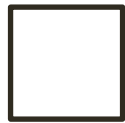
Pedigrees

Jason Ryan, MD, MPH

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

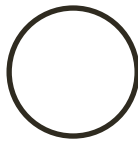
Pedigree Symbols



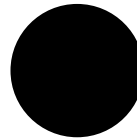
Unaffected
Male



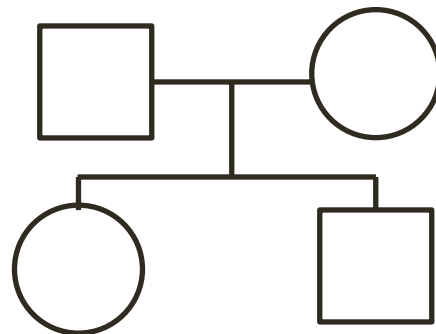
Affected
Male



Unaffected
Female



Affected
Female

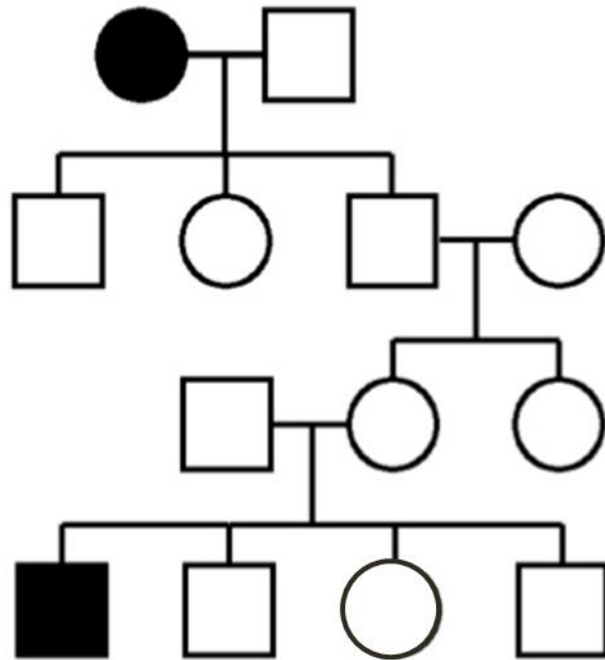


Marriage

Children

Autosomal Recessive

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



Autosomal Recessive

		Mother	
		A	a
Father	A	AA	Aa
	a	aA	aa

- **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

		Mother	
		A	a
Father	A	AA	Aa
	a	aA	aa

- **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

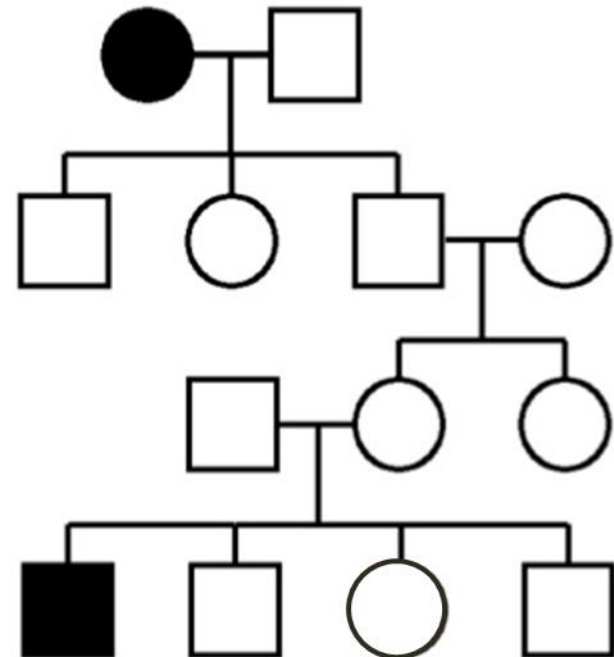
Autosomal Recessive

		Mother (1/50)	
		A	a
Father (1/100)	A	AA	Aa
	a	aA	aa

- 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

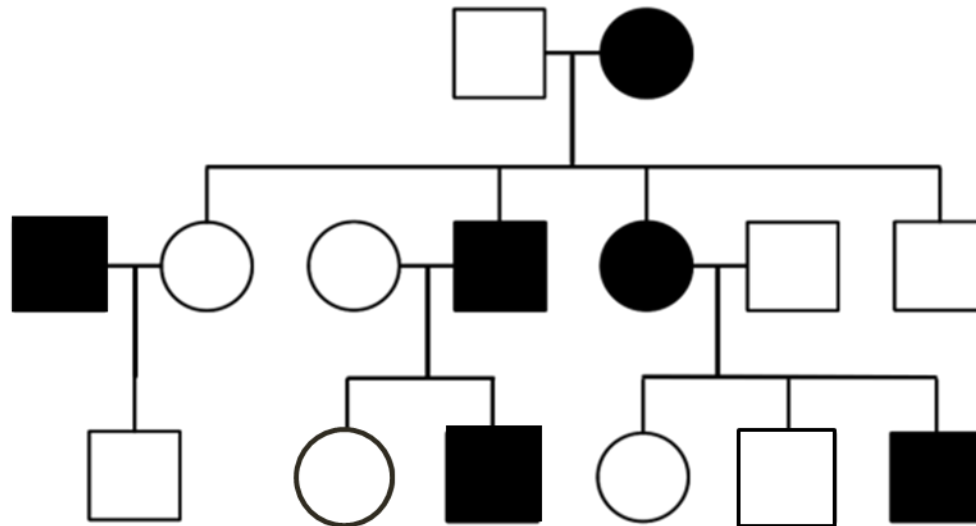


Autosomal Recessive

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

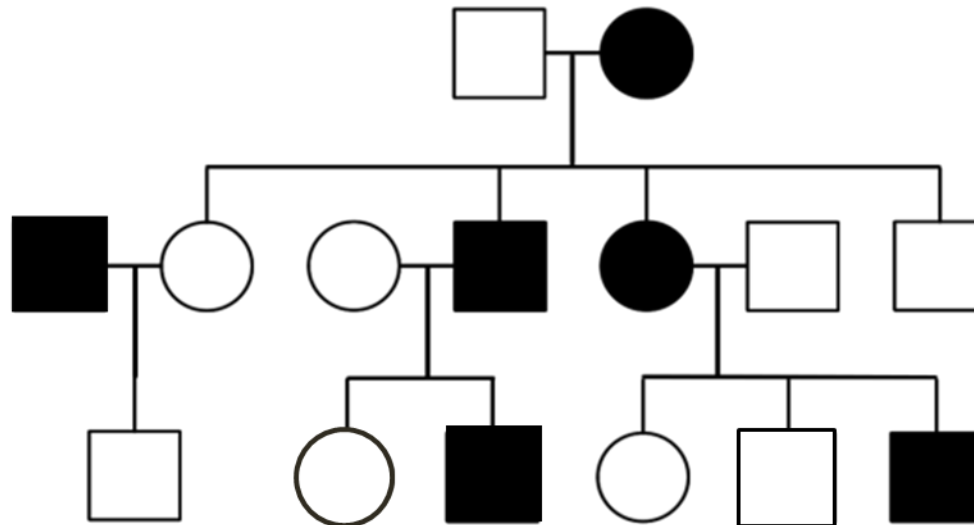
Autosomal Dominant

- 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 \rightarrow 50% offspring with disease
- Male-to-male transmission occurs



Autosomal Dominant

- 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

Incomplete Dominance

Semidominant

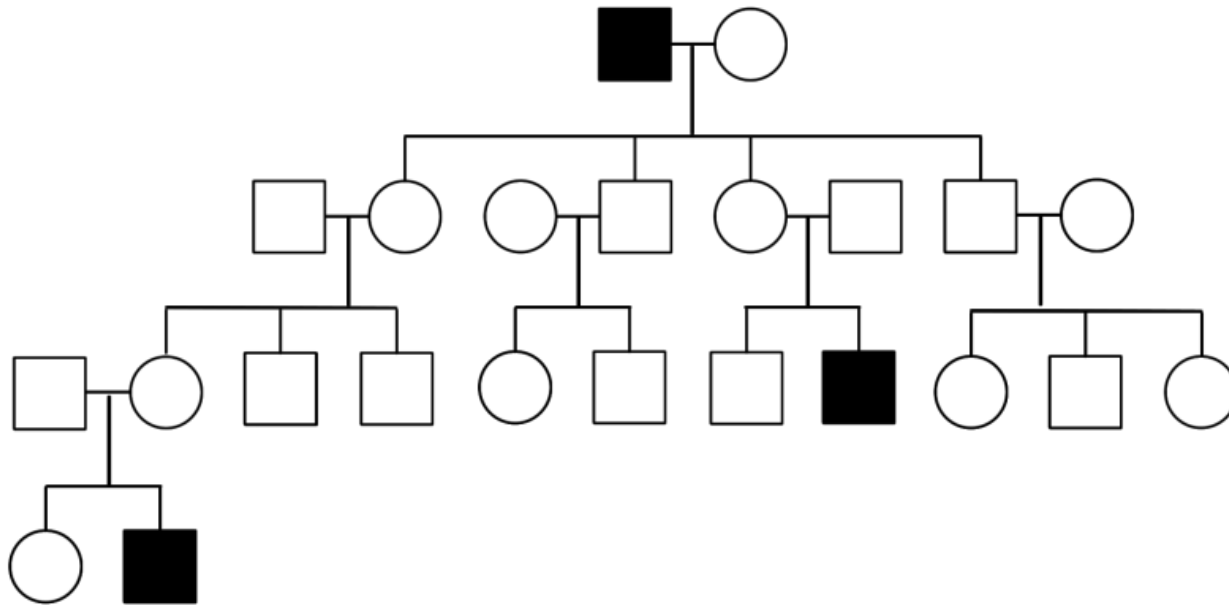
- Classic example: **Achondroplasia**
 - Autosomal dominant disorder of bone growth
 - Heterozygotes (Dd): Dwarfism
 - Homozygotes (DD): Fatal
- **Familial hypercholesterolemia**
 - Heterozygotes: total cholesterol 350–550mg/dL
 - Homozygotes: 650–1000mg/dL

X-linked Disorders

- Disease gene on X chromosome (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

