Genetic Principles

Jason Ryan, MD, MPH

Genetics

Terminology

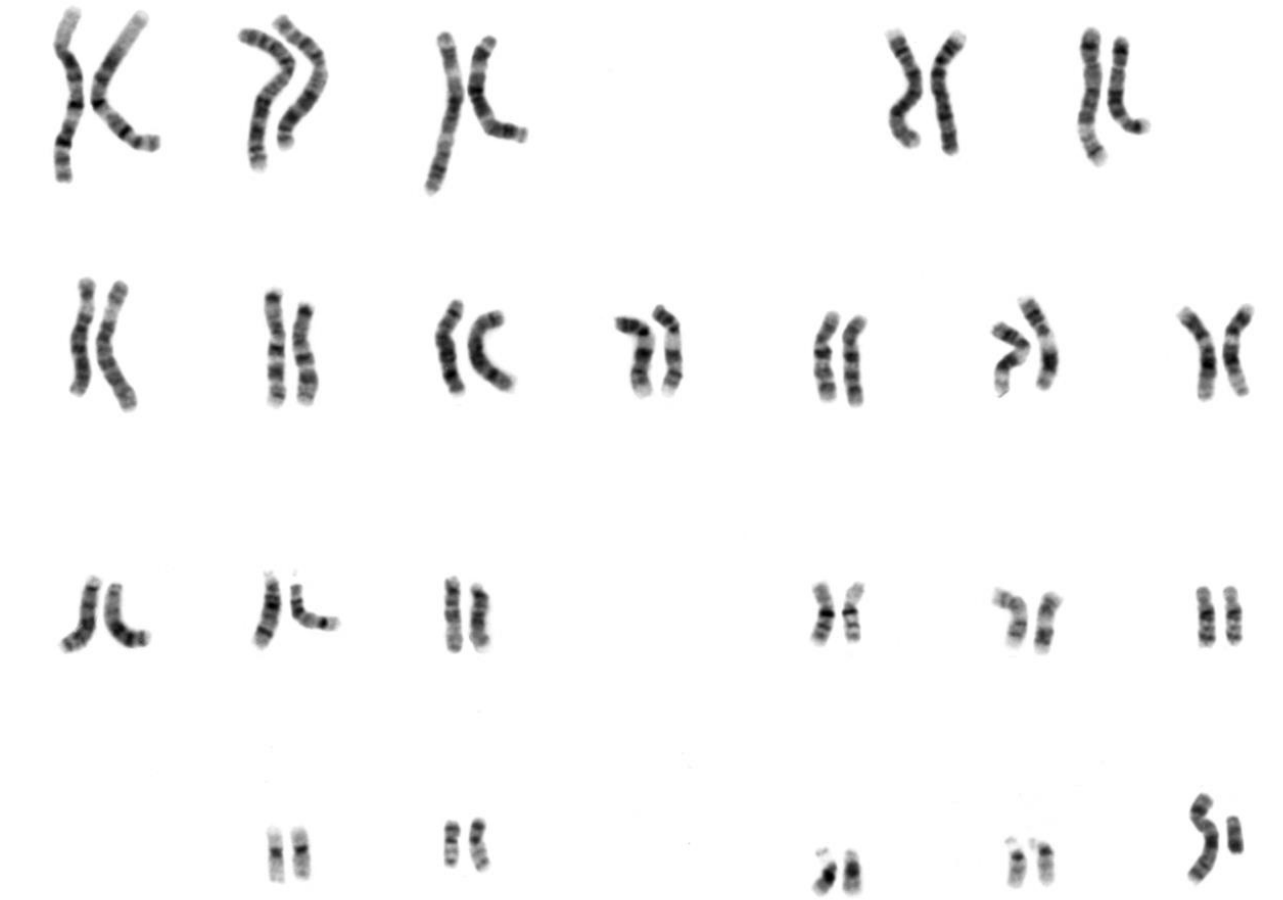
- Genome
  - DNA contained in nucleus of cells
  - “Hereditary material”
  - Passed to successive generations of cells
- Genes
  - Portions of DNA/genome
  - Code for proteins that carry out specific functions

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



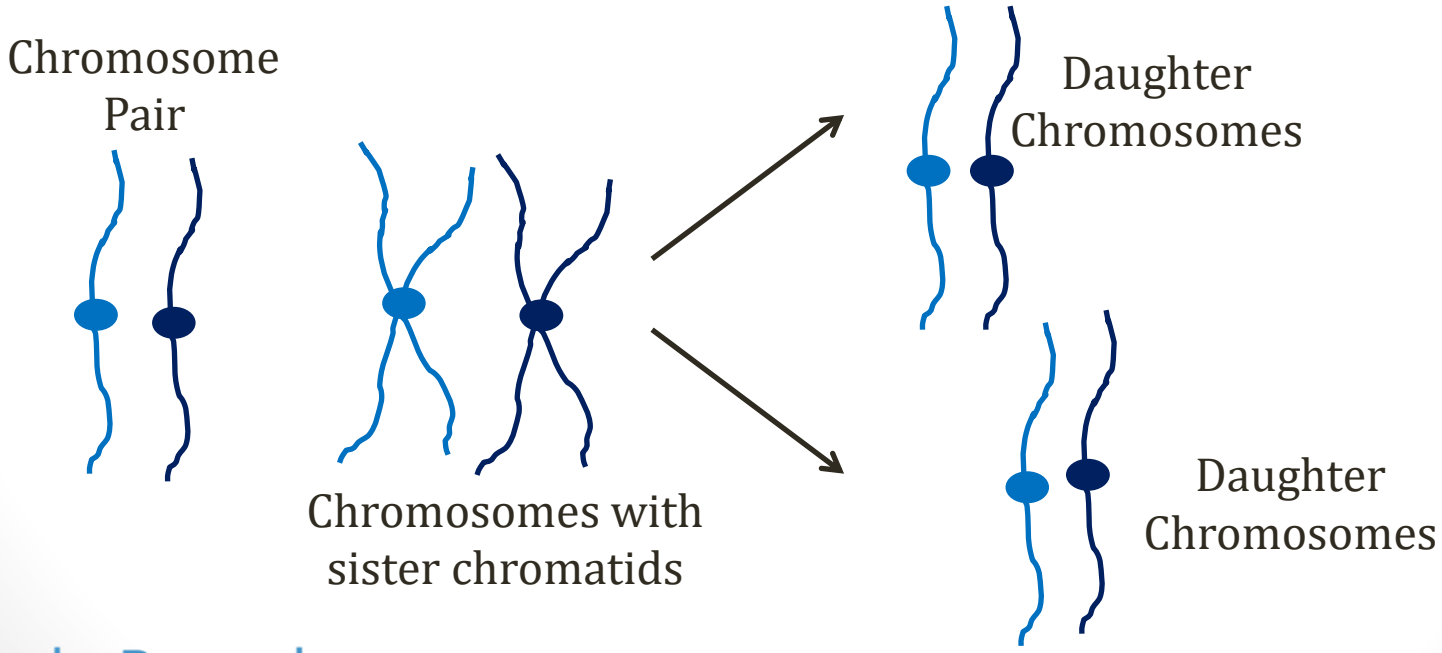
Cell Types

- 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 α1 antitrypsin)
  - M = normal allele
  - S = moderately low levels protein
  - Z = severely reduced protein levels
- Combination of alleles determines protein levels
  - MM = normal
  - ZZ = severe deficiency
  - Other combinations = variable risk of disease

Penetrance

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

BRCA1 and BRCA2

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

Expressivity

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

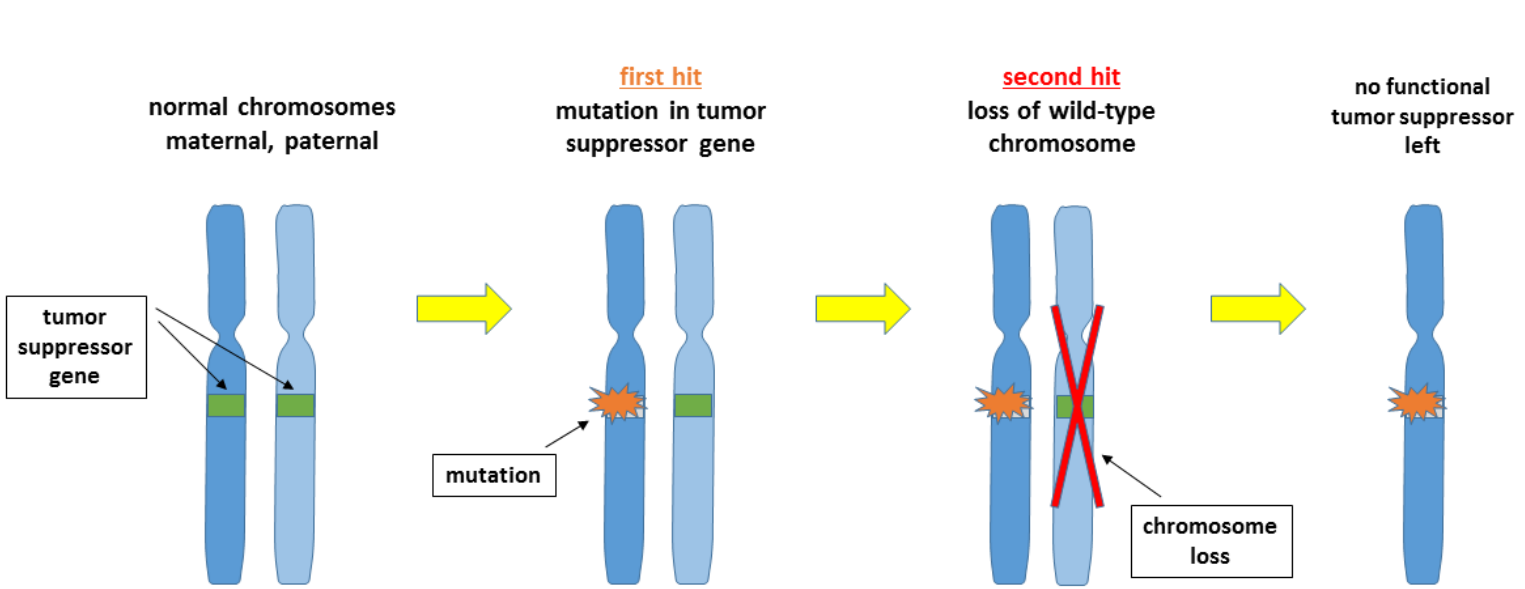
Pleiotropy

- 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



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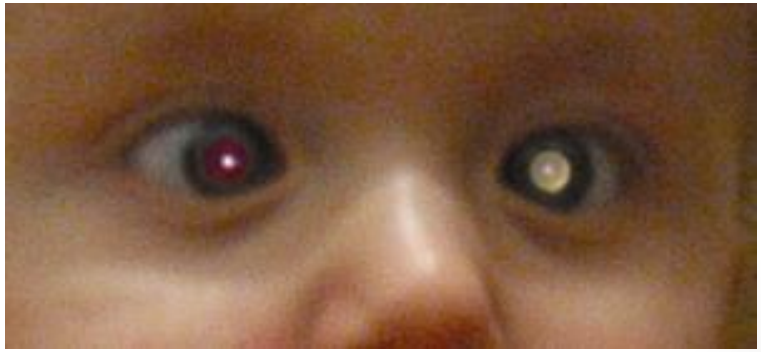
Two-Hit Origin of Cancer

- 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



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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)

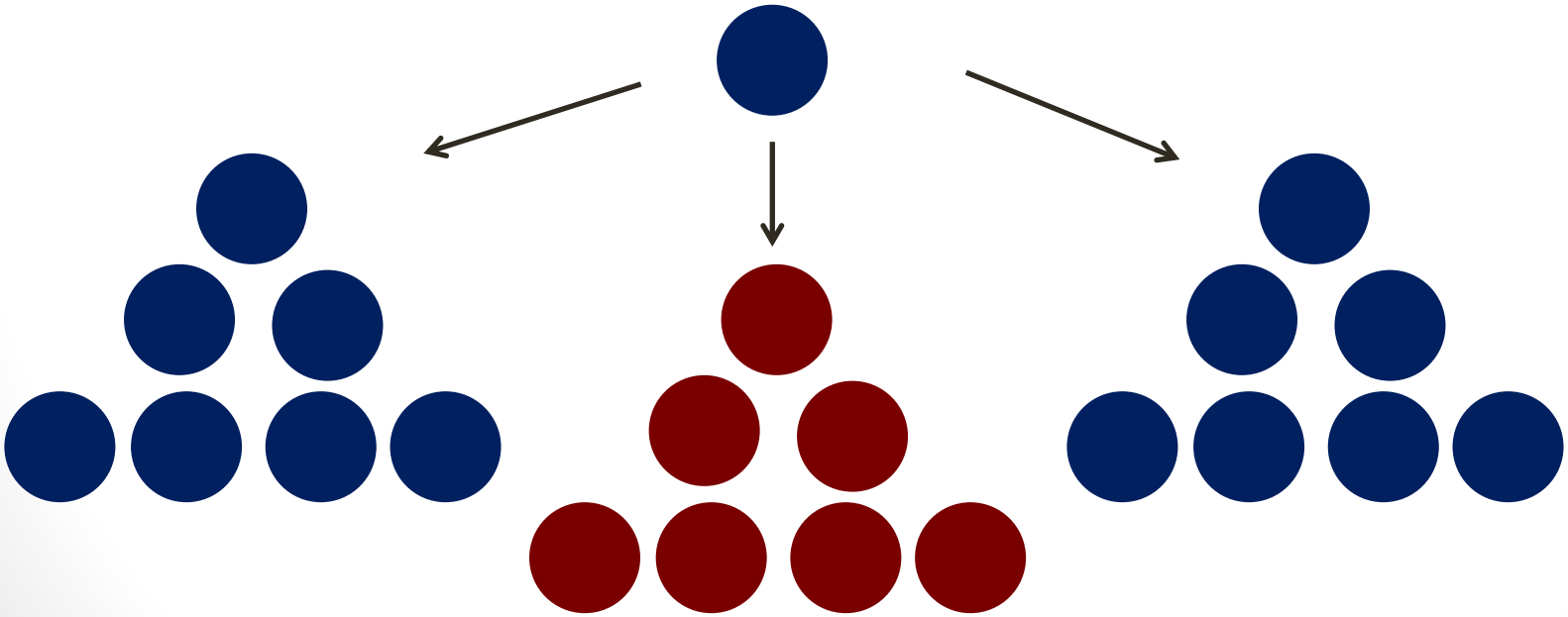
Two-Hit Origin of Cancer

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 is blood/tissue samples used for analysis
  - Offspring disease may appear sporadic
  - Can present as recurrent “sporadic” disease in offspring