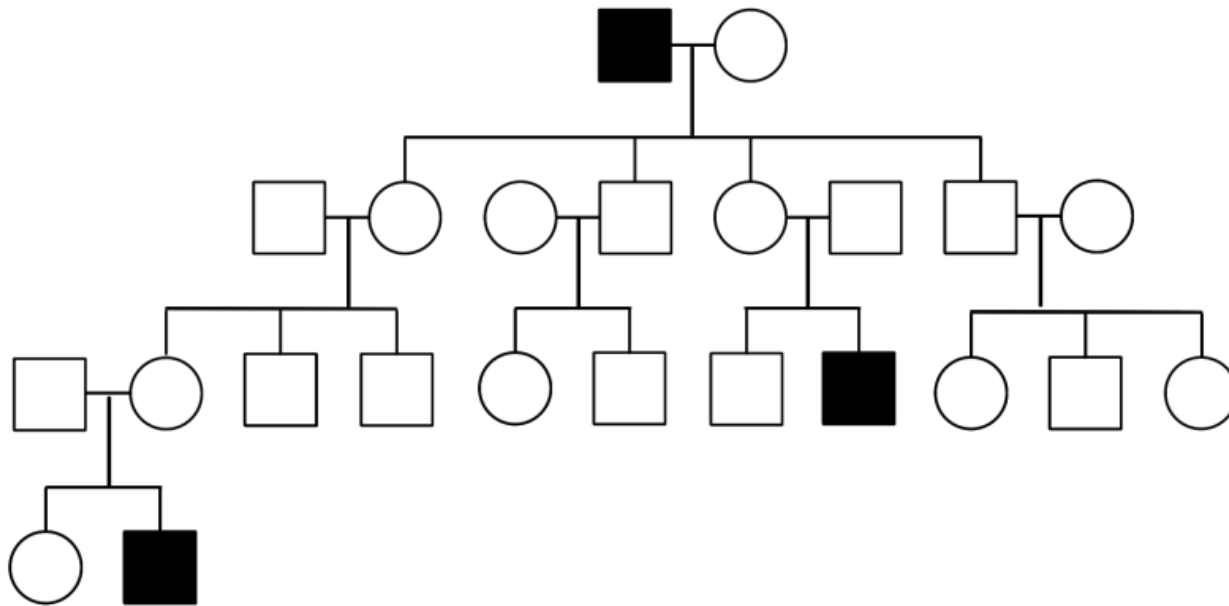
X-linked Recessive

- **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



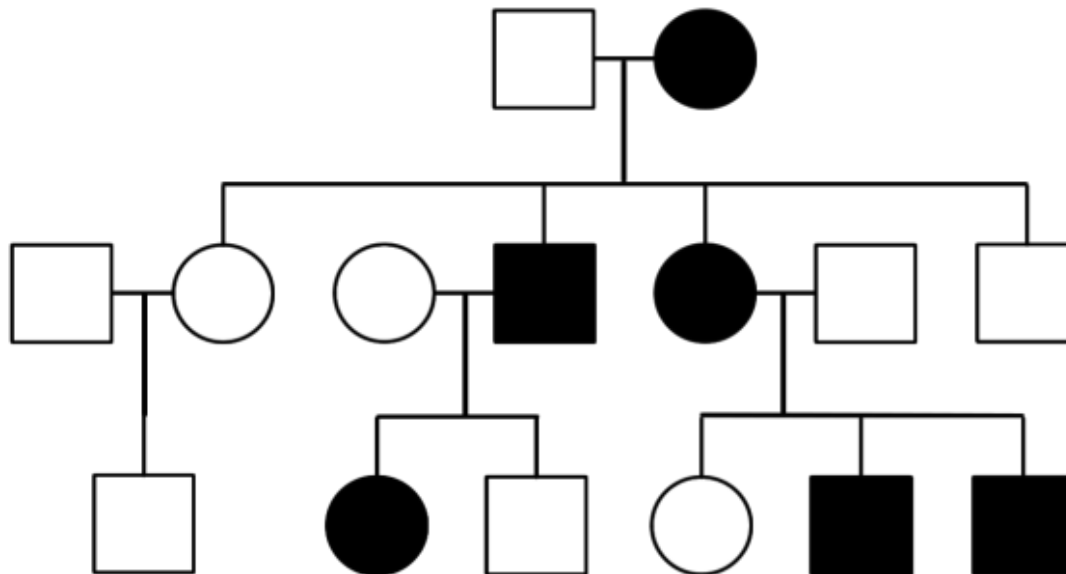
Barr Body

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”**

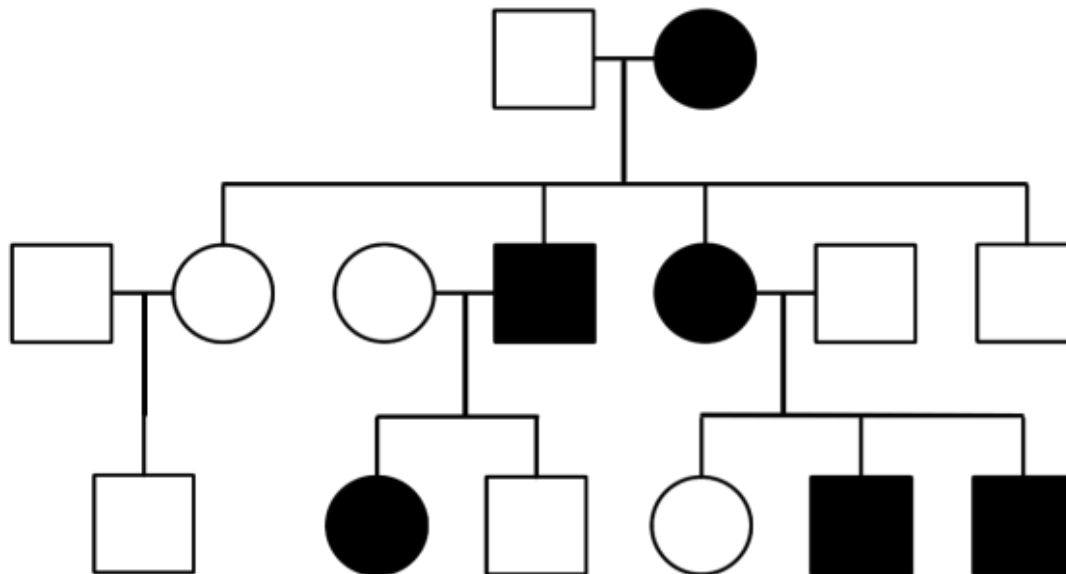
X-linked Dominant

- 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



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 intellectual disability (Down)
 - More severe in males
 - Often features of autism
 - Long, narrow face, large ears and jaw



Peter Saxon/Wikipedia

Mitochondrial Genes

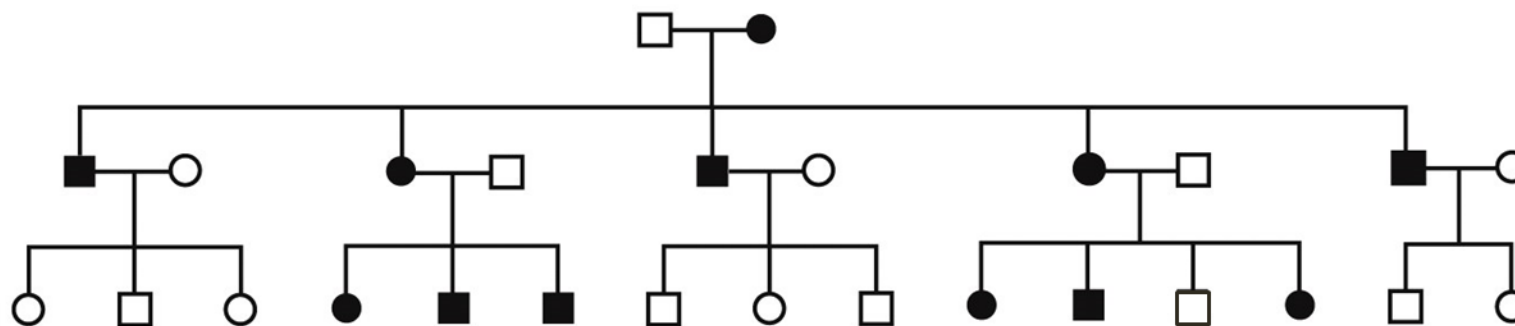
- Each mitochondria contains DNA (mtDNA)
 - Code for mitochondrial proteins
- Organs most affected by gene mutations:
 - CNS
 - Skeletal muscle
 - Rely heavily on aerobic metabolism

Mitochondrial Genes

- **Heteroplasmy**
 - Multiple copies of mtDNA in each mitochondria
 - 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