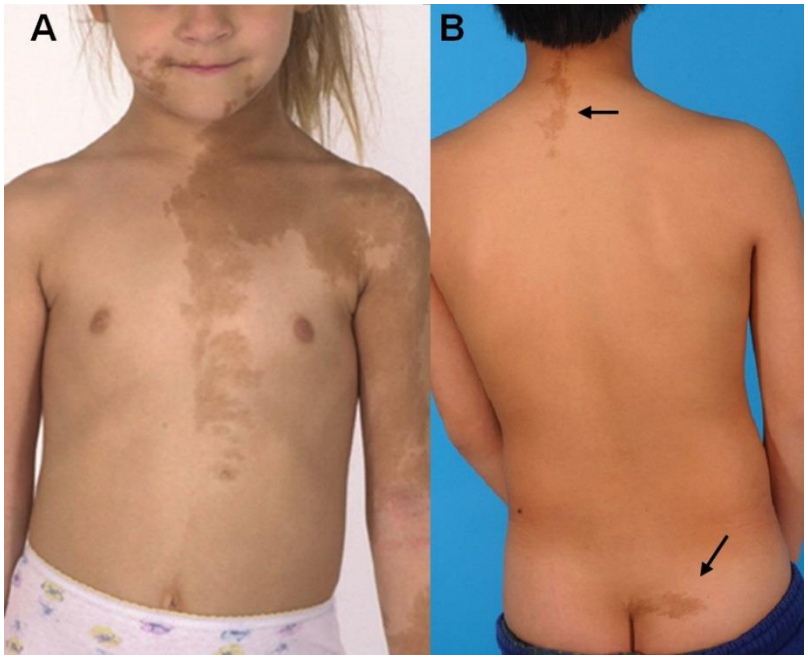
Mosaicism

- **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^o = no function; β^1 = some function
- Cystic Fibrosis
  - Mutation in CFTR gene
  - Over 1400 different mutations described

Locus heterogeneity

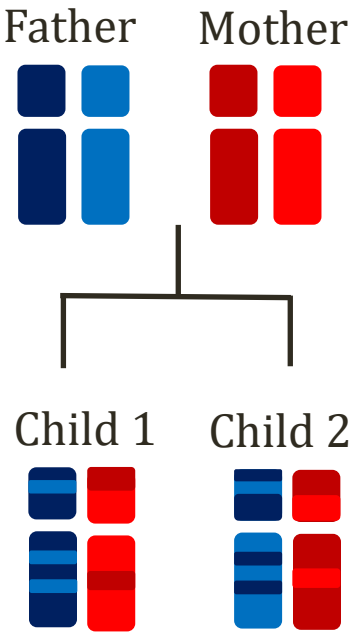
- Mutations in different loci cause same phenotype
- Example: Retinitis Pigmentosa
  - Causes visual impairment
  - Autosomal dominant, recessive, and X-linked forms
  - Mutations at 43 different loci can lead to disease
- **One disease = multiple genes = multiple locations**

Genetic Mapping

Jason Ryan, MD, MPH

Genetic Recombination

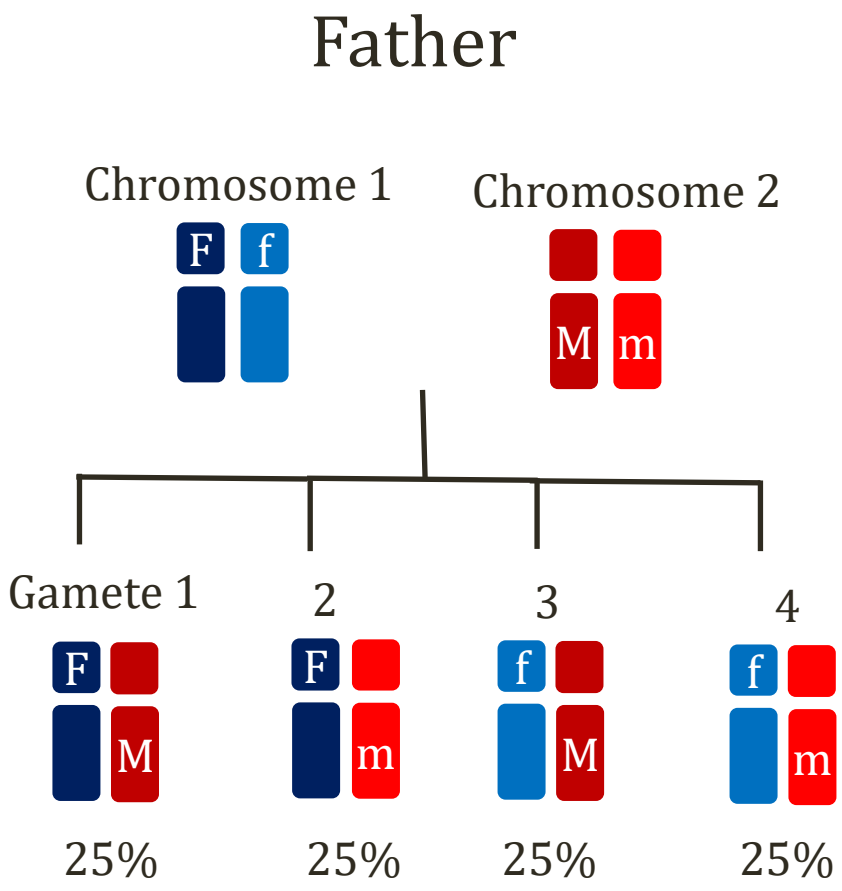
- During **meiosis** chromosomes exchange segments
- Child inherits "patchwork" of parental chromosomes
- Never exact copy of parental chromosomes



Independent Assortment

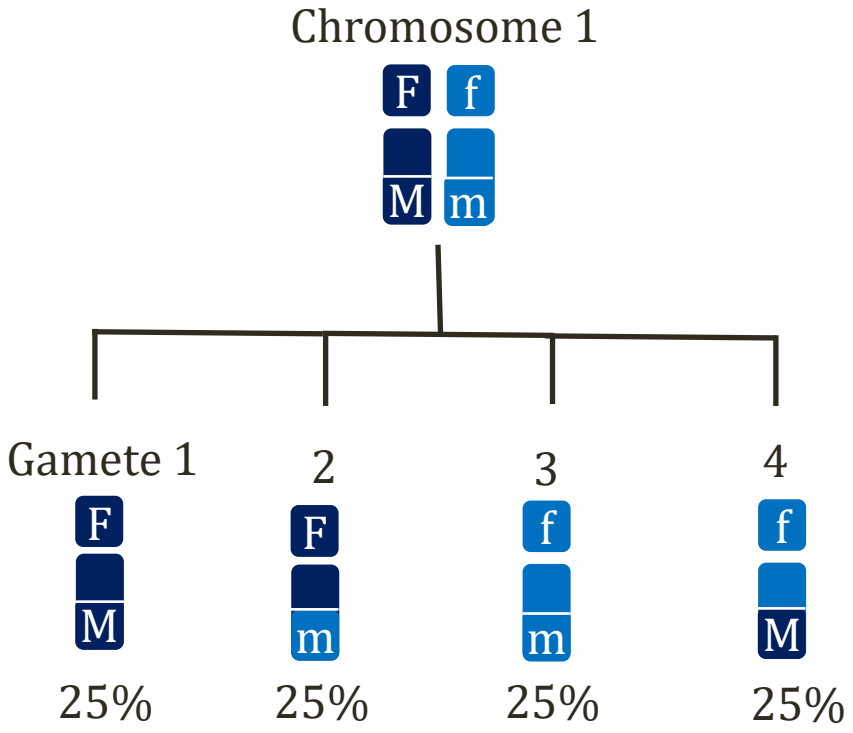
- Suppose father has two alleles of F and M genes
  - F and f
  - M and m
- F and M found on different chromosomes
- Independent assortment
  - Occurs if F and M genes can independently recombine
  - 25% chance of each combination in gamete

Independent Assortment



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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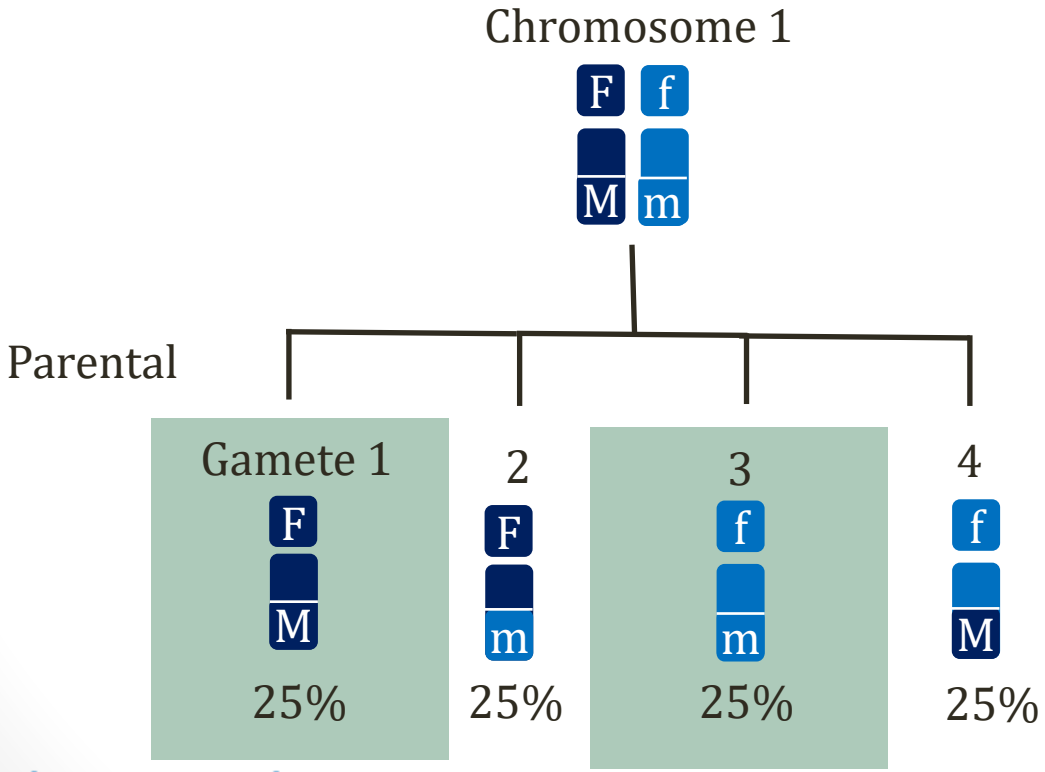

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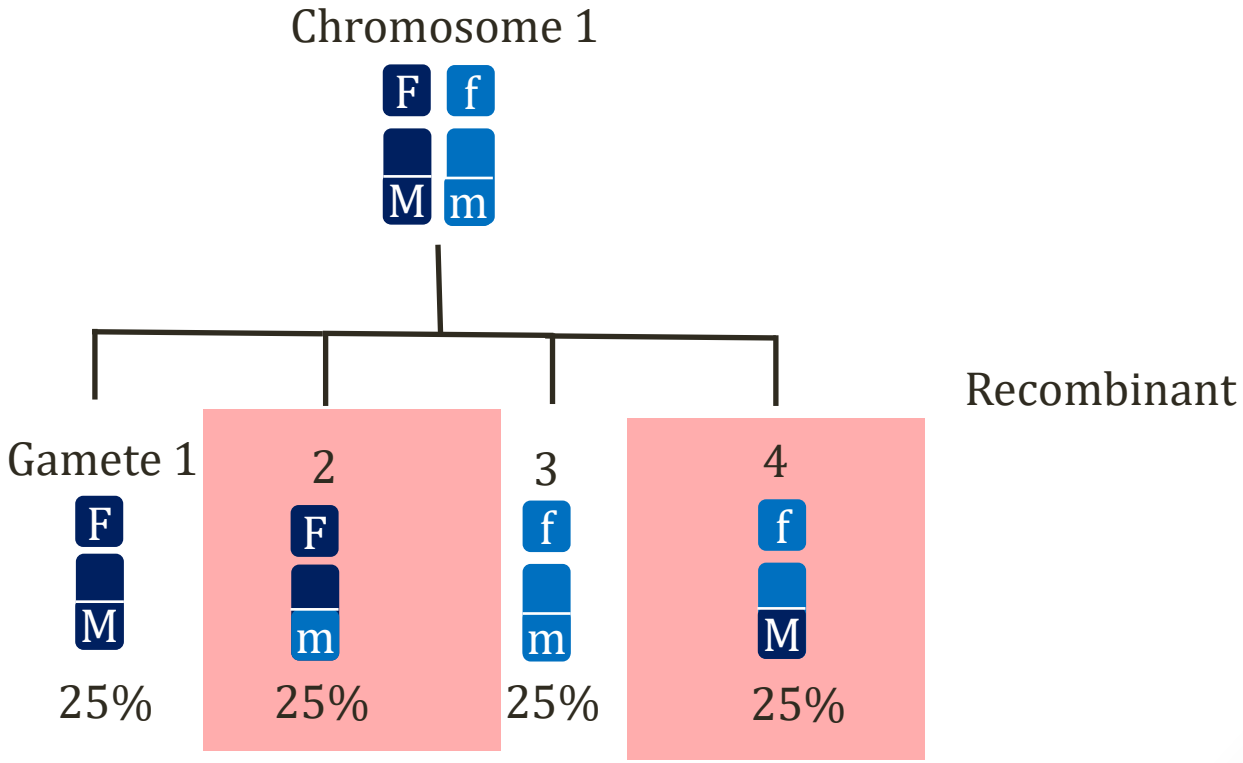
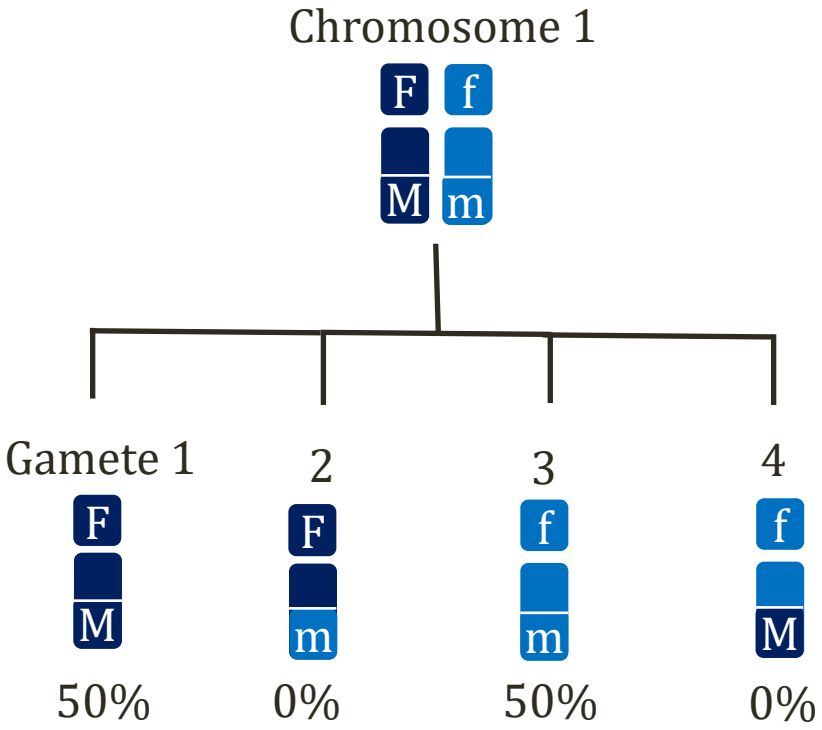
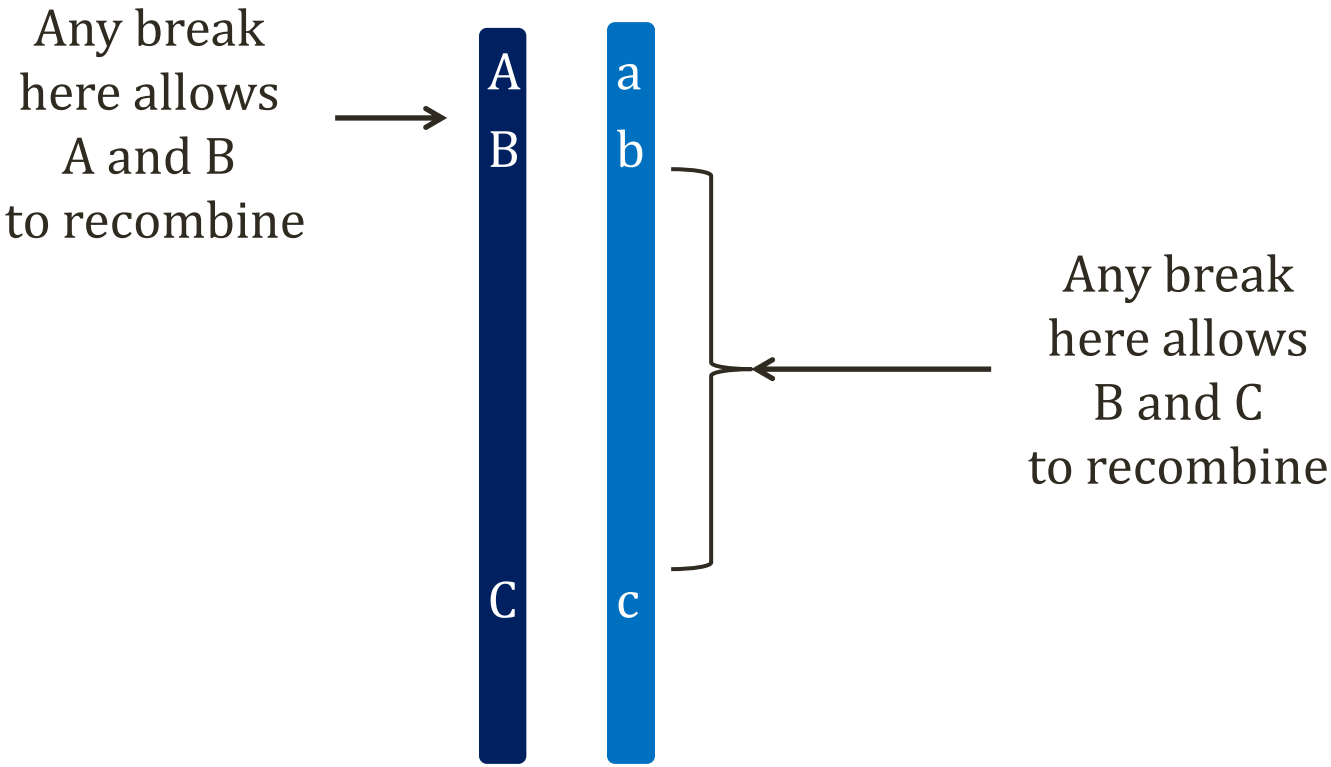


Independent Assortment

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



Recombination



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

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) x (0.9) = 0.45
  - aB = (0.5) x (0.9) = 0.45
  - Ab = (0.5) x (0.1) = 0.05
  - 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

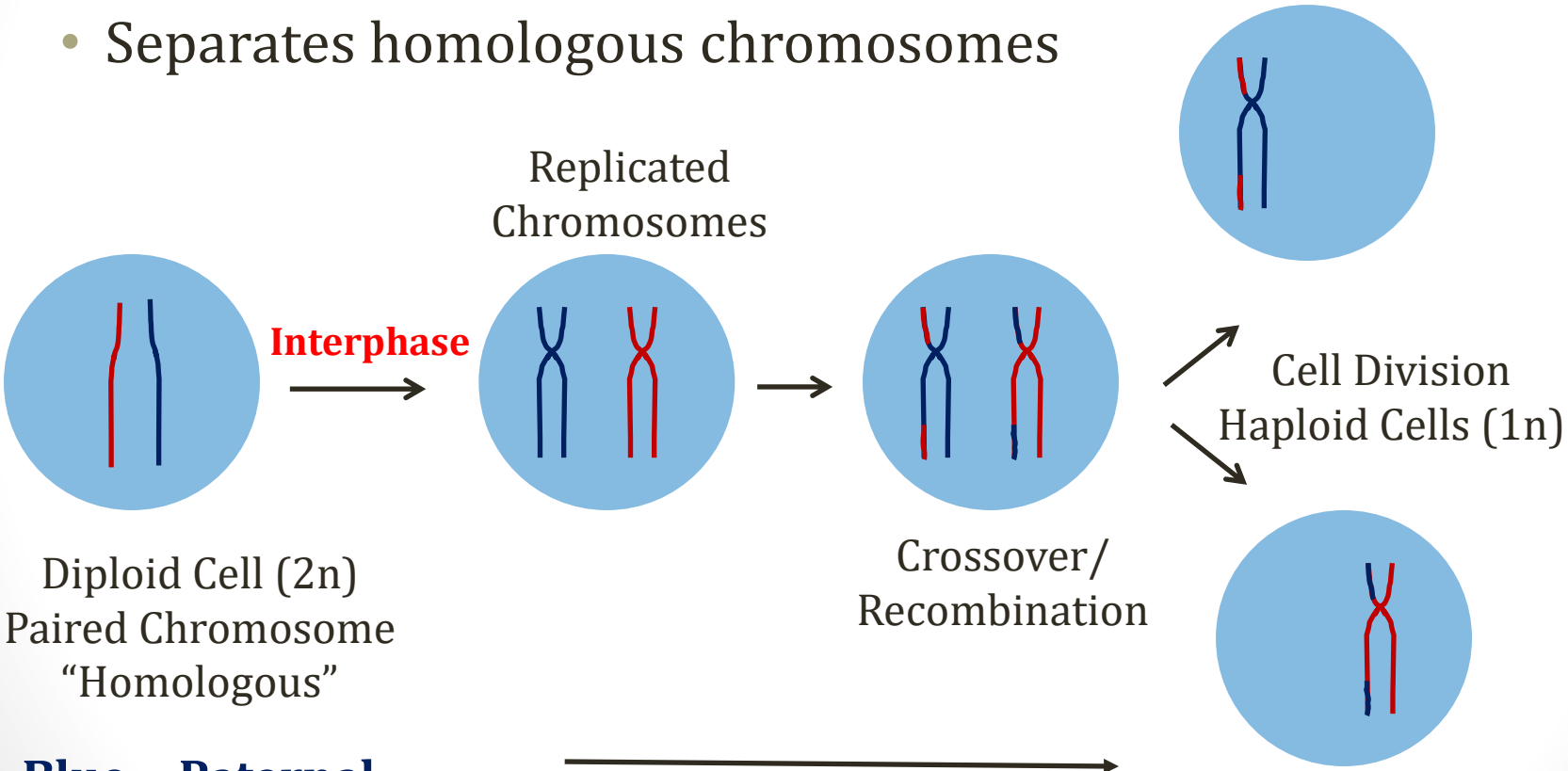
Jason Ryan, MD, MPH

Meiosis

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

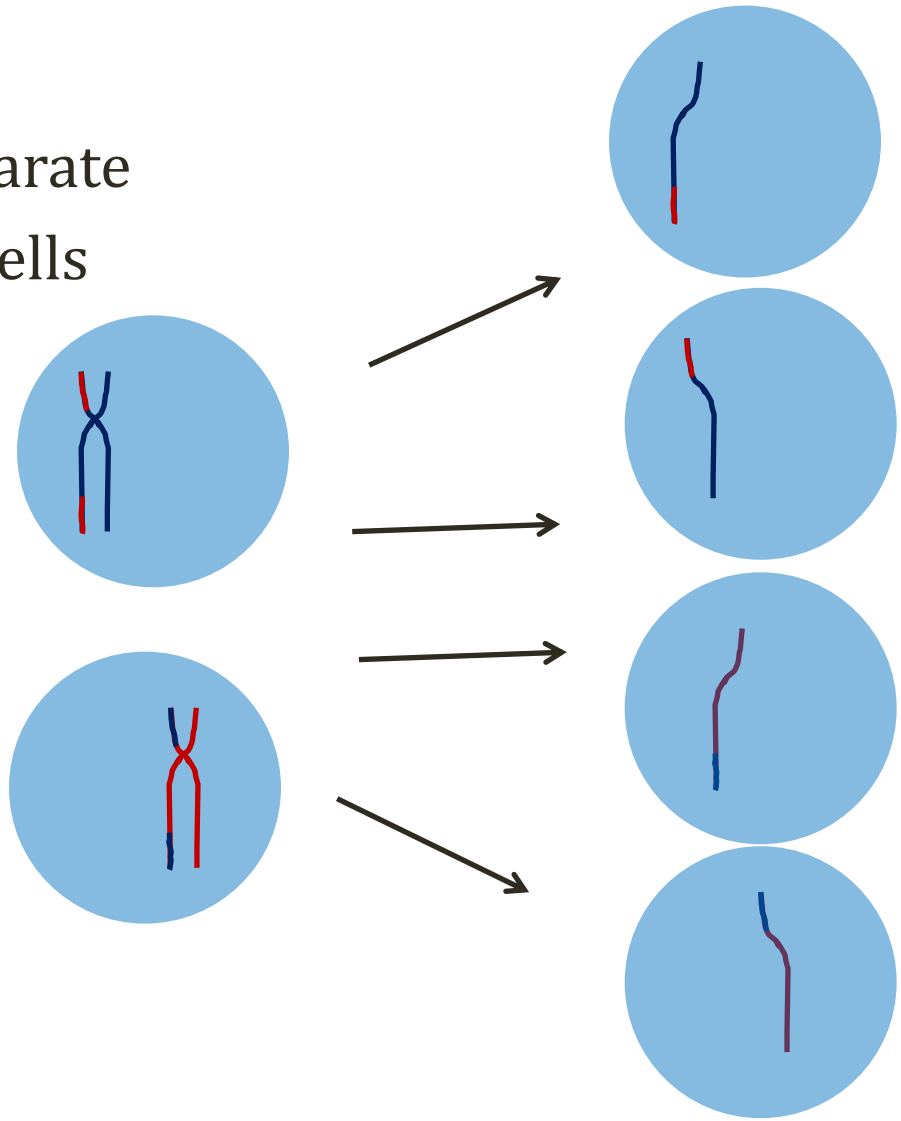
Meiosis I

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



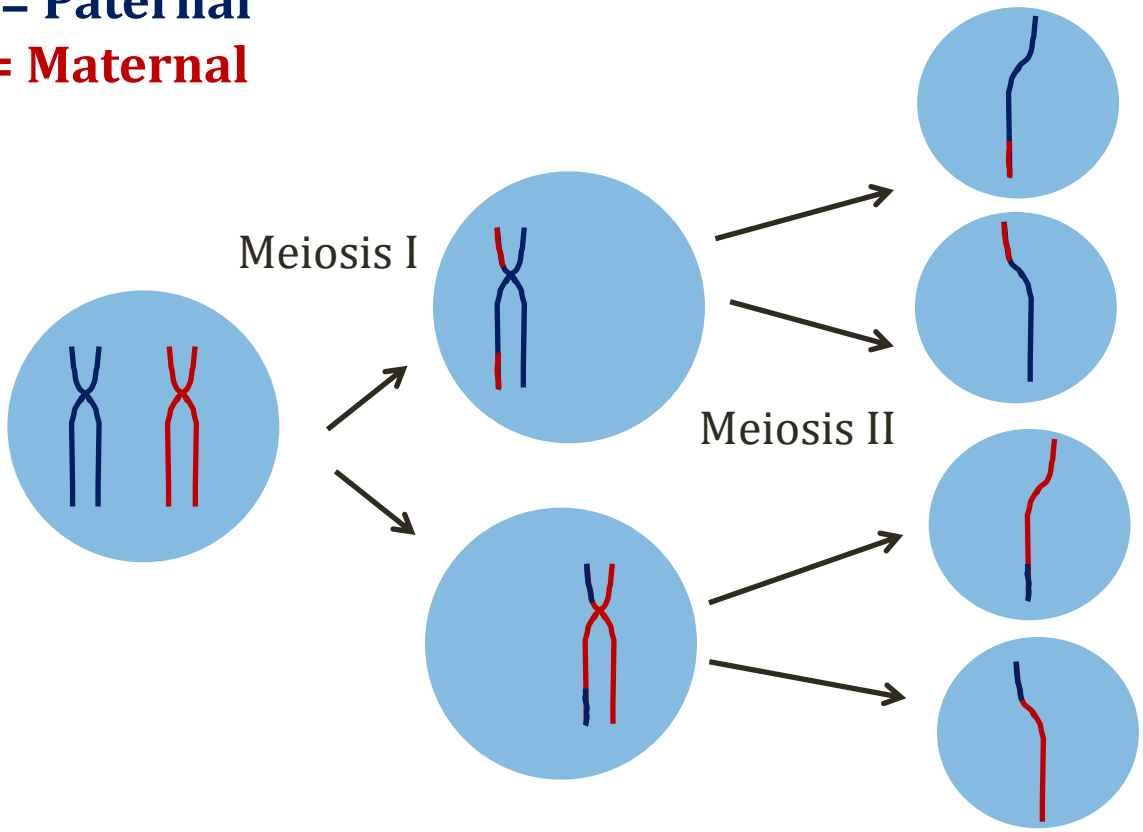
Meiosis II

- Chromatids separate
- Four daughter cells



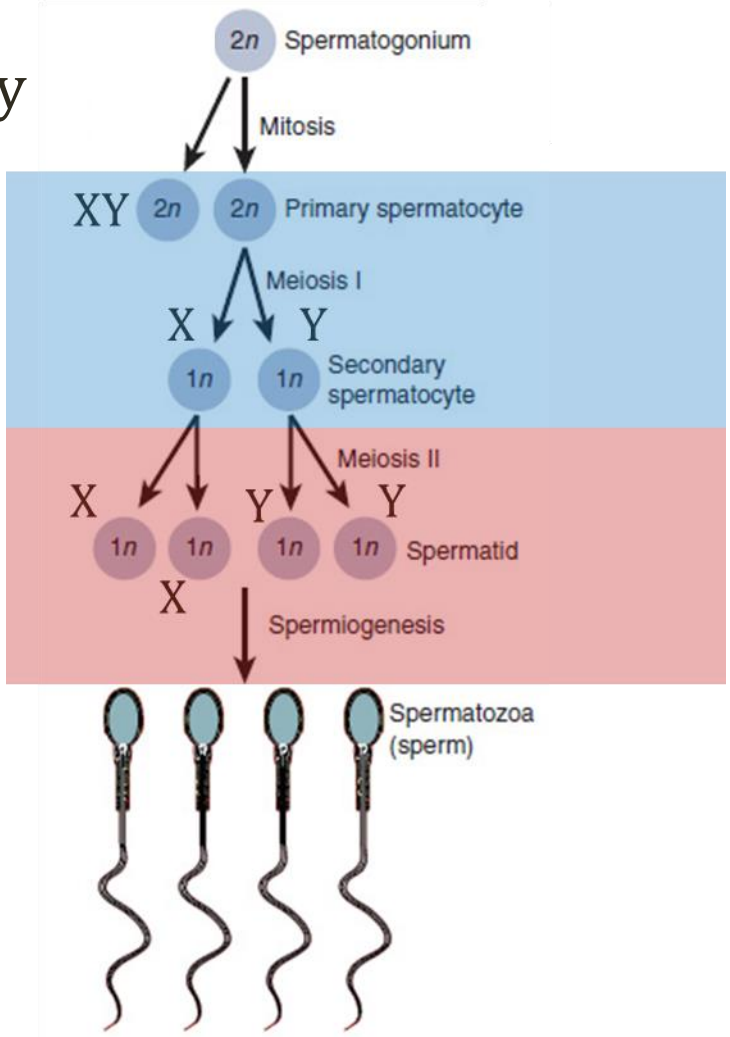
Meiosis