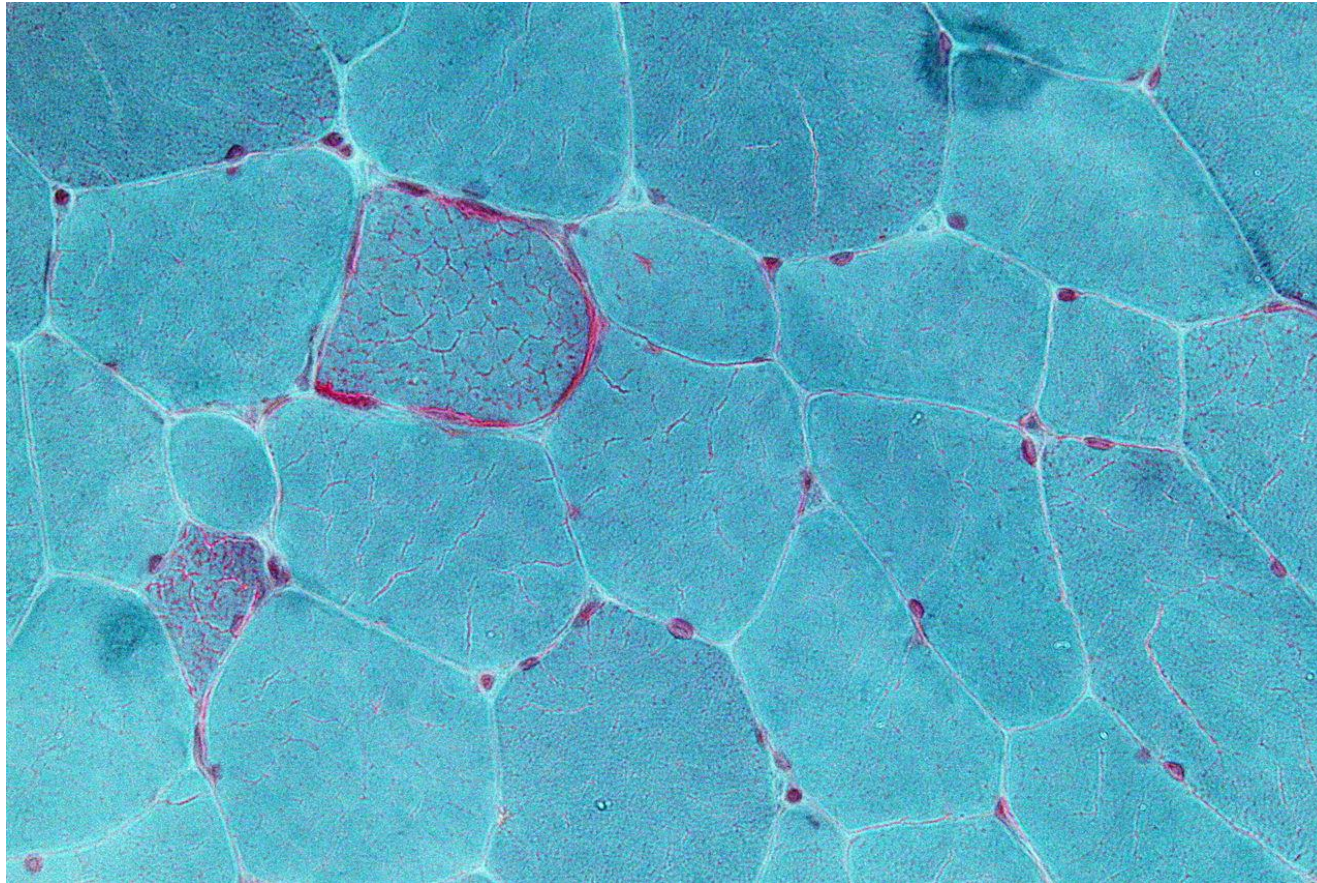
- Mitochondrial DNA inherited from mother
 - Sperm mitochondria eliminated from embryos
- Homoplasmic mothers → all children have mutation
- Heteroplasmic mothers → variable



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

Ragged Red Fibers

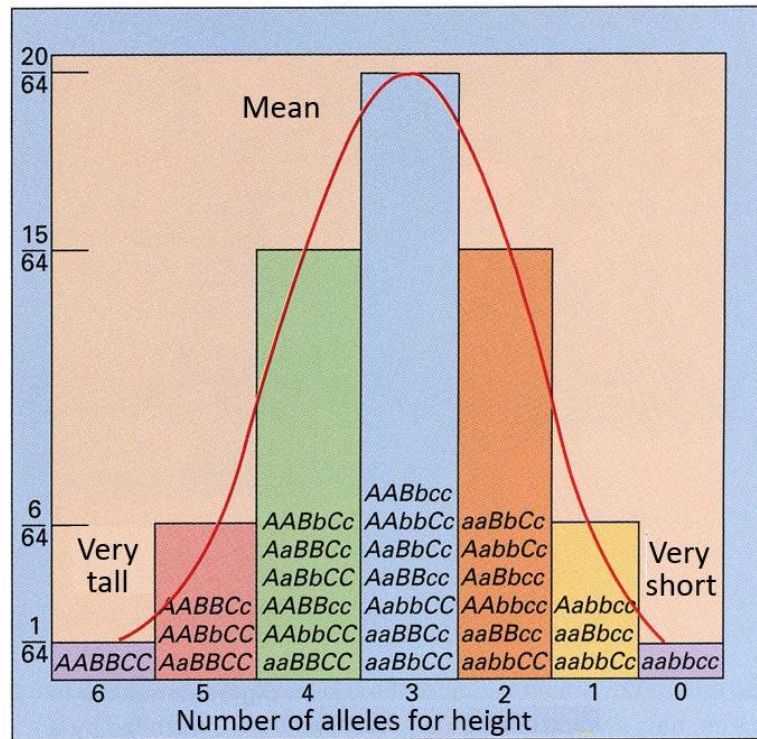
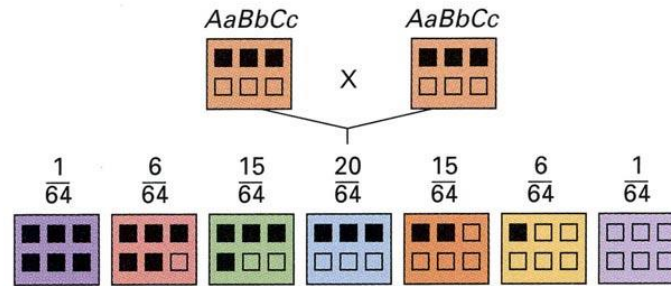


Nephron/Wikipedia

Polygenic Inheritance

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

Polygenic Inheritance



Multifactorial Inheritance

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

Imprinting

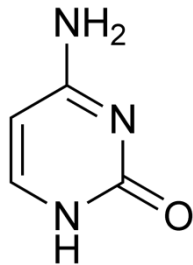
Jason Ryan, MD, MPH

Imprinting

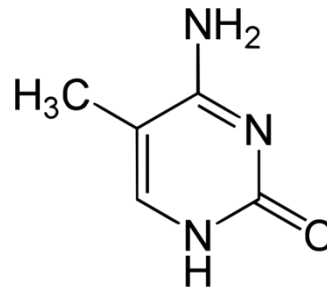
- **Epigenetic** phenomenon
 - Alteration in gene expression
 - Different expression in maternal/paternal genes

Imprinting

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



Cytosine



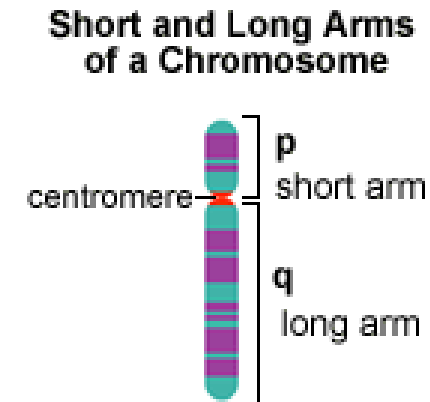
Methylcytosine

Imprinting

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

Imprinting Syndromes

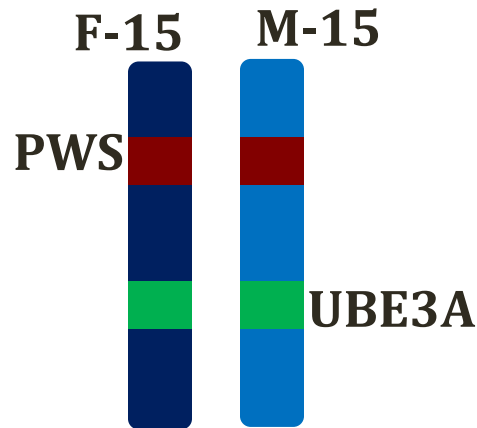
- Prader-Willi and Angelman syndromes
- Both involve abnormal **chromosome 15q11-q13**
 - “PWS/AS region”
- Paternal copy abnormal: Prader-Willi
- Maternal copy abnormal: Angelman
- Differences due to imprinting



Wikipedia/Public Domain

Imprinting Syndromes

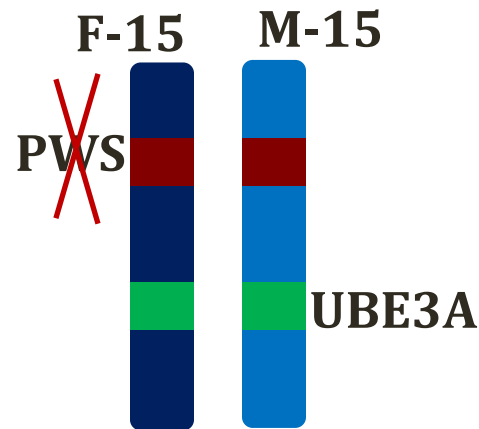
- PWS genes
 - Normally expressed on **paternal** chromosome 15
 - NOT normally expressed on maternal copy
- UBE3A
 - Normally expressed on **maternal** chromosome 15
 - NOT normally expressed on paternal copy



Prader-Willi Syndrome

PWS

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



Prader-Willi Syndrome

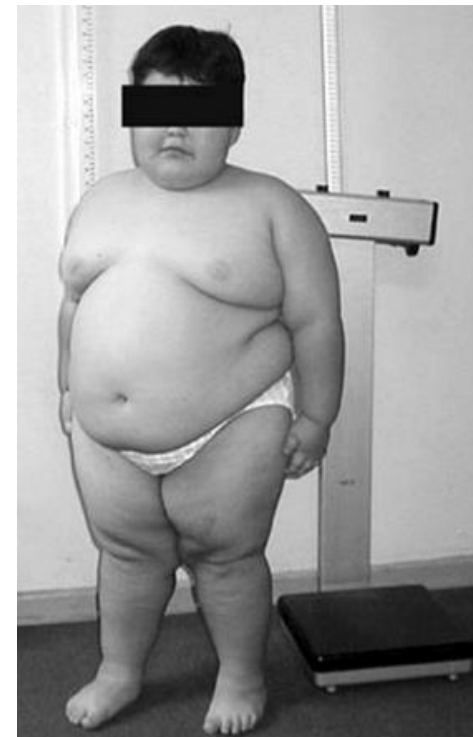
PWS

- ~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

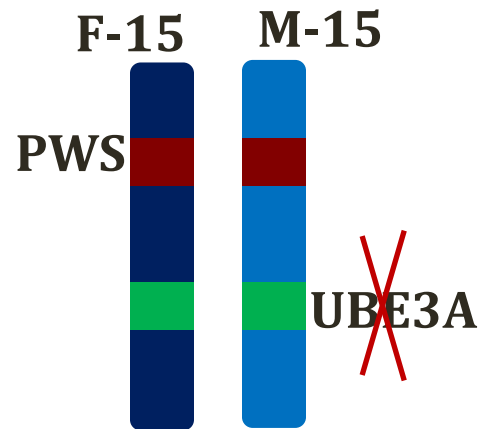
- Most common “syndromic” cause of **obesity**
- Hypotonia
 - Newborn feeding problems
 - Poor suck reflex
 - Delayed milestones
- Hyperphagia and obesity
 - Begins in early childhood
- Intellectual disability (mild)
 - Contrast with AS (severe)
- Hypogonadism
 - Delayed puberty