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

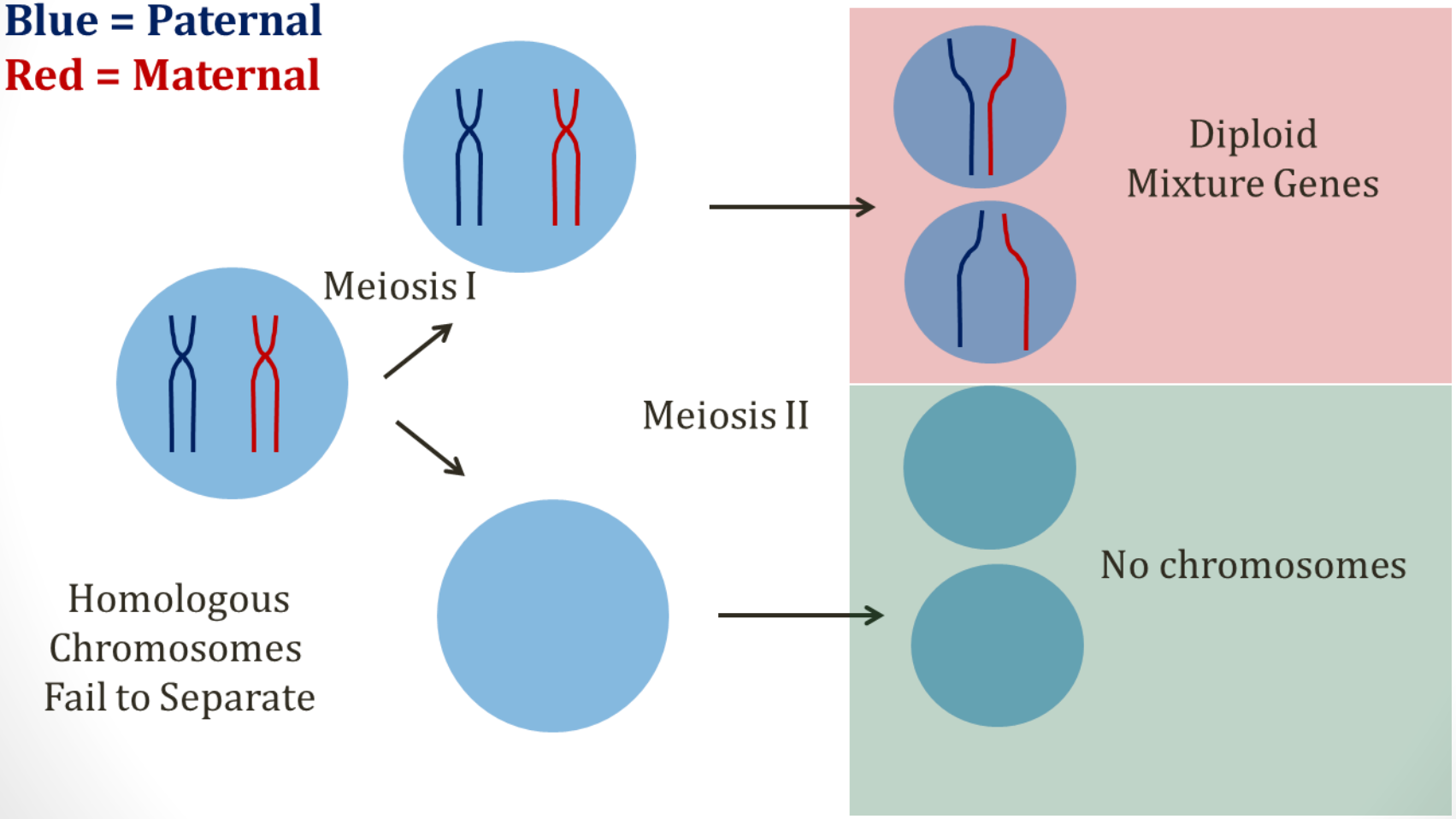
Aneuploidy

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

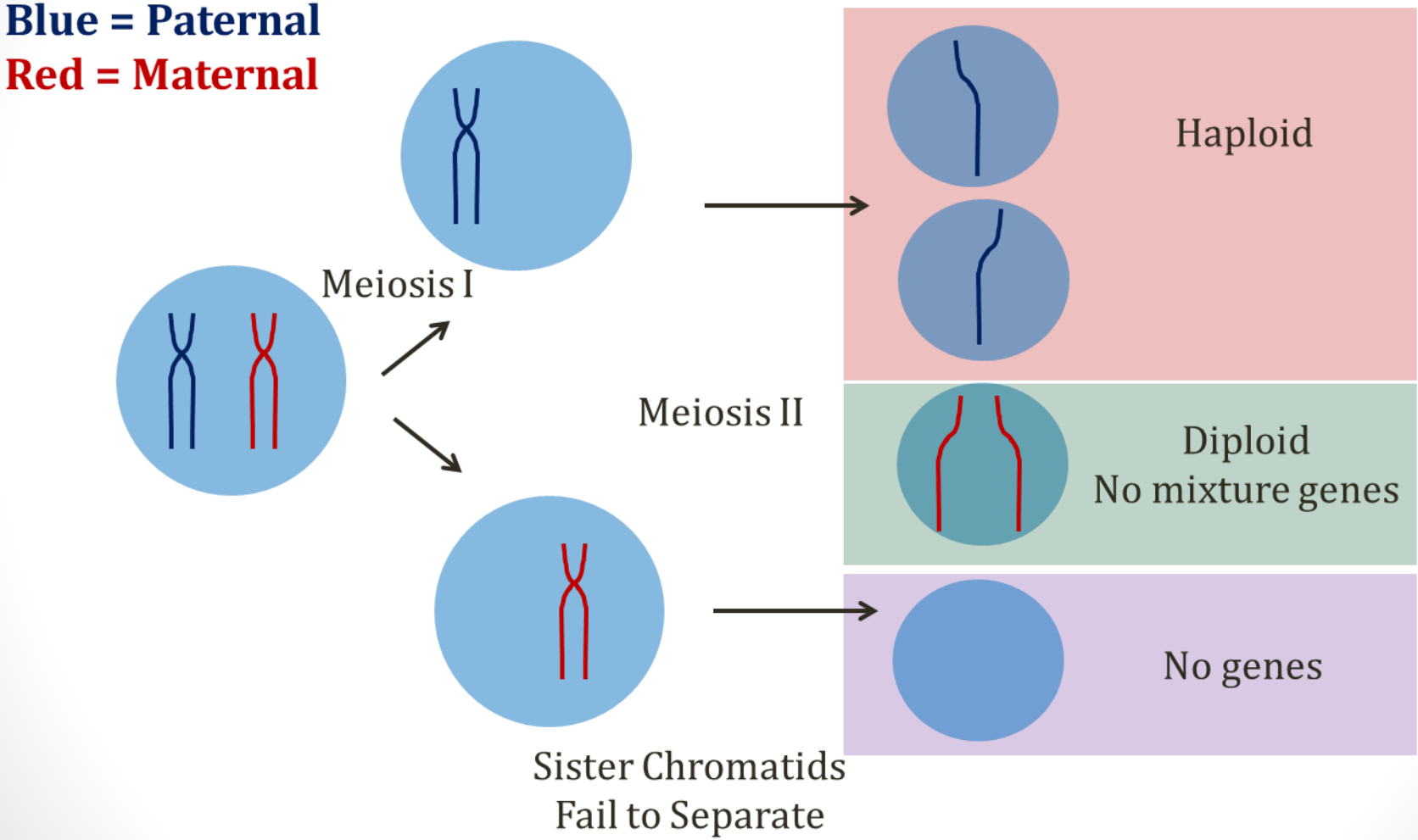
Meiotic Nondisjunction

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

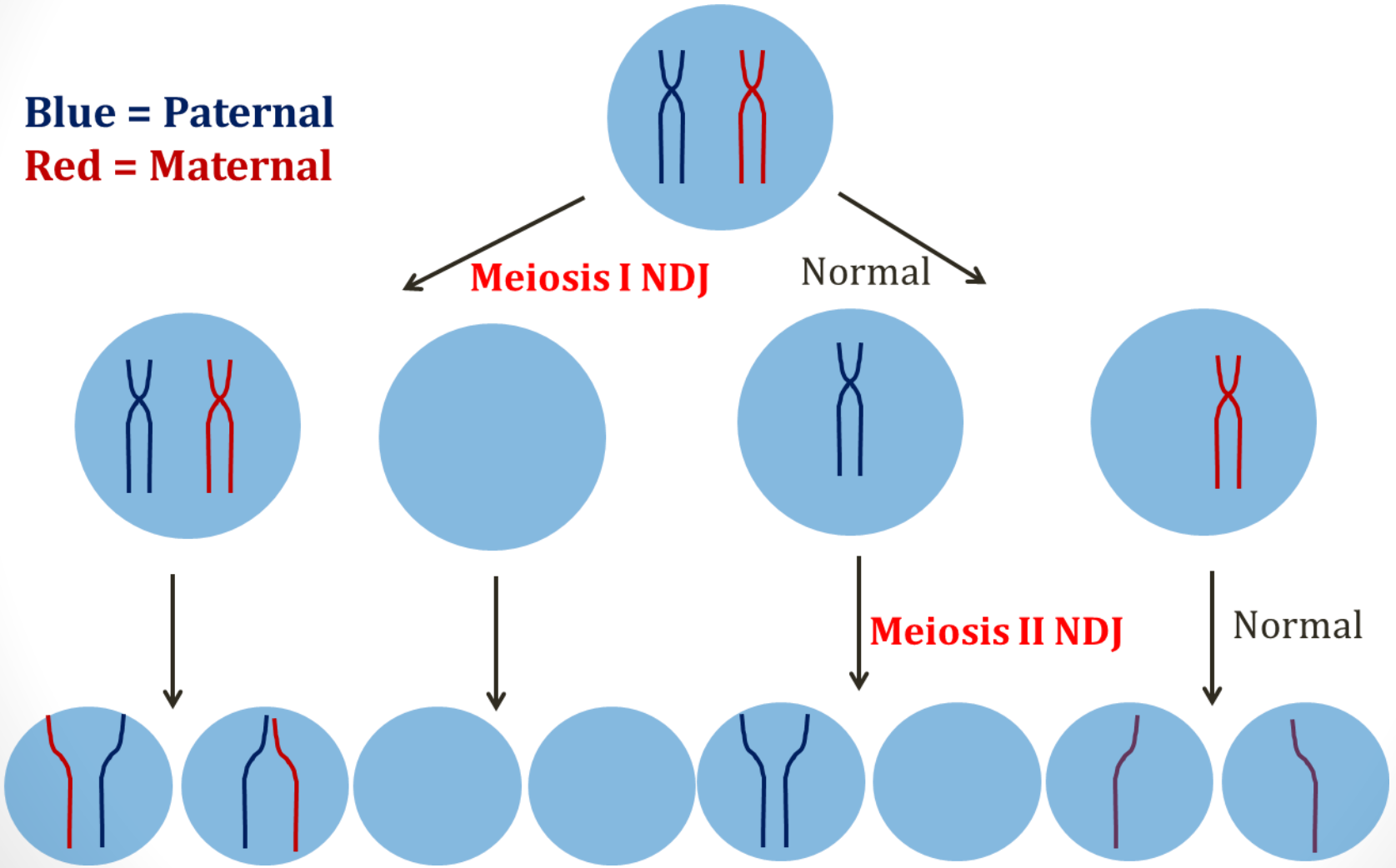
Meiosis I Nondisjunction



Meiosis II Nondisjunction



Nondisjunction



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

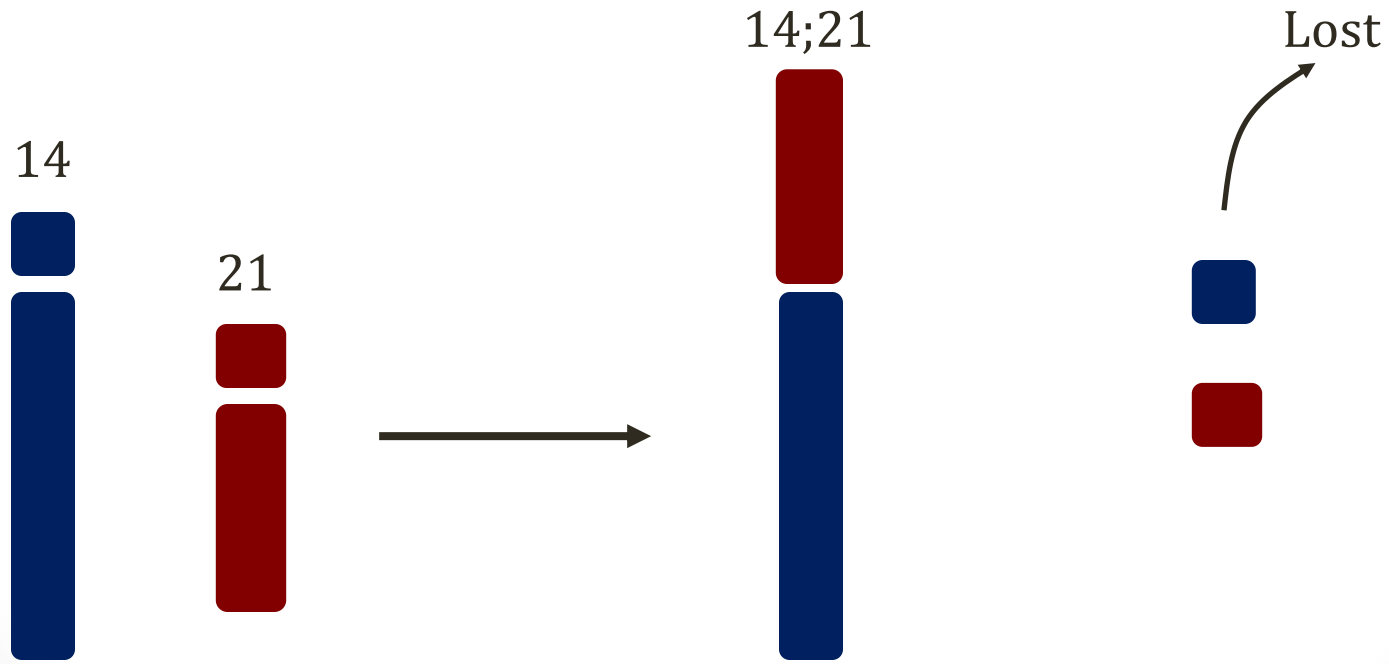
- Child has **two copies** of **one parent's chromosomes**
- No copies of other parent's chromosomes
- Father = **21A** and **21B**; Mother = **21C** and **21D**
- Child **AA** (isodisomy) = Meiosis II error (father)
- Child **CD** (heterodisomy) = Meiosis I error (mother)

Uniparental Disomy

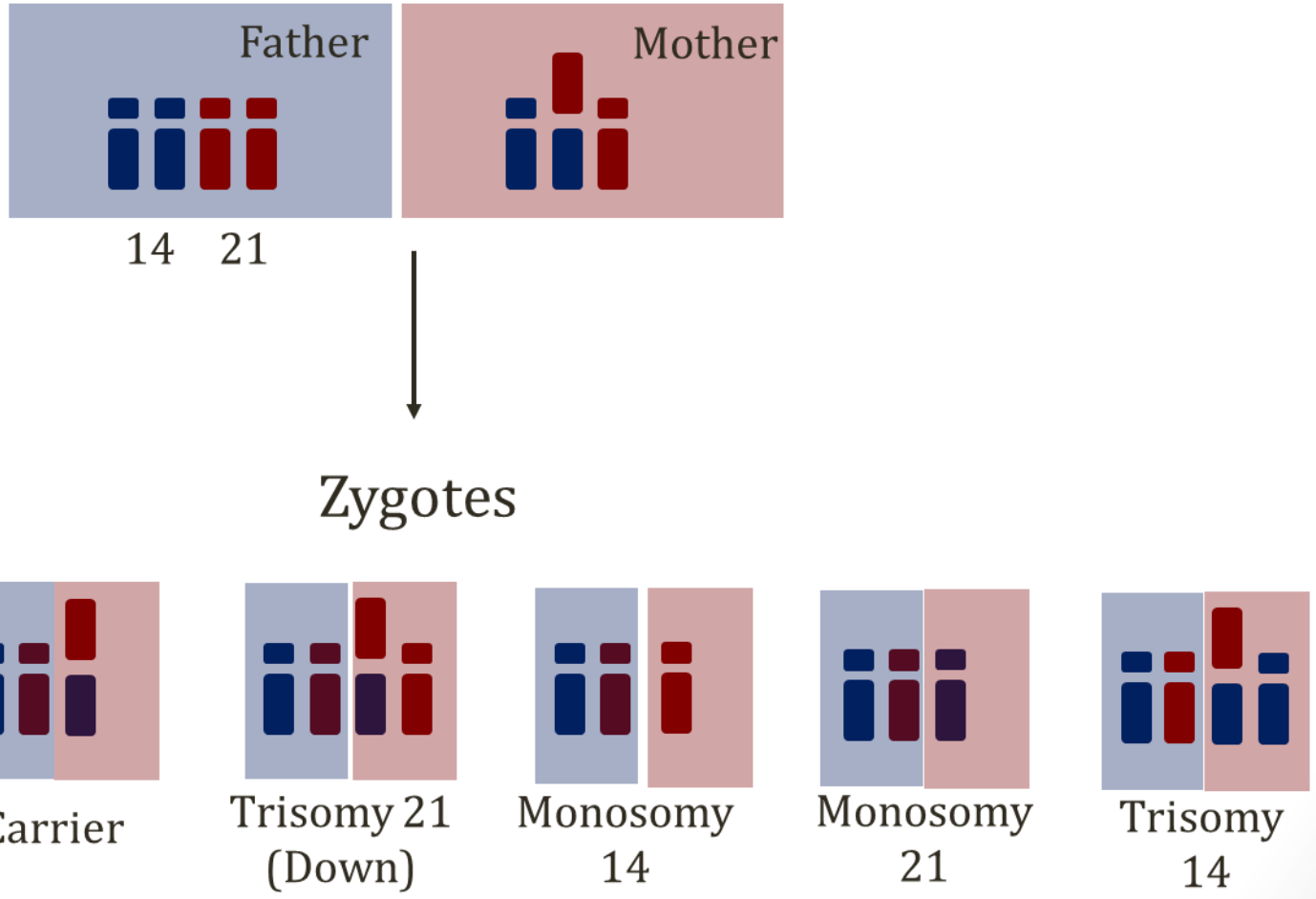
- Child is euploid
  - Normal number of chromosomes
  - No aneuploidy
- Usually normal phenotype
- Can lead to phenotype of **recessive disease**
  - Father = Aa (recessive gene for disease)
  - Child = aa (two copies of a from father)

Robertsonian Translocation

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



Robertsonian Translocation

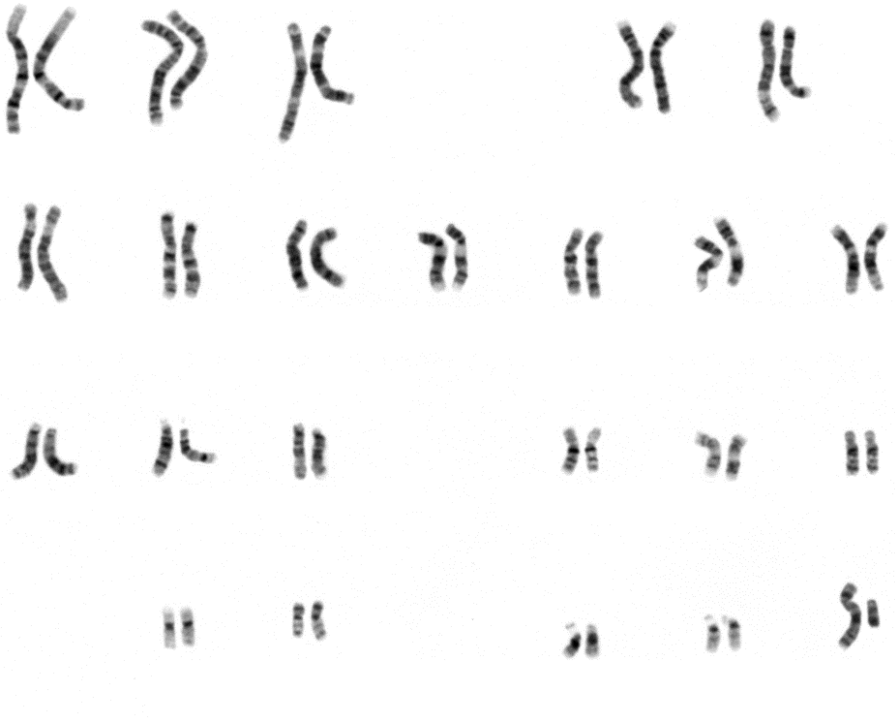


Robertsonian Translocation

- 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



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Hardy-Weinberg Law

Jason Ryan, MD, MPH

Hardy-Weinberg Law

- Used in studies of populations
- Used to derive **genotypes** from **allele frequencies**
  - Allelle: 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

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

1.00

p = 0.4
q = 0.6

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

$p + q = 1$

Hardy-Weinberg Law

$p = 0.4$
$q = 0.6$
$p^2 = 0.16$
$2pq = 0.48$
$q^2 = 0.36$

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

Hardy-Weinberg Law

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
  - $2\ (0.985)\ (0.015) = 0.029 =$ **3%**
- Very rare diseases p close to 1.0
- Carrier frequency ≈ 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)

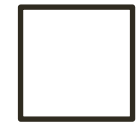
Pedigrees

Jason Ryan, MD, MPH

Pedigree

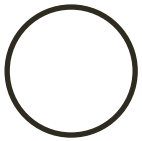
- Visual representation of a family
- Often used to study single gene disorders
  - Gene passed down through generations
  - Some members have disease
  - Some members are carriers
- Several typical patterns
  - Autosomal recessive genes
  - Autosomal dominant genes
  - X-linked genes

Pedigree Symbols

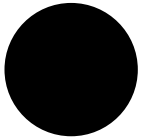


Unaffected Male

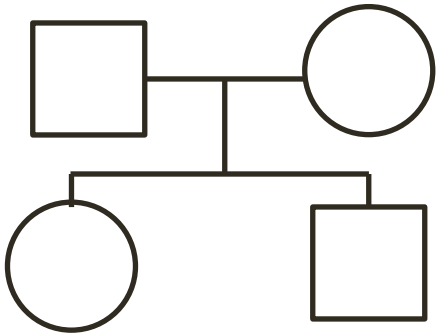
Affected Male



Unaffected Female



Affected Female

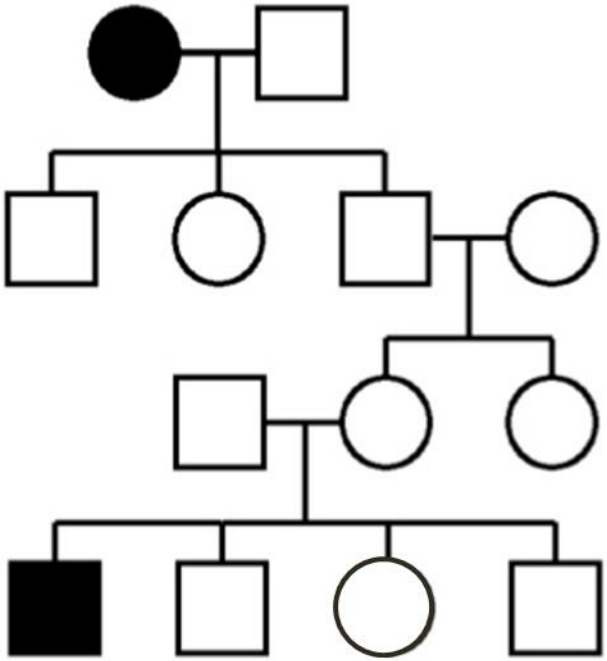


Marriage

Children

Autosomal Recessive

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



Autosomal Recessive

Mother

Father	**A**	**a**
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) x (0.5) = 0.25 chance child has disease

Autosomal Recessive

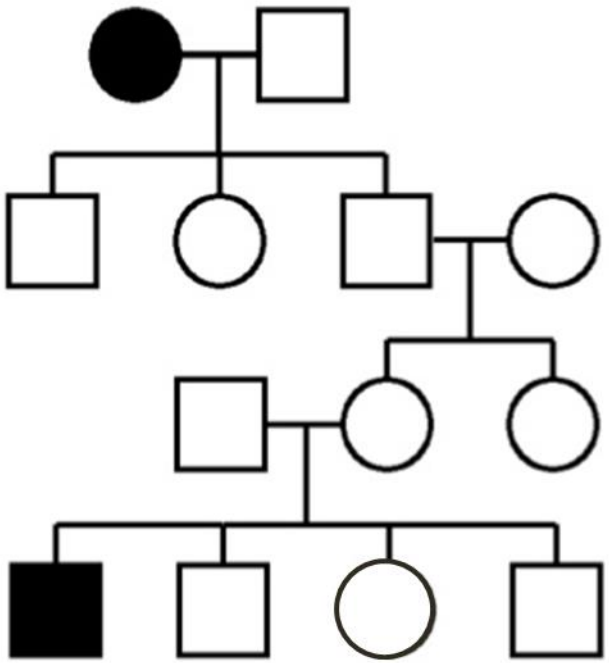
Mother (1/50)

Father (1/100)	**A**	**a**
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

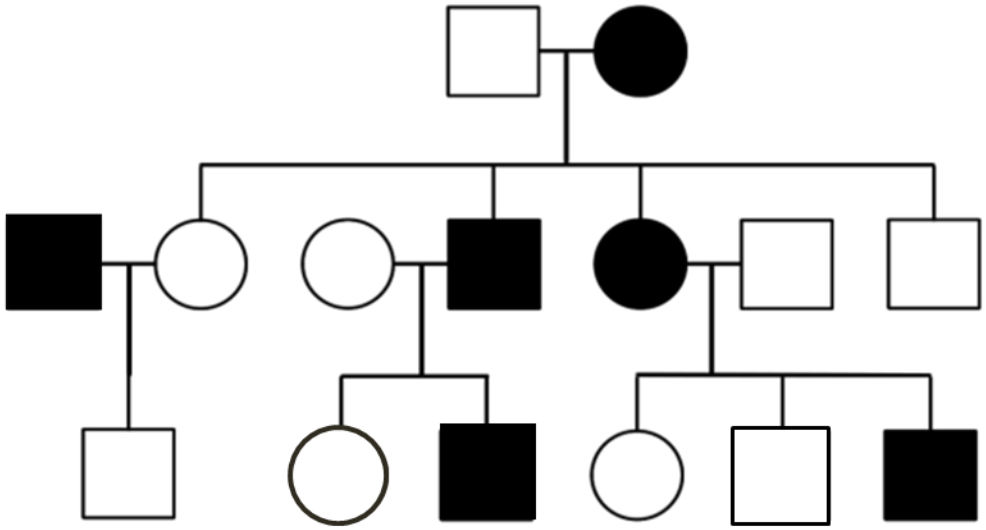


Autosomal Recessive

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

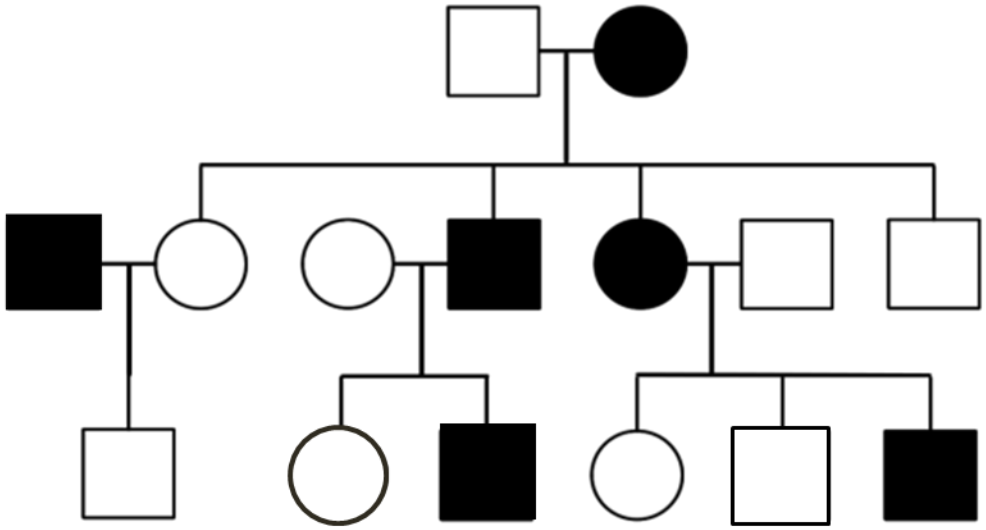
Autosomal Dominant

- 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 → 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