Fanny Cortés et al. Rev. méd.
Chile v.133 n.1 Santiago ene. 2005

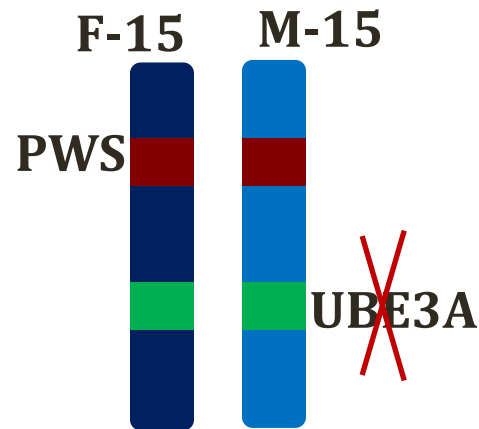
Angelman Syndrome

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



Angelman 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

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

Down Syndrome

Jason Ryan, MD, MPH

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)



Wikipedia/Public Domain

Dysmorphic Features

- 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



Brushfield Spots

- White spots on iris



Erin Ryan/Wikipedia/Public Domain

Dysmorphic Features

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



Wikipedia/Public Domain

Other Physical Features

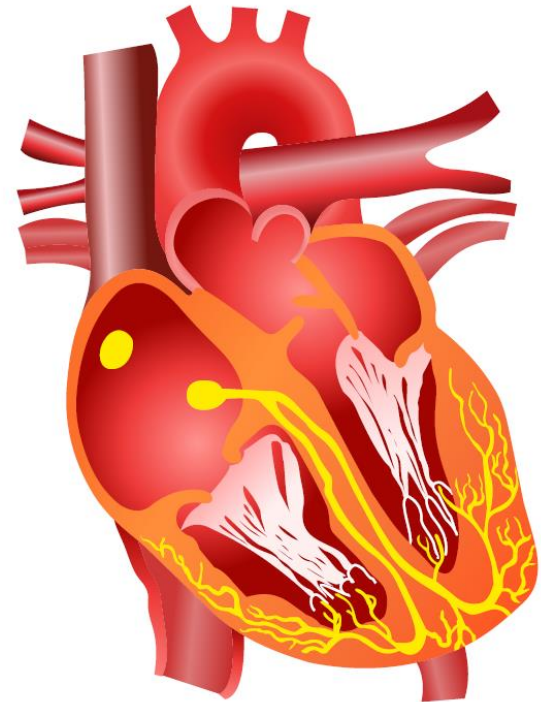
- Hypotonia
 - Often identified at birth
- Short stature

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

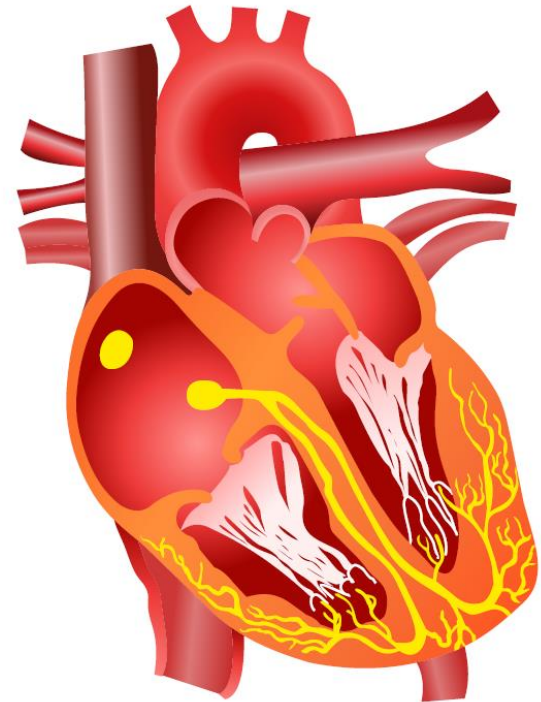
Congenital Heart Disease

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



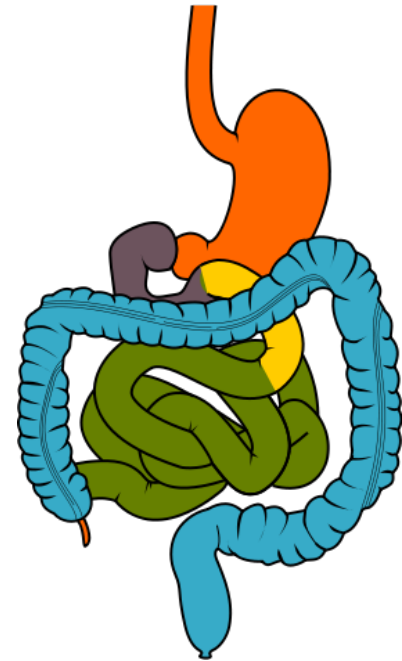
Congenital Heart Disease

- 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



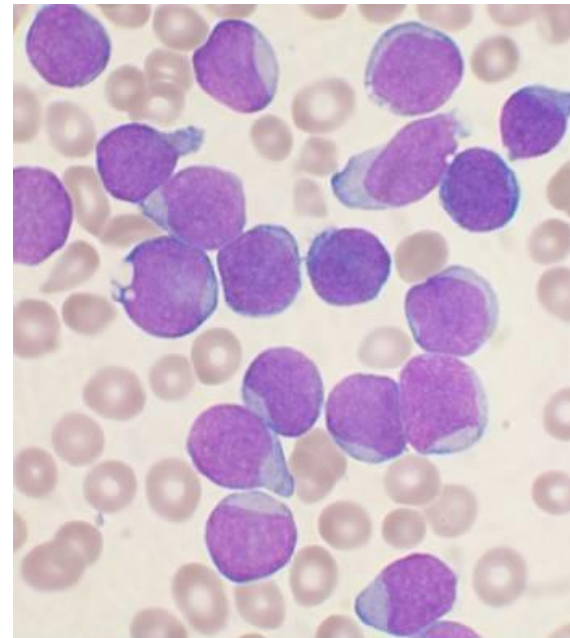
Olek Remesz/Wikipedia

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



VashiDonsk /Wikipedia

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)

Karyogram

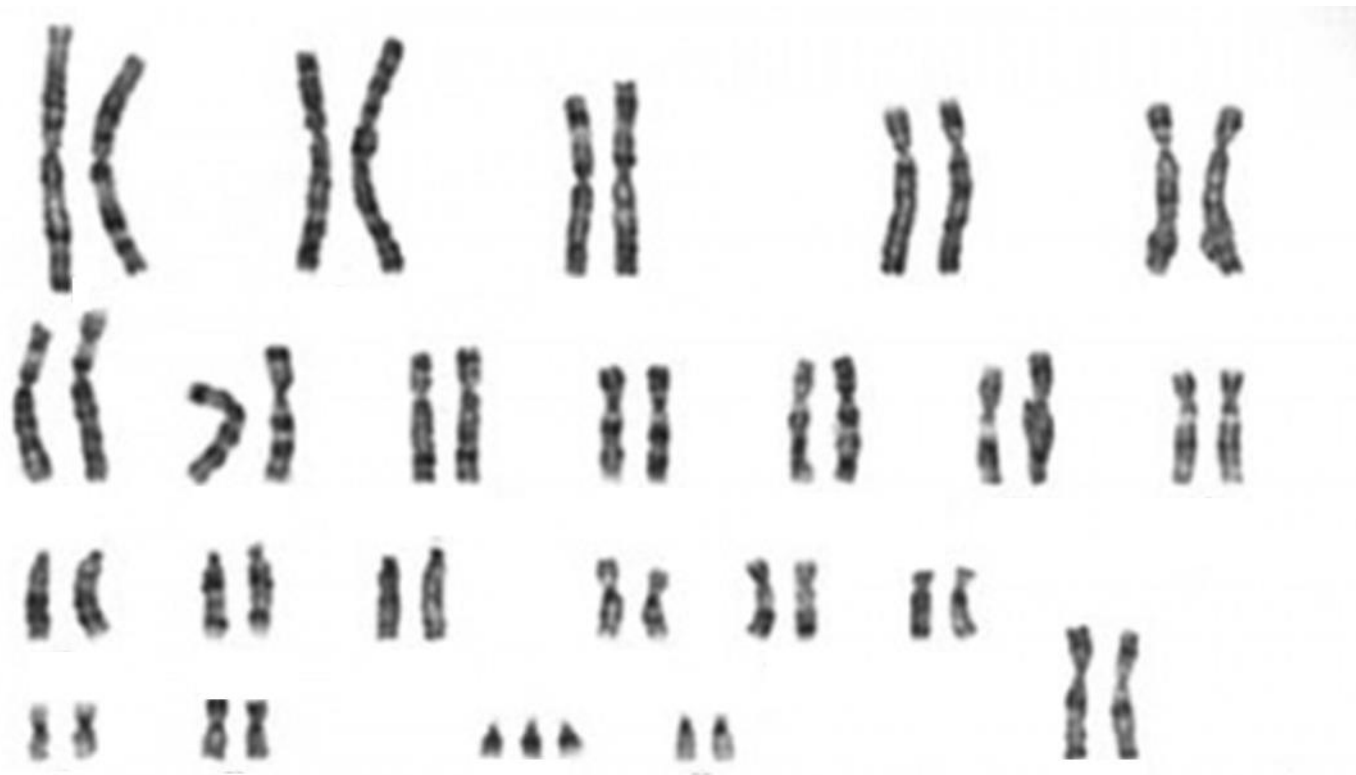
Normal



Wikipedia/public domain

Karyogram

Trisomy



Wikipedia/public domain

Down Syndrome

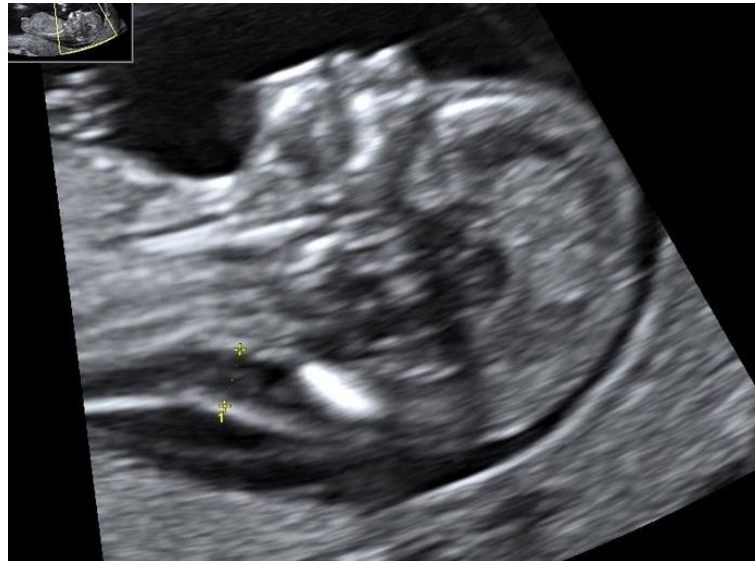
Prenatal Screening

- Noninvasive tests
 - Ultrasound
 - Maternal serum testing

Down Syndrome

First Trimester Screening

- Fetal ultrasound
- Small, poorly-formed **nasal bones**
- **Nuchal translucency**
 - Fluid under at back of neck



Wolfgang Moroder/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

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
- “Quad screen”

Trisomy

Jason Ryan, MD, MPH

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



Bobjgalindo/Wikipedia

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

First Trimester

	Down	Edward
PAPP-A	↓	↓
B-hCG	↑	↓

Edward Syndrome

Screening

Second Trimester

	Down	Edward
AFP	↓	↓
Estriol	↓	↓
B-hCG	↑	↓
Inhibin-A	↑	↓

Patau Syndrome

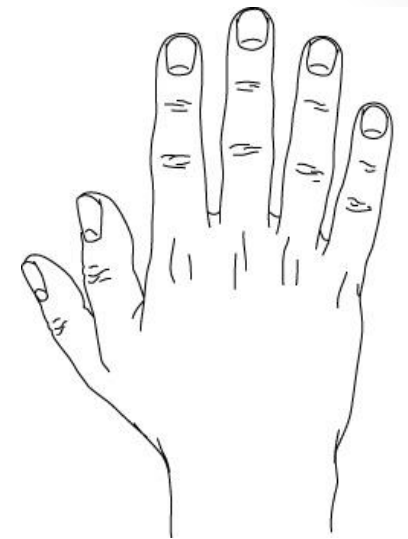
Trisomy 13

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

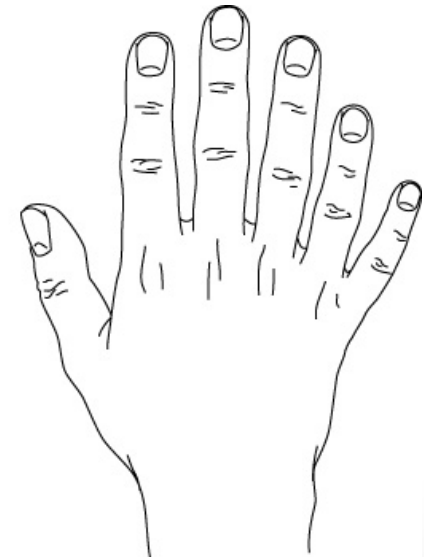
Patau Syndrome

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)



Pre-axial



Post-axial

Patau Syndrome

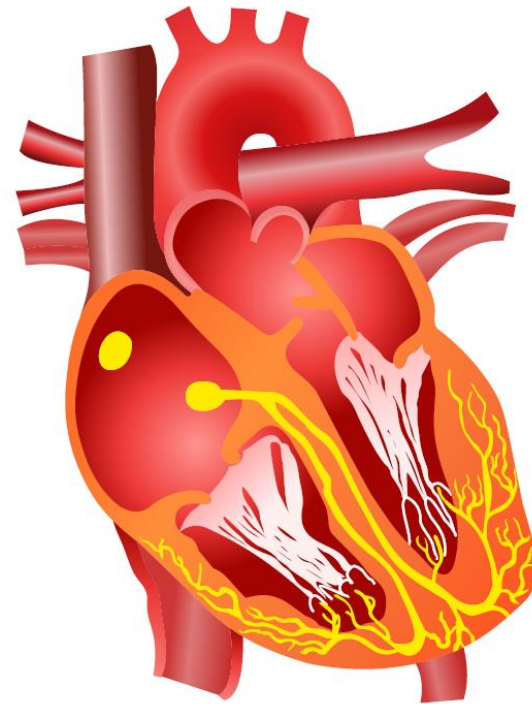
Trisomy 13

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

Patau Syndrome

Trisomy 13

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



Patau Syndrome

Trisomy 13

- 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

	Down	Edward	Patau
PAPP-A	↓	↓	↓
B-hCG	↑	↓	↓

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

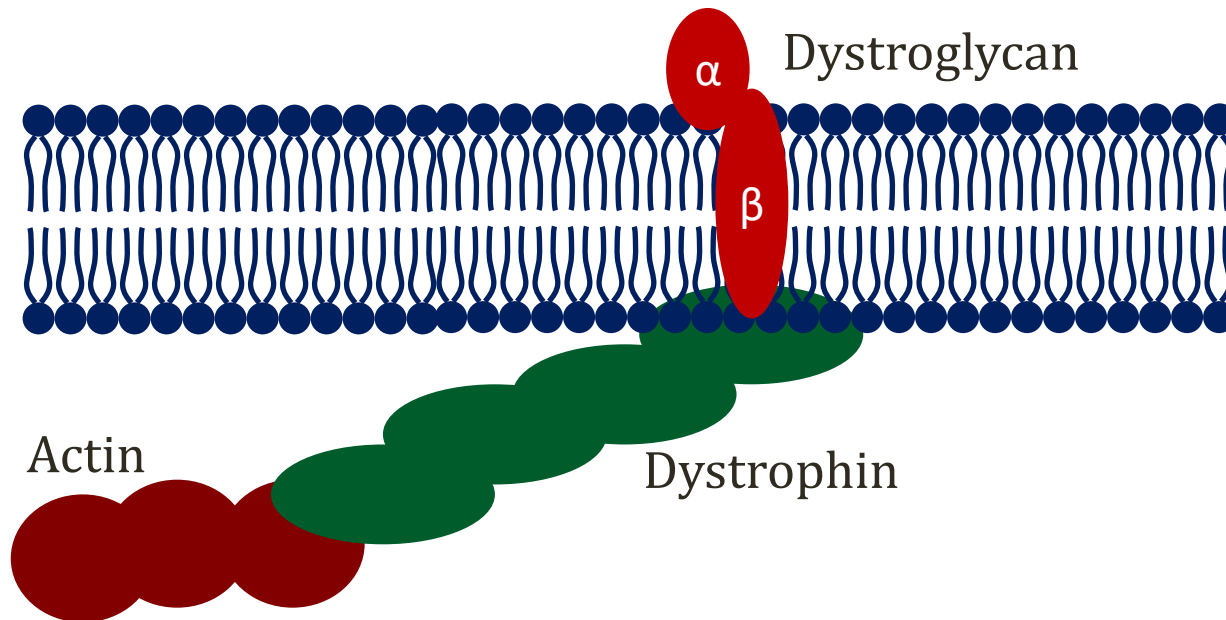
DMD

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**

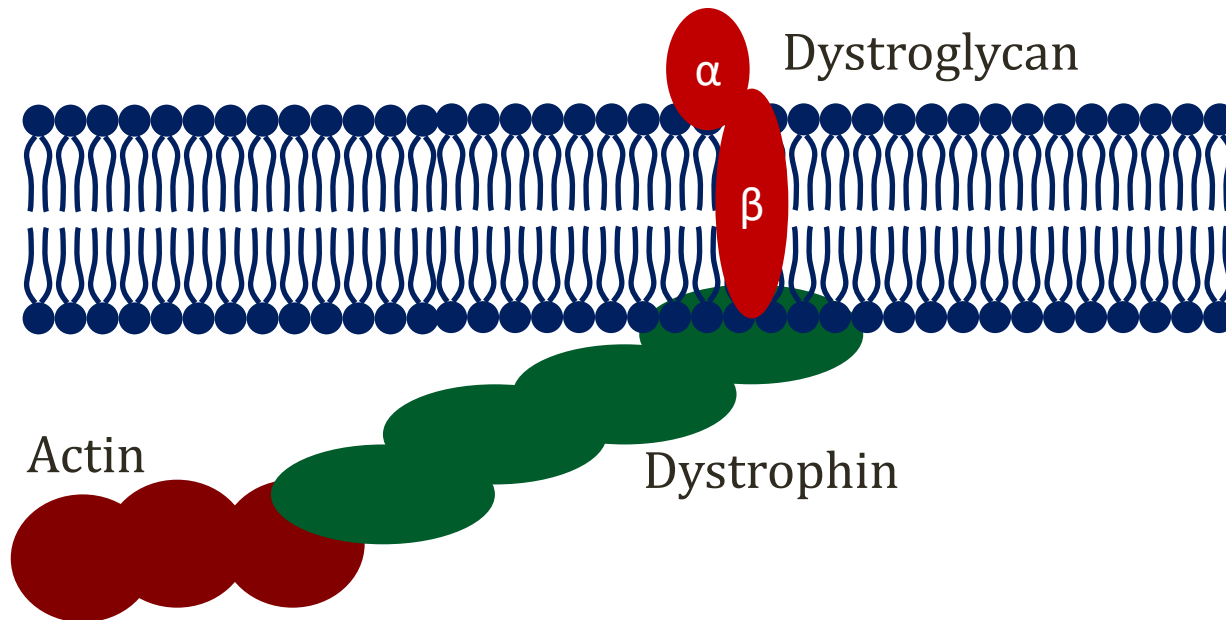
Dystrophin

- 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

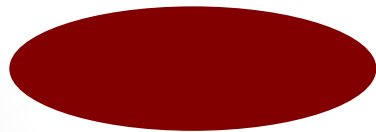


Dystrophin Gene Mutations

- 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

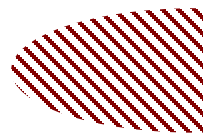
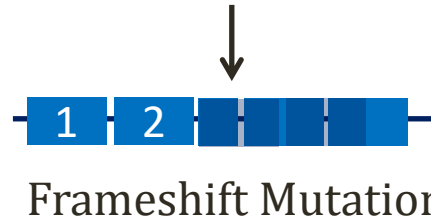
Dystrophin Gene Mutations