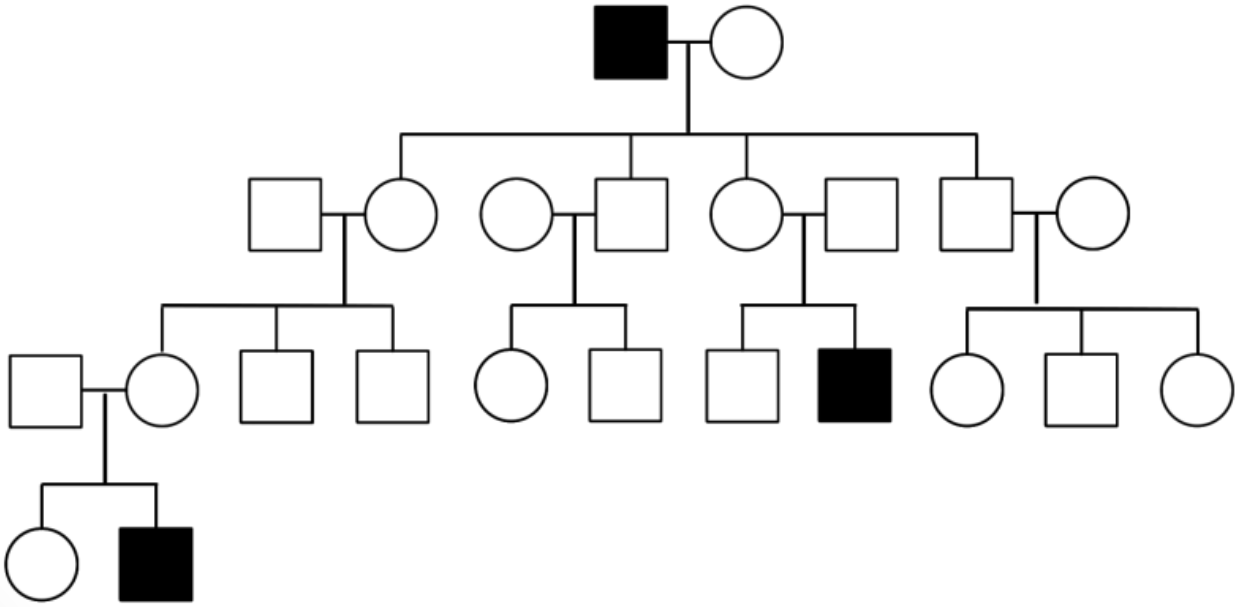
- Classic example: **Achondroplasia**
  - Autosomal dominant disorder of bone growth
  - Heterozygotes (Dd): Dwarfism
  - Homozygotes (dd): Fatal
- **Familial hypercholesterolemia**
  - Heterozygotes: total cholesterol 350–550mg/dL
  - Homozygotes: 650–1000mg/dL

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

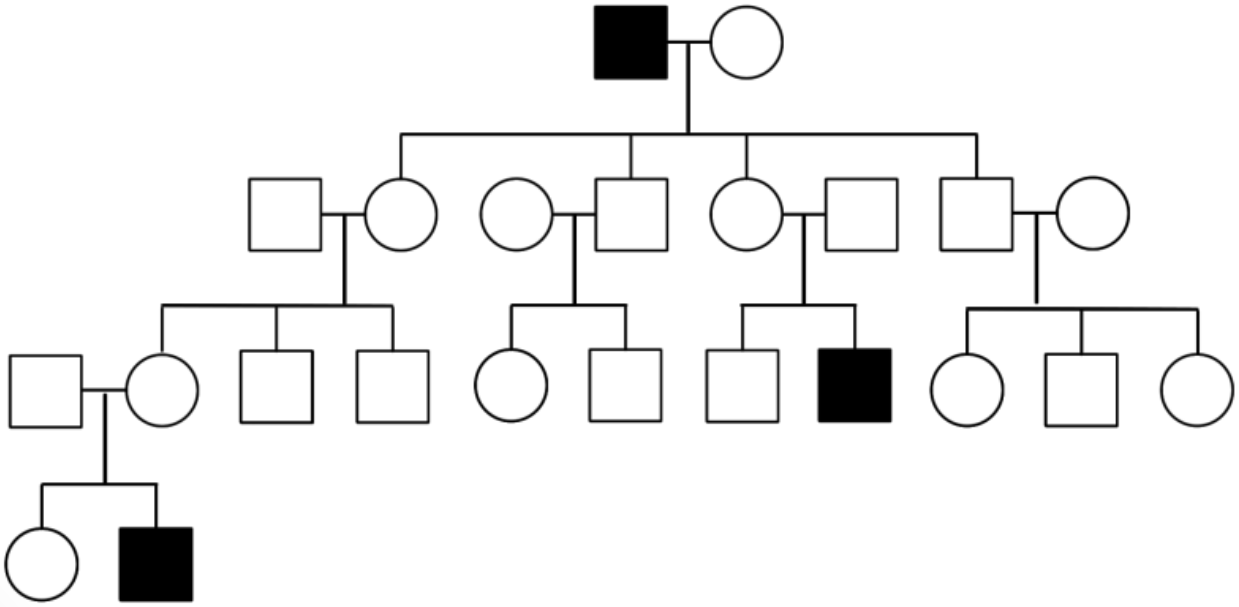
X-linked Recessive

- **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**

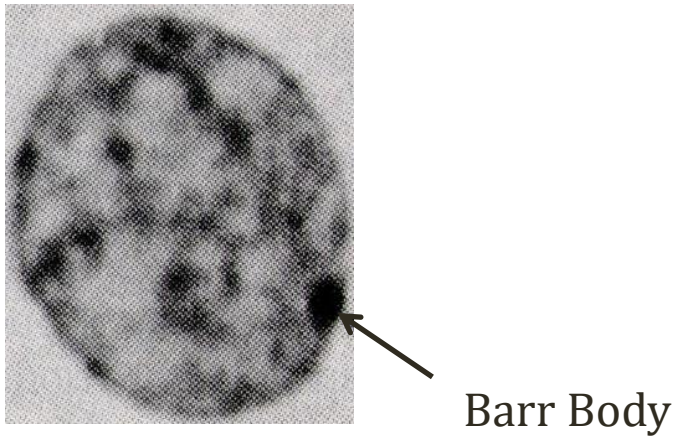


X-linked Recessive

- 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

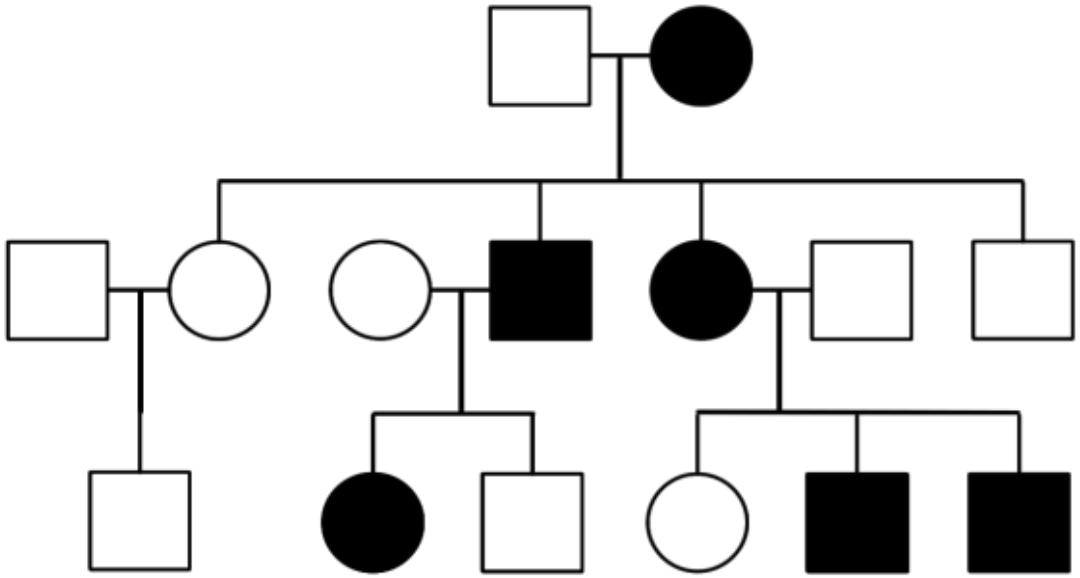


Lyonization

- 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"**

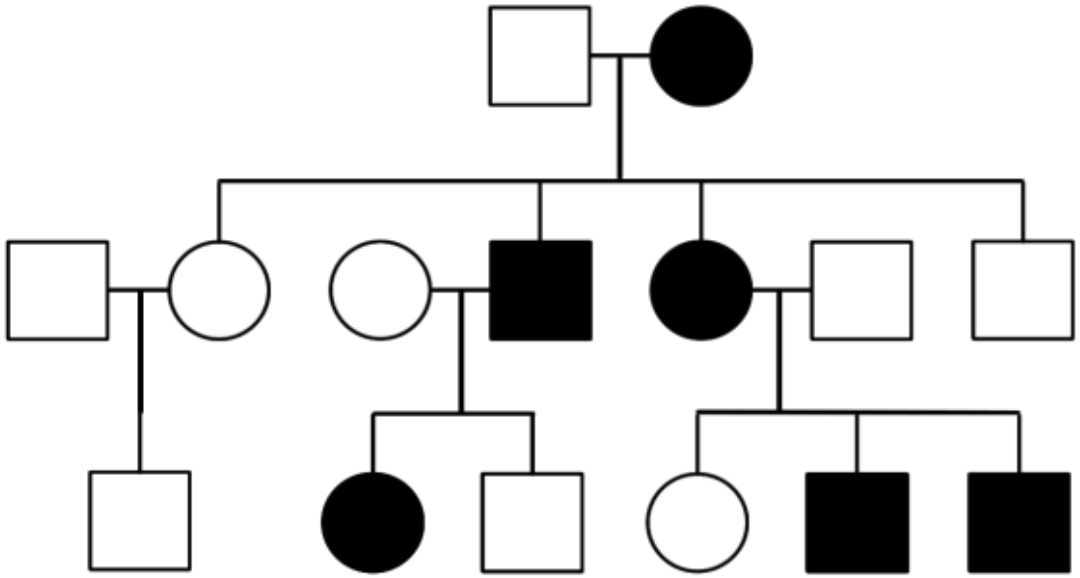
X-linked Dominant

- 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

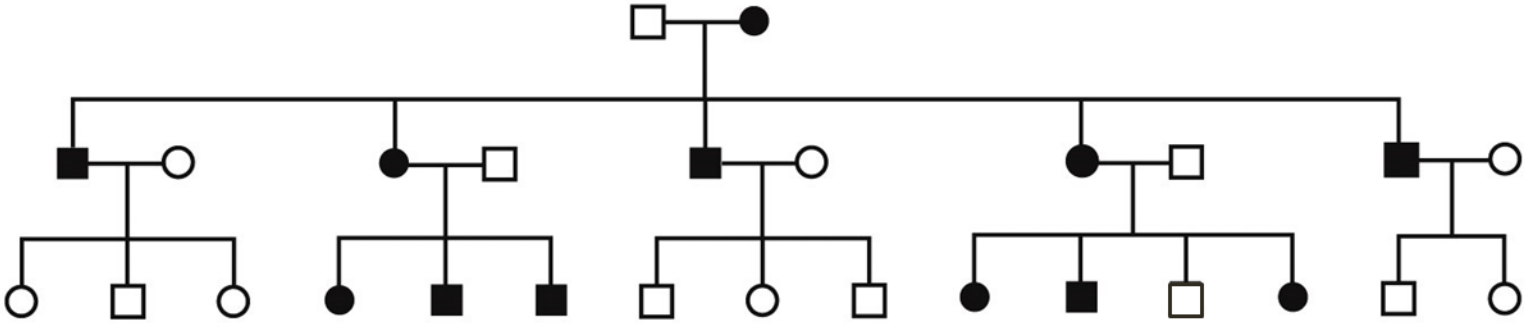
- Each mitochondria contains DNA (mtDNA)
  - Code for mitochondrial proteins
- Organs most affected by gene mutations:
  - CNS
  - Skeletal muscle
  - Rely heavily on aerobic metabolism

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

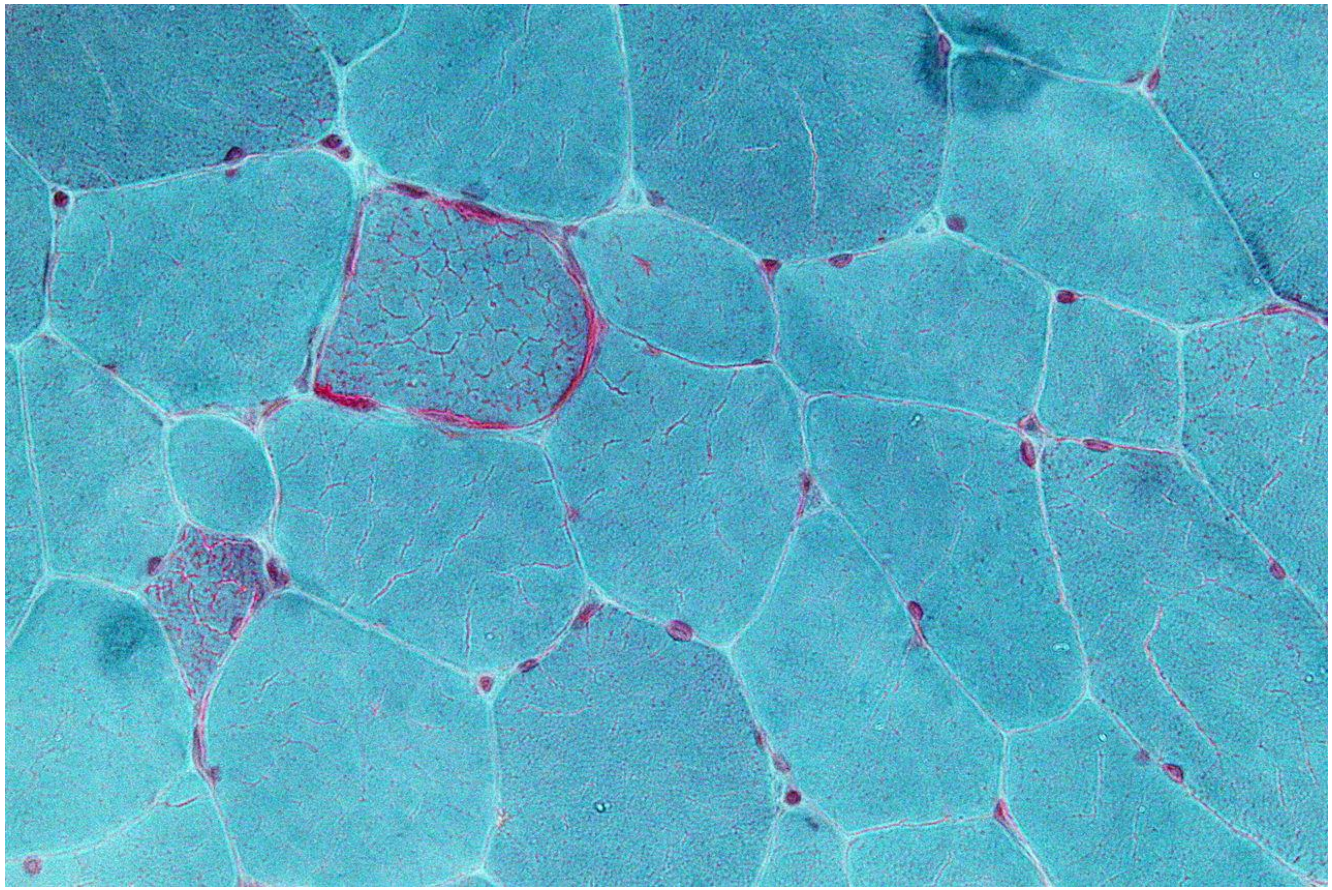
- Mitochondrial DNA inherited from mother
  - Sperm mitochondria eliminated from embryos
- Homoplasmic mothers → all children have mutation
- Heteroplasmic mothers → variable