Normal



Normal Protein

Duchenne



Absent or
Truncated
Protein

Becker



Abnormal Protein

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

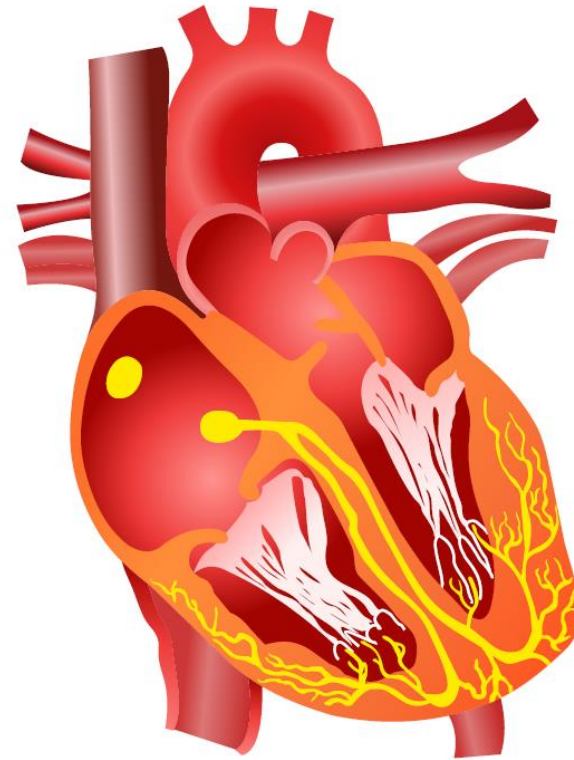
Duchenne Muscular Dystrophy

- 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

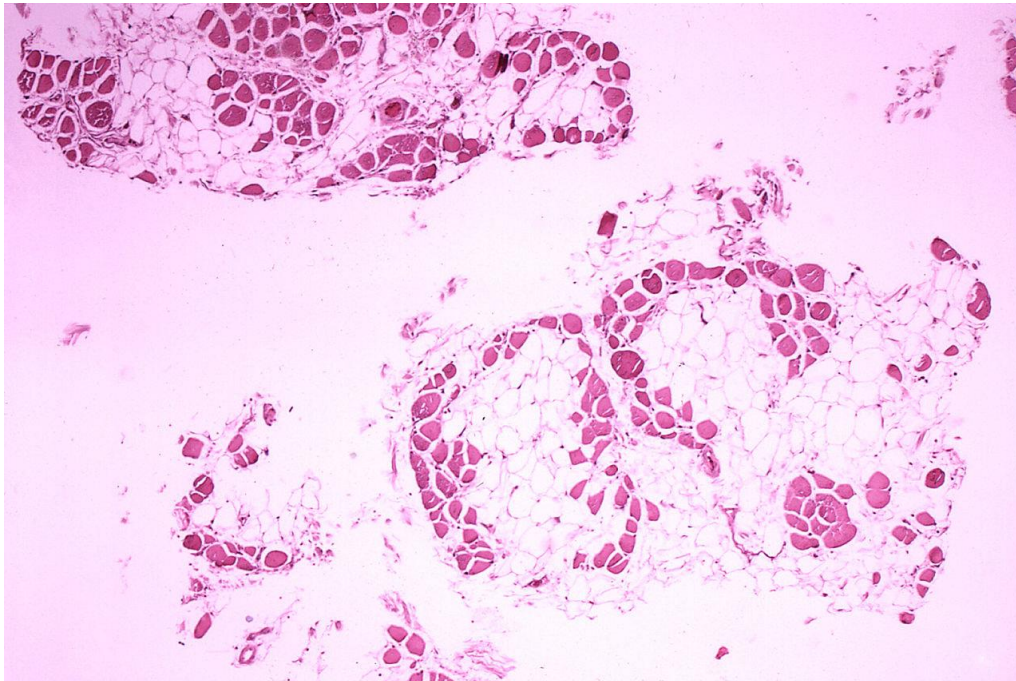
- **Cardiomyopathy**
 - Depressed LVEF
 - Systolic heart failure
 - Myocardial fibrosis
- Conduction abnormalities
 - AV block
 - Arrhythmias



DMD

Duchenne Muscular Dystrophy

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



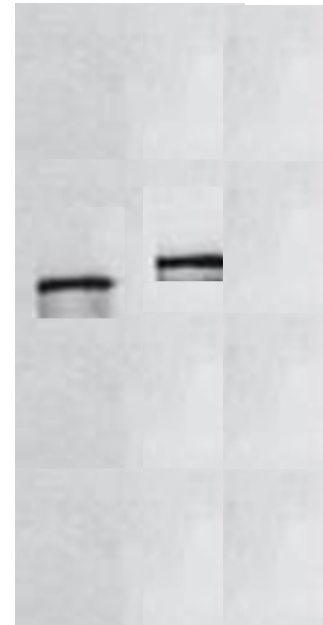
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DMD

Duchenne Muscular Dystrophy

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

Becker Normal Duchenne



DMD

Duchenne Muscular Dystrophy

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

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

BMD

Becker Muscular Dystrophy

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

Trinucleotide Repeat Disorders

Jason Ryan, MD, MPH

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



Peter Saxon/Wikipedia

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

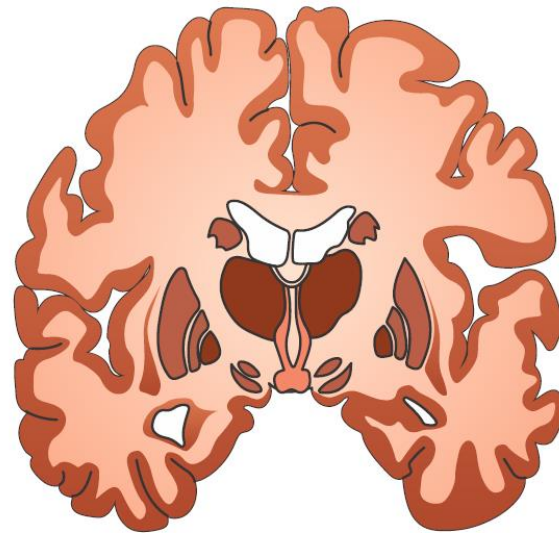
- Begins in adolescence with progressive symptoms
- Cerebellar and spinal cord degeneration
 - Loss of balance
 - Weakness
- Associated with **hypertrophic cardiomyopathy**
- Physical deformities:
 - Kyphoscoliosis
 - Foot abnormalities

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 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)

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



Herbert L. Fred, MD, Hendrik A. van Dijk

Myotonic Dystrophy

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



Herbert L. Fred, MD, Hendrik A. van Dijk

Myotonic Dystrophy

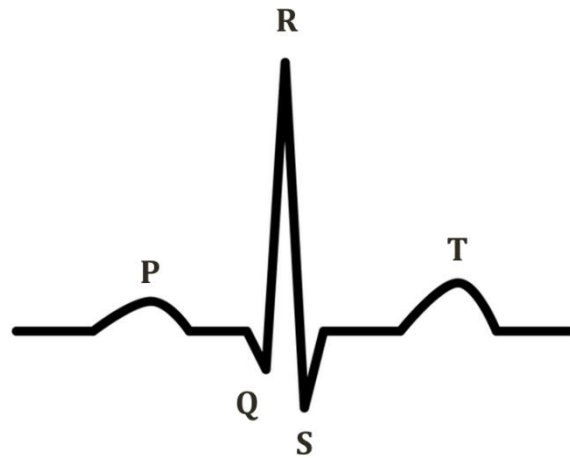
Endocrine Involvement

- 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

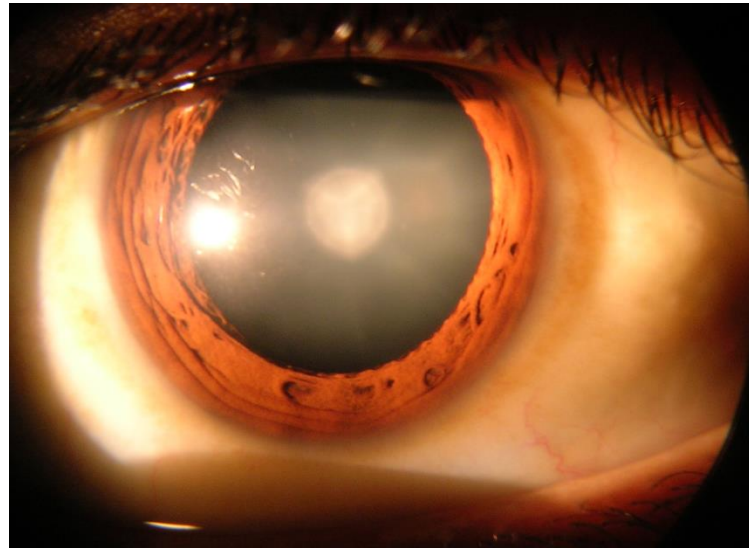


Image courtesy of Rakesh Ahuja, MD

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

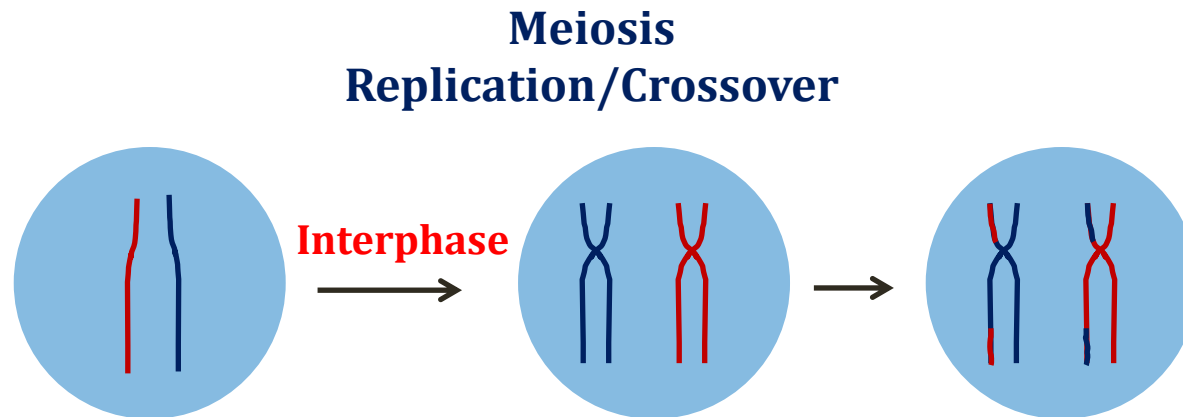
Jason Ryan, MD, MPH

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

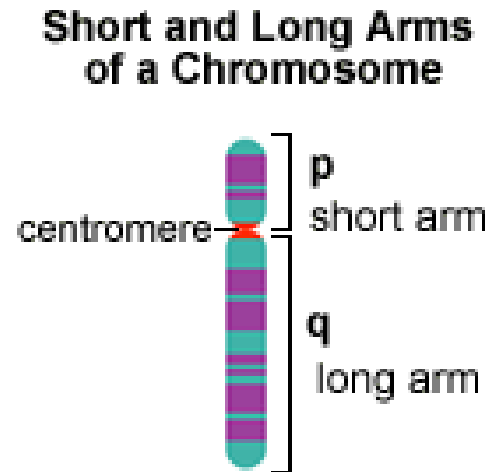


Deletion Syndromes

- 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
 - “5p- syndrome”