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

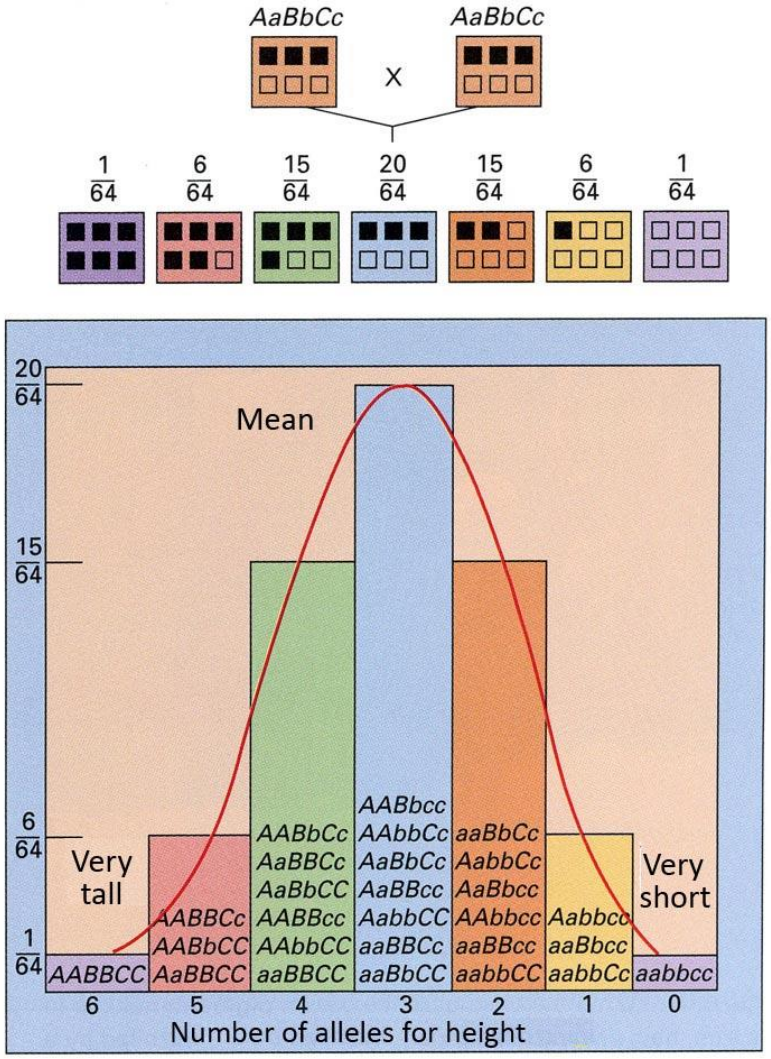


Nephron/Wikipedia

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



Wikipedia

Multifactorial Inheritance

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

Imprinting

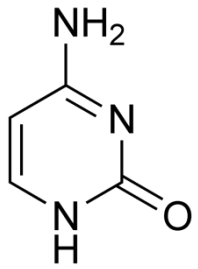
Jason Ryan, MD, MPH

Imprinting

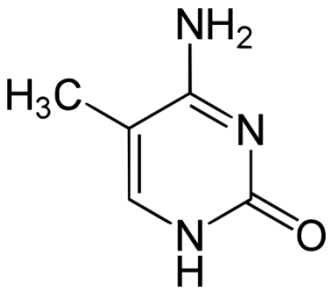
- **Epigenetic** phenomenon
  - Alteration in gene expression
  - Different expression in maternal/paternal genes

Imprinting

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



Cytosine



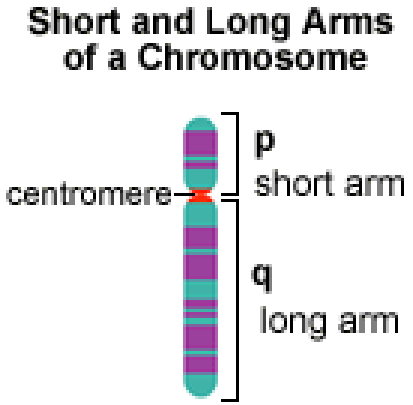
Methylcytosine

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



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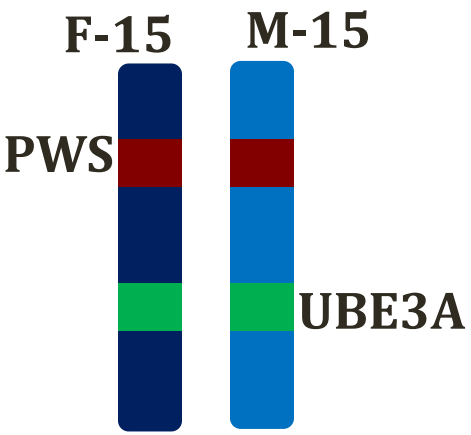
Imprinting Syndromes

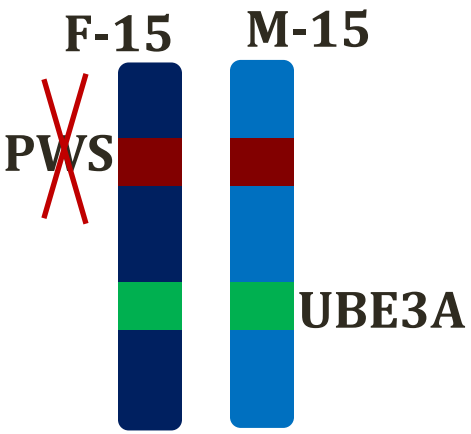
- PWS genes
  - Normally expressed on **paternal** chromosome 15
  - NOT normally expressed on maternal copy
- UBE3A
  - Normally expressed on **maternal** chromosome 15
  - NOT normally expressed on paternal copy



Prader-Willi Syndrome

PWS

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



Prader-Willi Syndrome

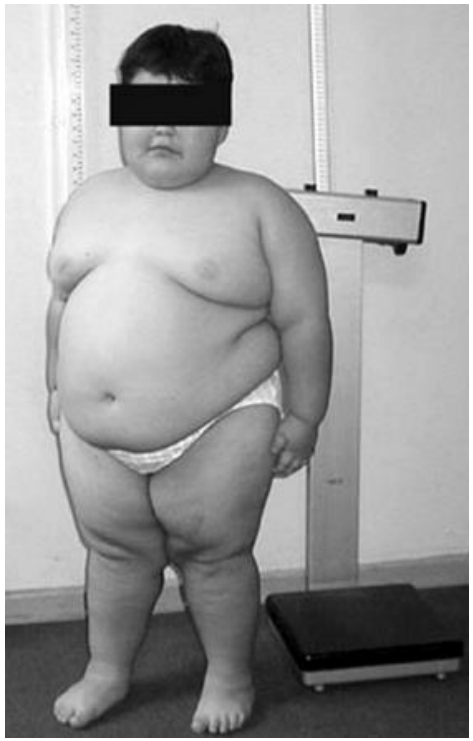
PWS

- ~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

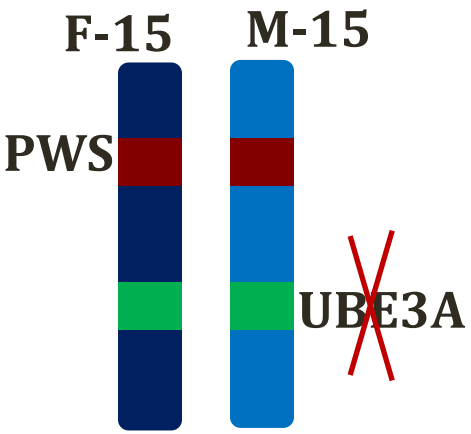
- Most common "syndromic" cause of **obesity**
- Hypotonia
  - Newborn feeding problems
  - Poor suck reflex
  - Delayed milestones
- Hyperphagia and obesity
  - Begins in early childhood
- Intellectual disability (mild)
  - Contrast with AS (severe)
- Hypogonadism
  - Delayed puberty



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

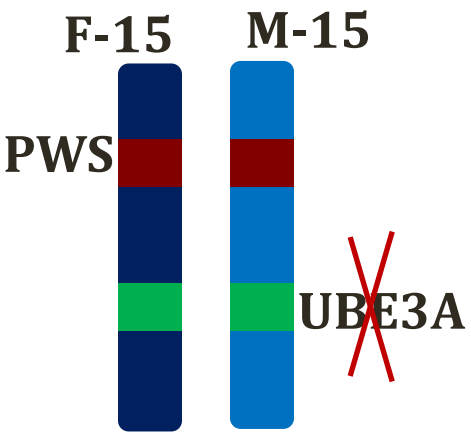
Angelman Syndrome

- 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

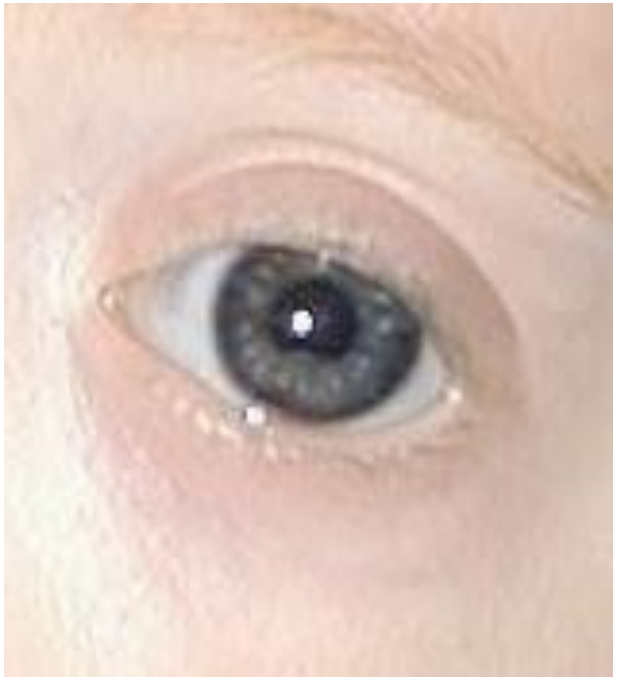
Dysmorphic Features

- 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

Wikipedia/Public Domain

Brushfield Spots

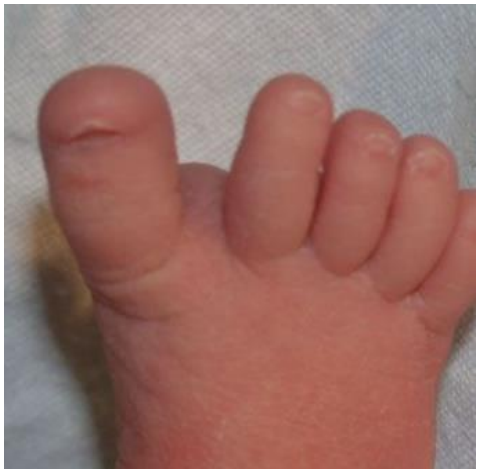
- White spots on iris

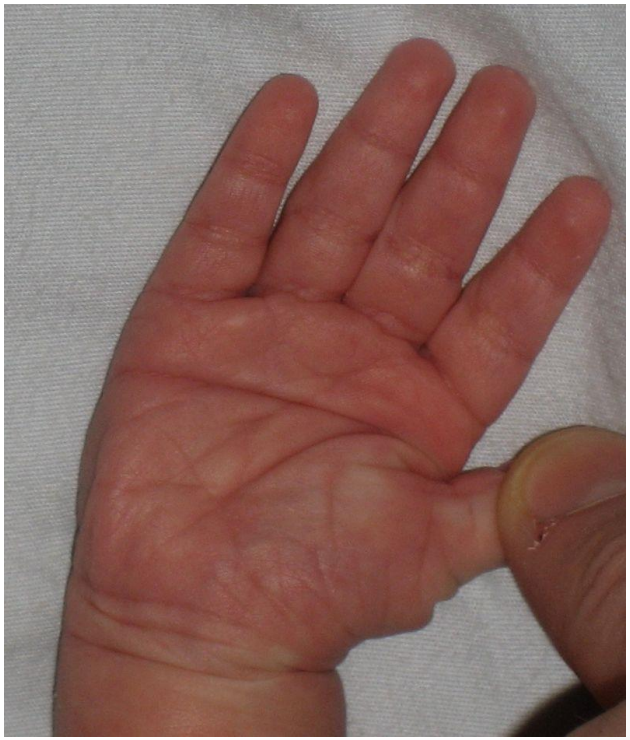


Erin Ryan/Wikipedia/Public Domain

Dysmorphic Features

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





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Other Physical Features

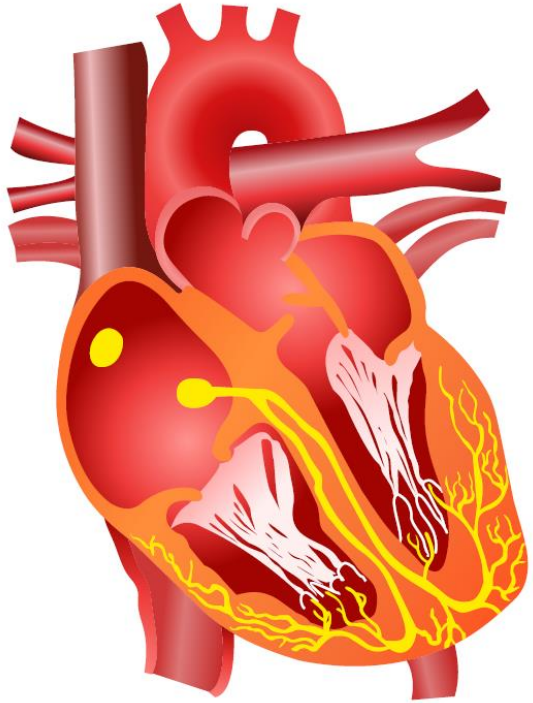
- Hypotonia
  - Often identified at birth
- Short stature