Wikipedia/Public Domain

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

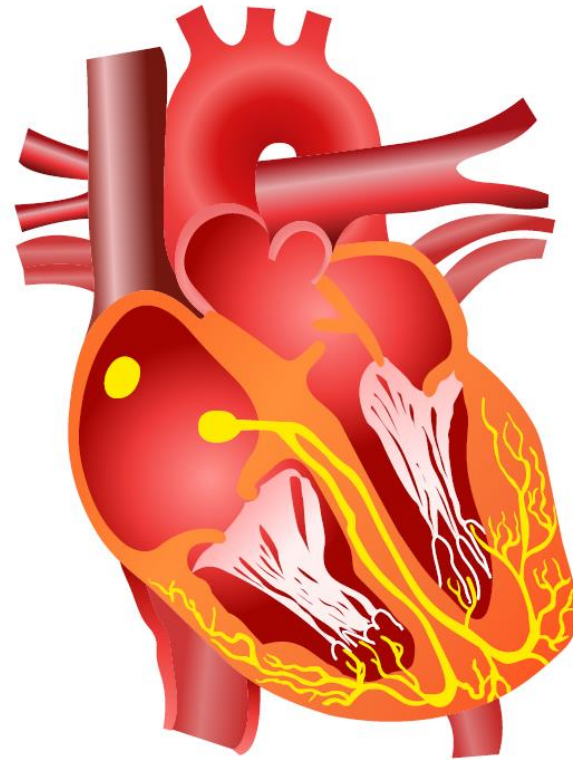


Paola Cerruti Mainardi.

Cri-du-chat Syndrome

- **Congenital heart defects**

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

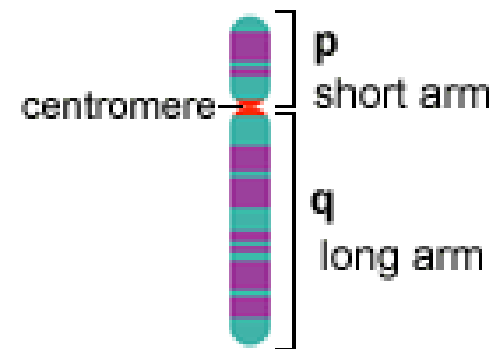


Williams Syndrome

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”

Short and Long Arms of a Chromosome



Wikipedia/Public Domain

Williams Syndrome

Williams-Beuren syndrome

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

Williams Syndrome

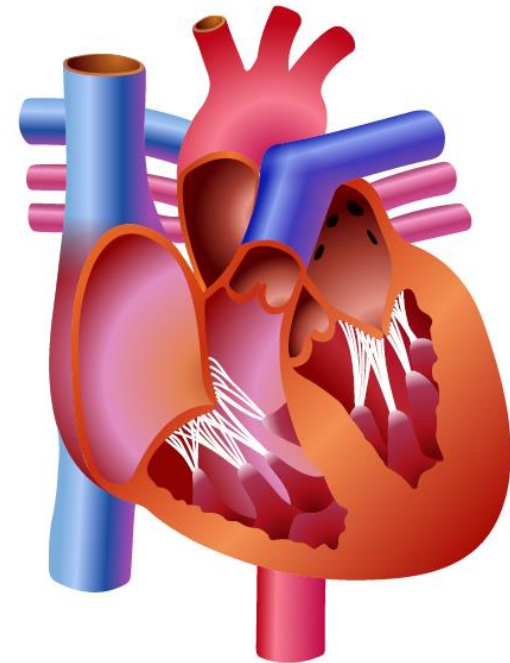
Williams-Beuren syndrome

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

Williams Syndrome

Vascular Manifestations

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



Williams Syndrome

Hypercalcemia

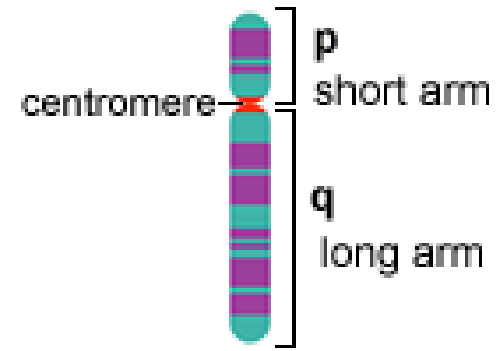
- **Higher calcium** than general pediatric population
 - Evidence of ↑ vitamin D levels and ↑ vitamin D sensitivity
- Usually mild to moderate
- Does not usually cause symptoms
- May lead to constipation

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

Short and Long Arms of a Chromosome



Wikipedia/Public Domain

Klinefelter and Turner Syndromes

Jason Ryan, MD, MPH

Klinefelter and Turner

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

Karyotype

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

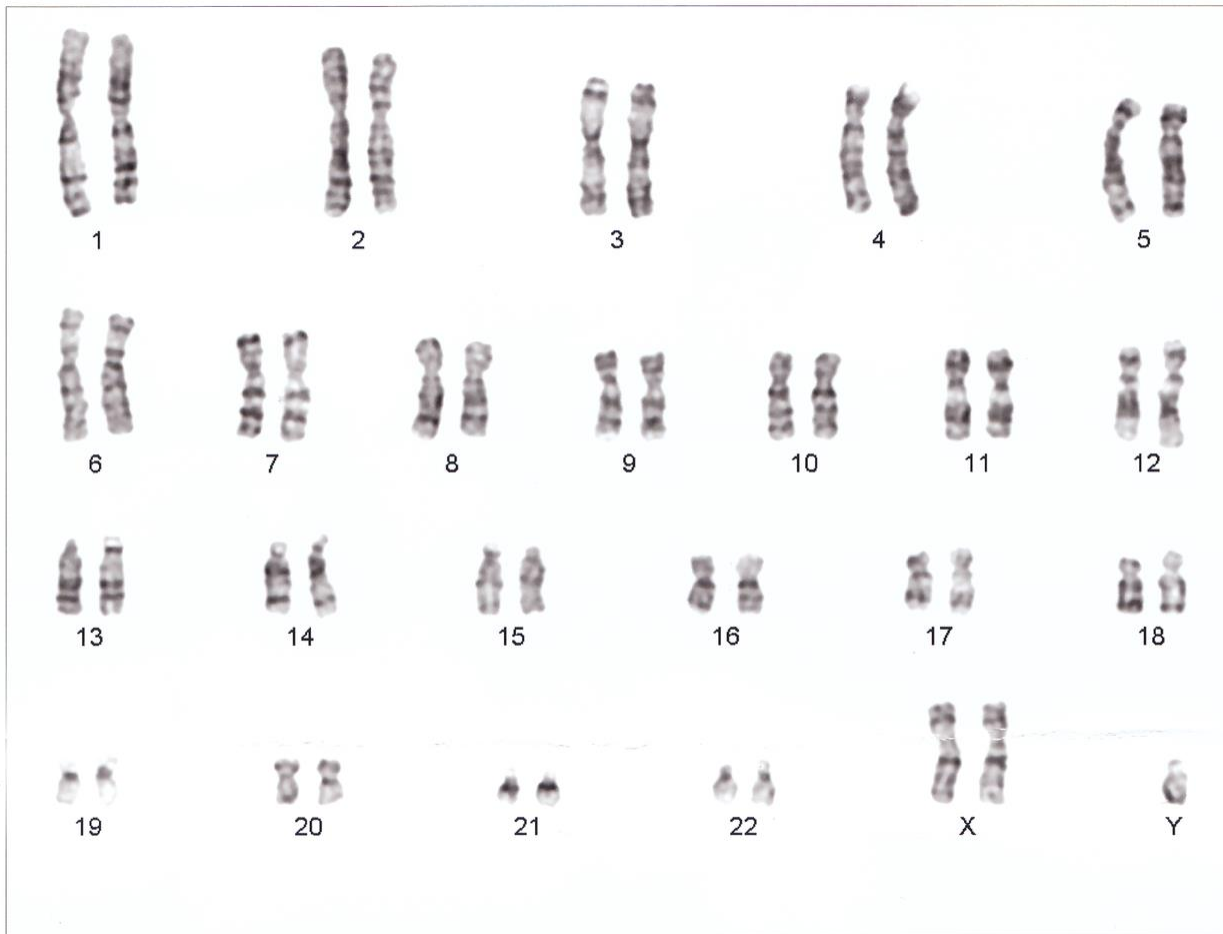


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Klinefelter Syndrome

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

Klinefelter Syndrome



核型 : 47, XXY

Cell No. : 003

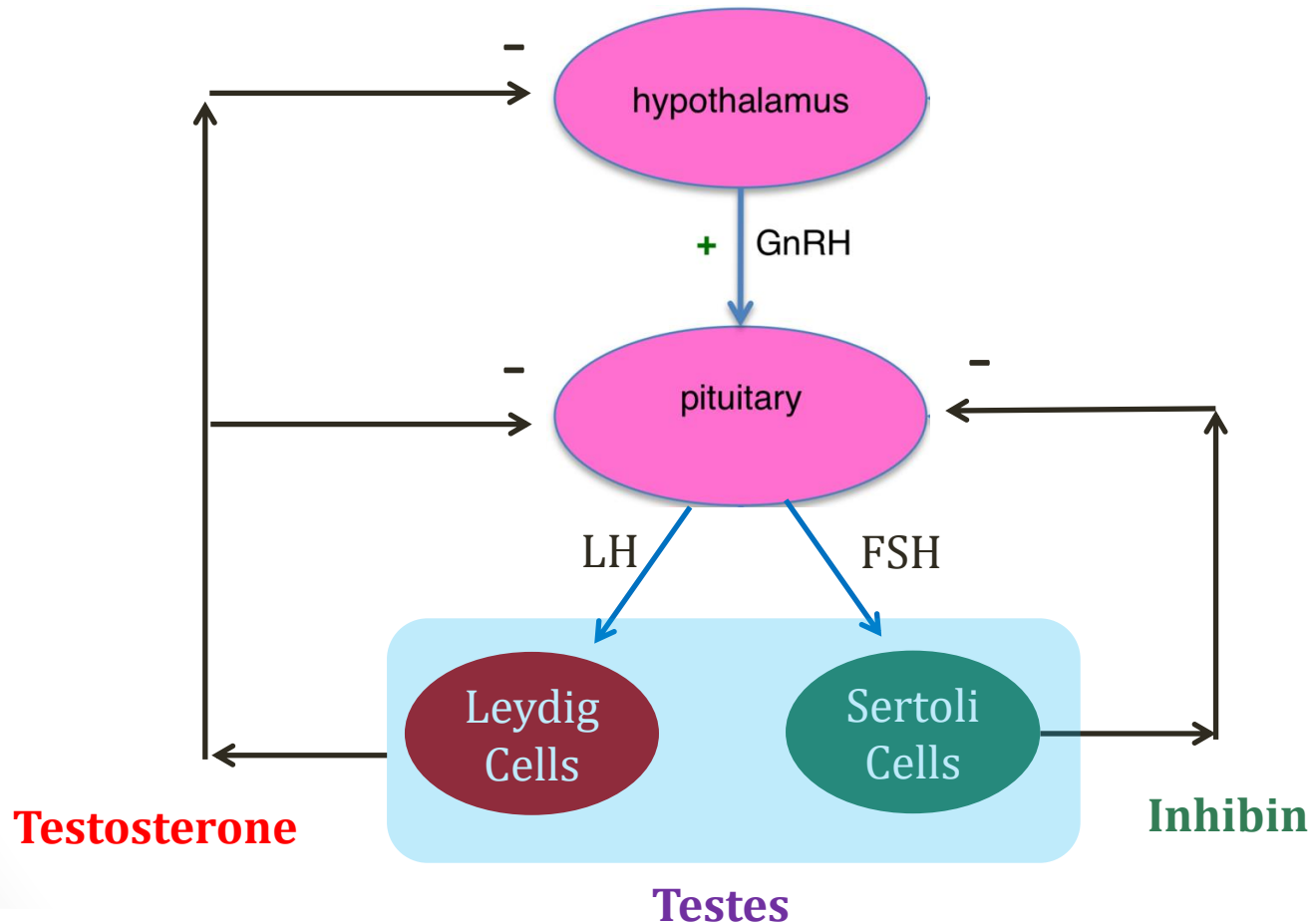
Klinefelter Syndrome

- **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**

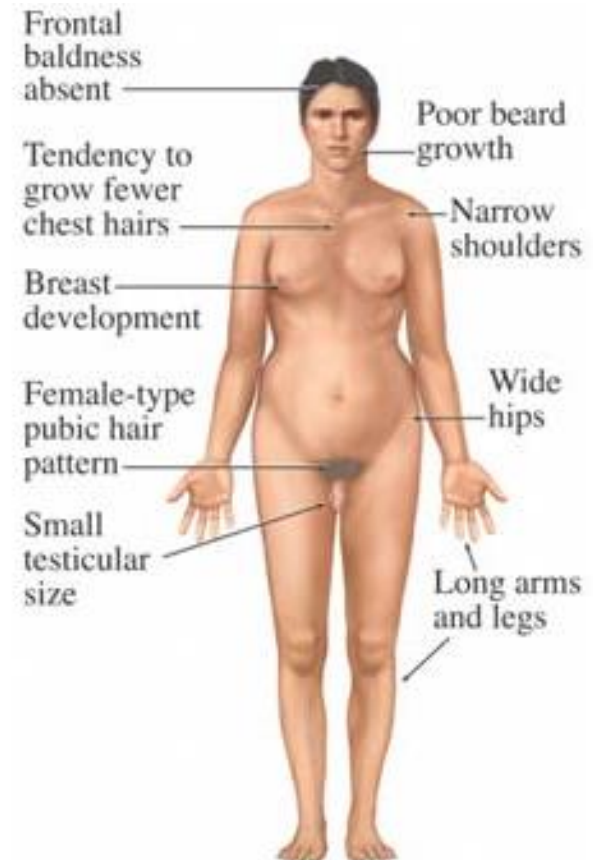
FSH and LH



Klinefelter Syndrome

Low Testosterone Features

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



Wikipedia

Klinefelter Syndrome

Genital Abnormalities

- Cryptorchidism (undescended testes)
- Hypospadias
- Micropenis



Subcoronal



Midshaft



Penoscrotal

Klinefelter Syndrome

Physical Appearance

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



Malcolm Gin/Wikipedia

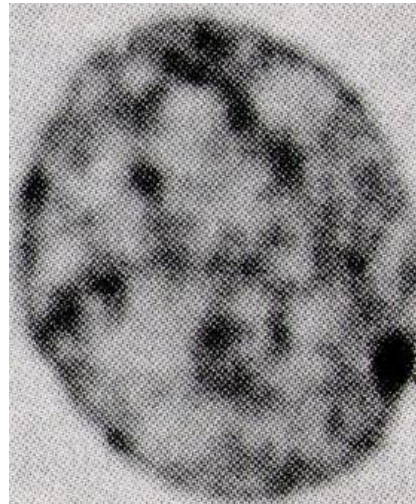
Klinefelter Syndrome

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



Barr Body

Turner Syndrome

- 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

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

General Features

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



Wikipedia



Johannes Nielsen/Wikipedia

Cystic Hygroma

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

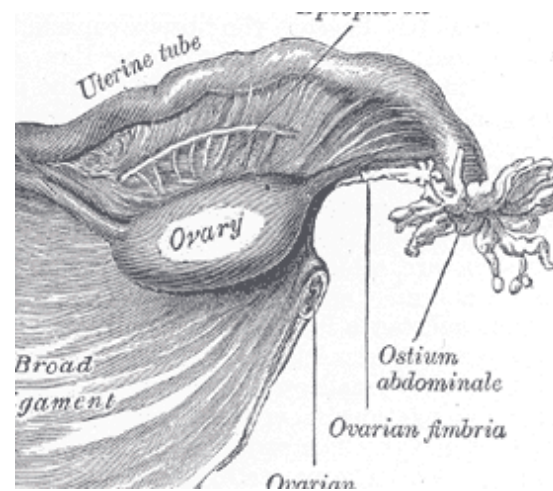


Vardhan Kothapalli

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



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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)

Turner Syndrome

Ovarian Function

- Delayed puberty
 - Absence of breast development
 - Failure to menstruate
 - Can be treated with **estrogen** to induce puberty
- **Primary amenorrhea** (most common cause)
 - “Menopause before menarche”
- Some girls menstruate with menopause in teens/20s
 - More common in cases with mosaicism

Turner Syndrome

Ovarian Function

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

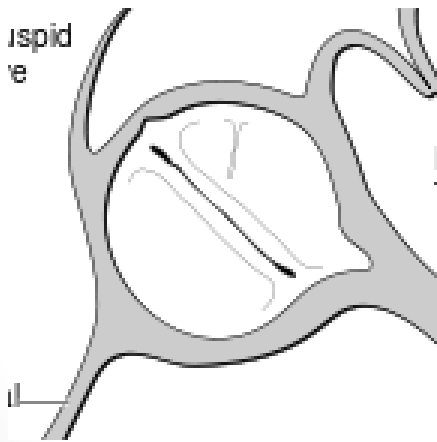


Øyvind Holmstad/Wikipedia

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

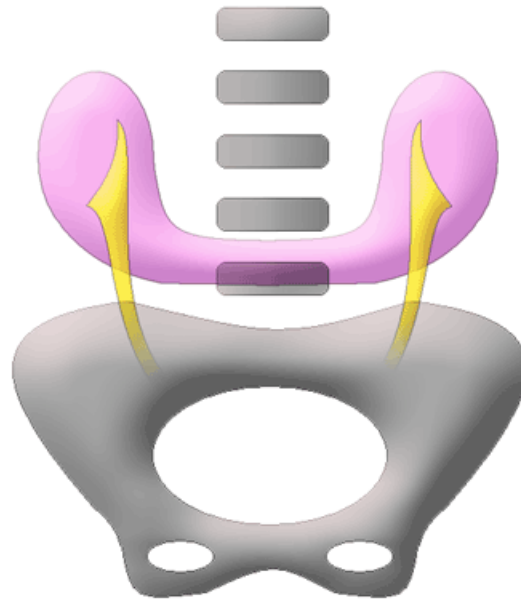


Patrick J. Lynch, medical illustrator

Turner Syndrome

Renal Manifestations

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

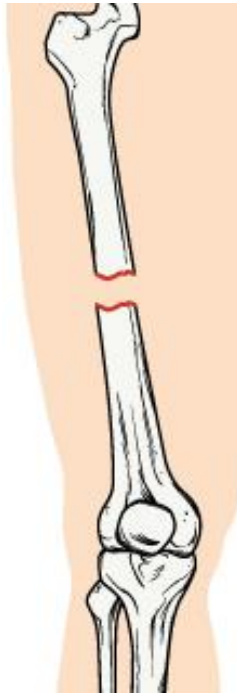


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Turner Syndrome

Osteoporosis

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



Open Stax College

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