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

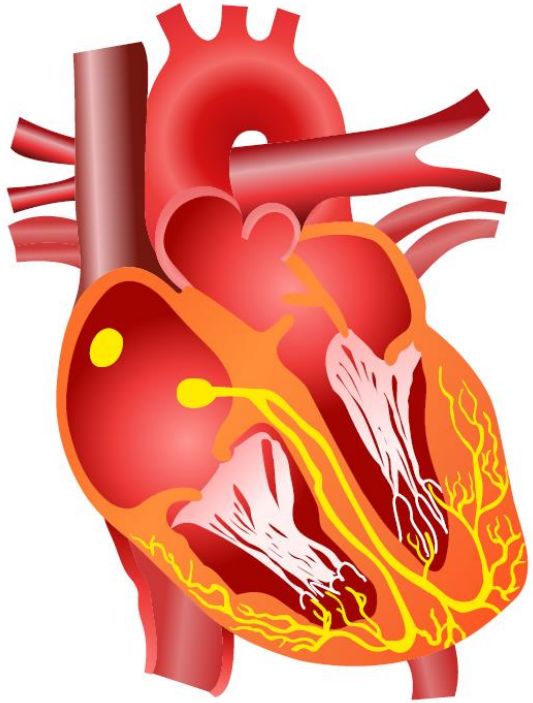
Congenital Heart Disease

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



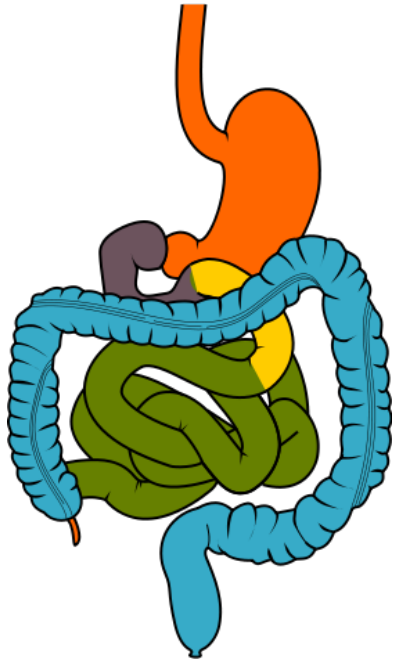
Congenital Heart Disease

- 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



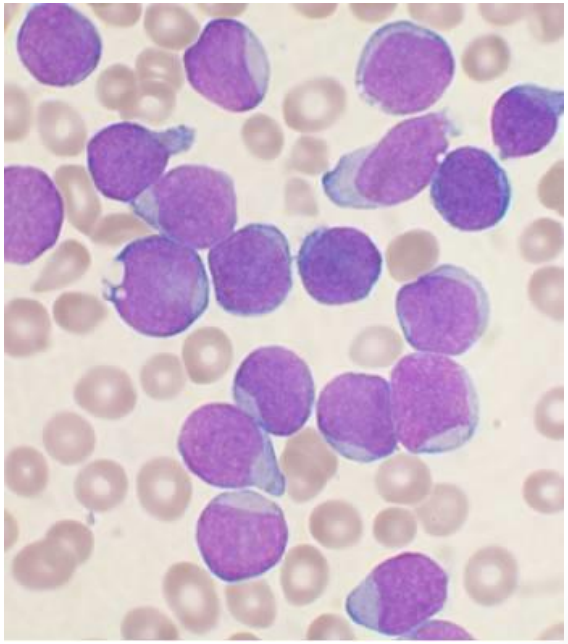
Olek Remesz/Wikipedia

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

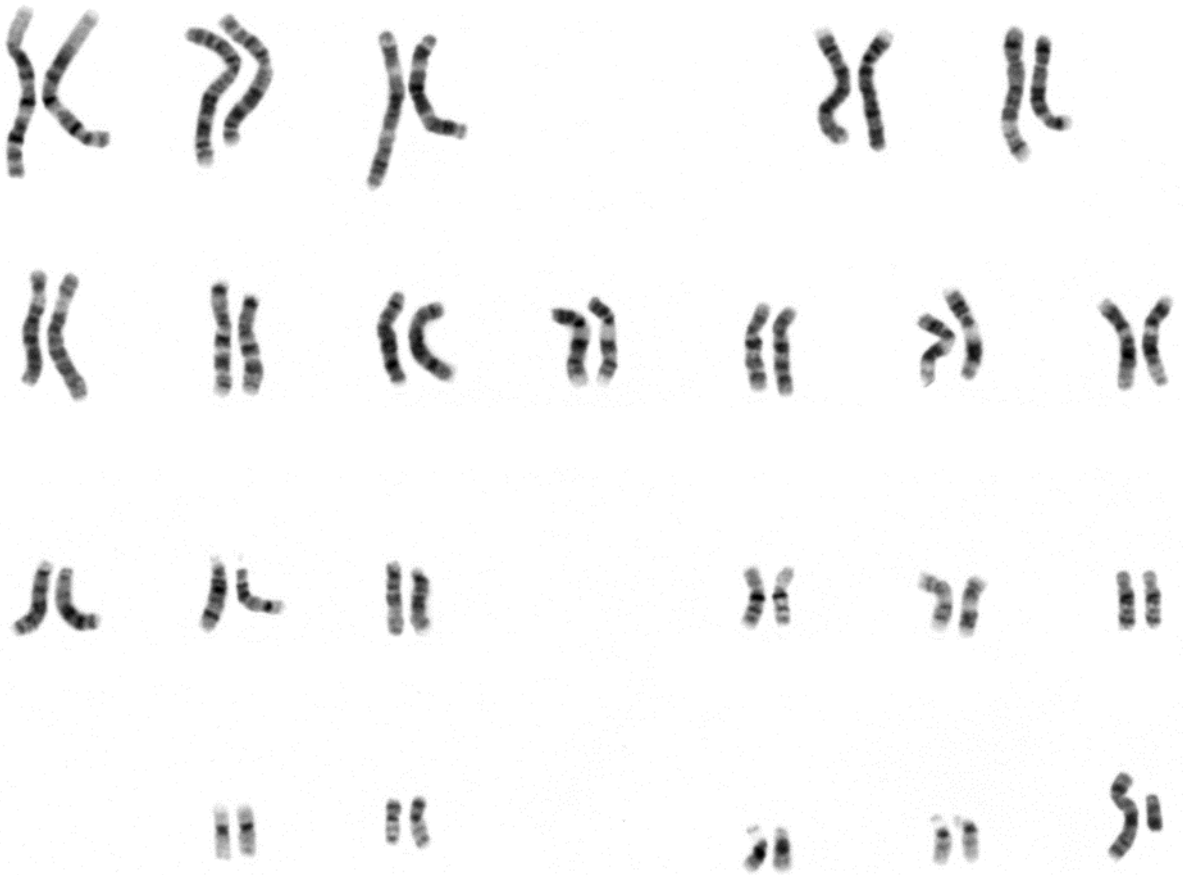
Down Syndrome

Prenatal Screening

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

Karyogram

Normal



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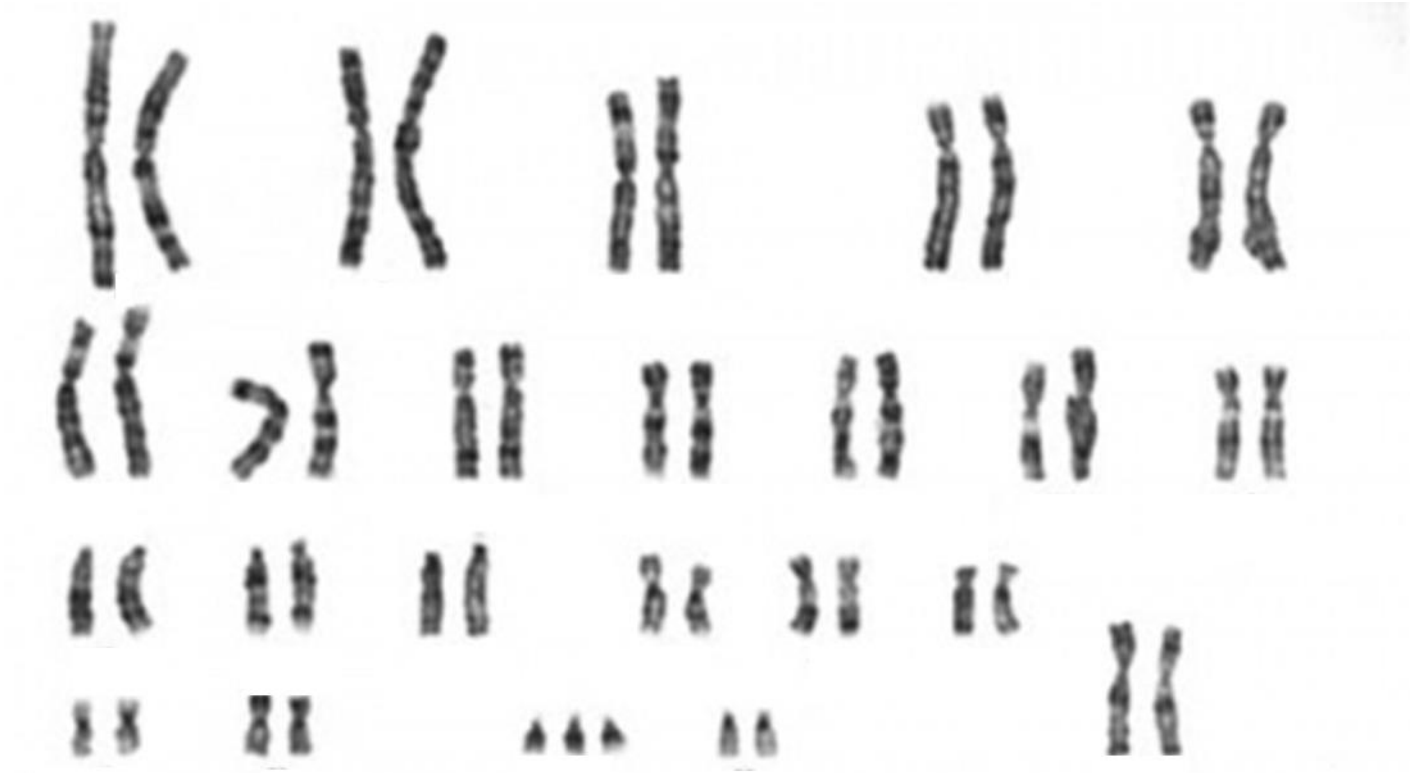
Karyogram

Trisomy



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Down Syndrome

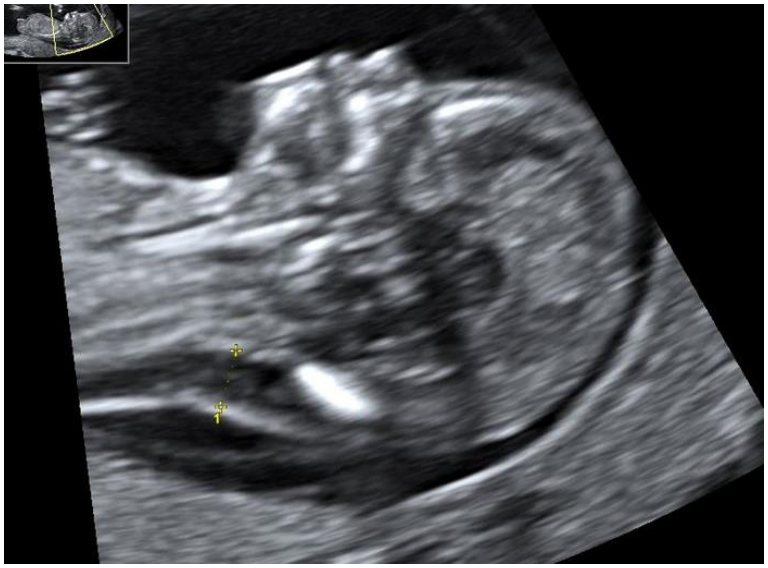
Prenatal Screening

- 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

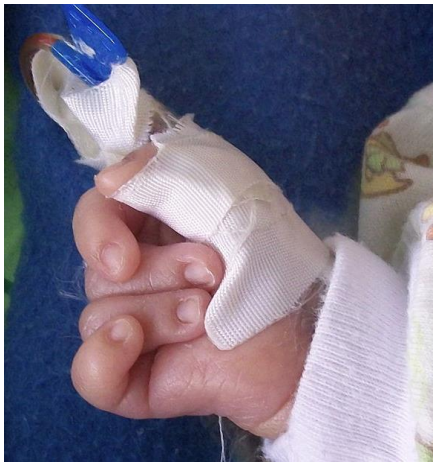
Trisomy 18

- 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

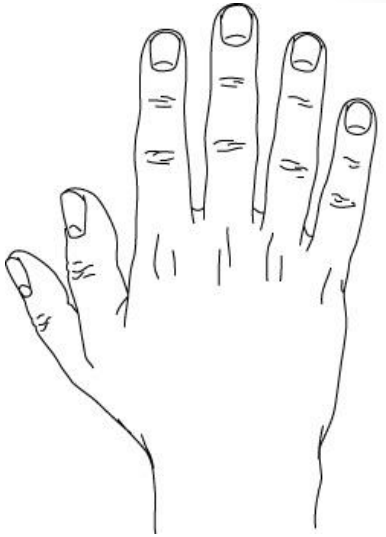
Trisomy 13

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

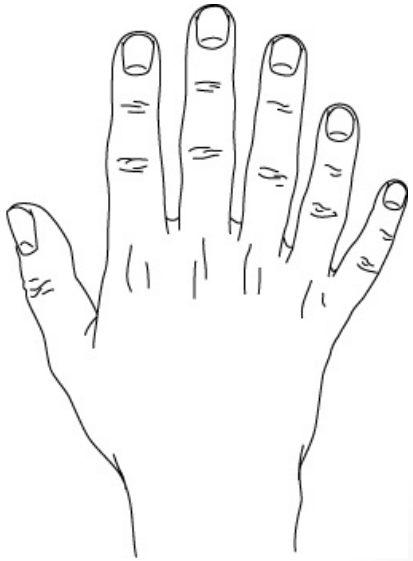
Patau Syndrome

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

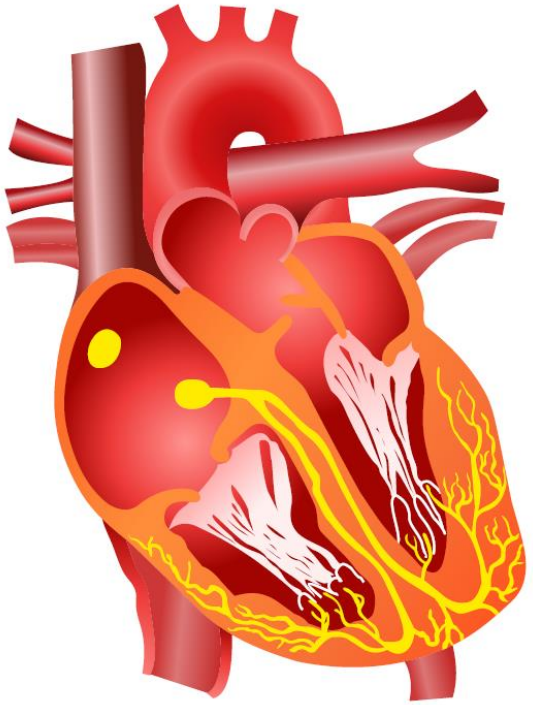
Trisomy 13

- **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

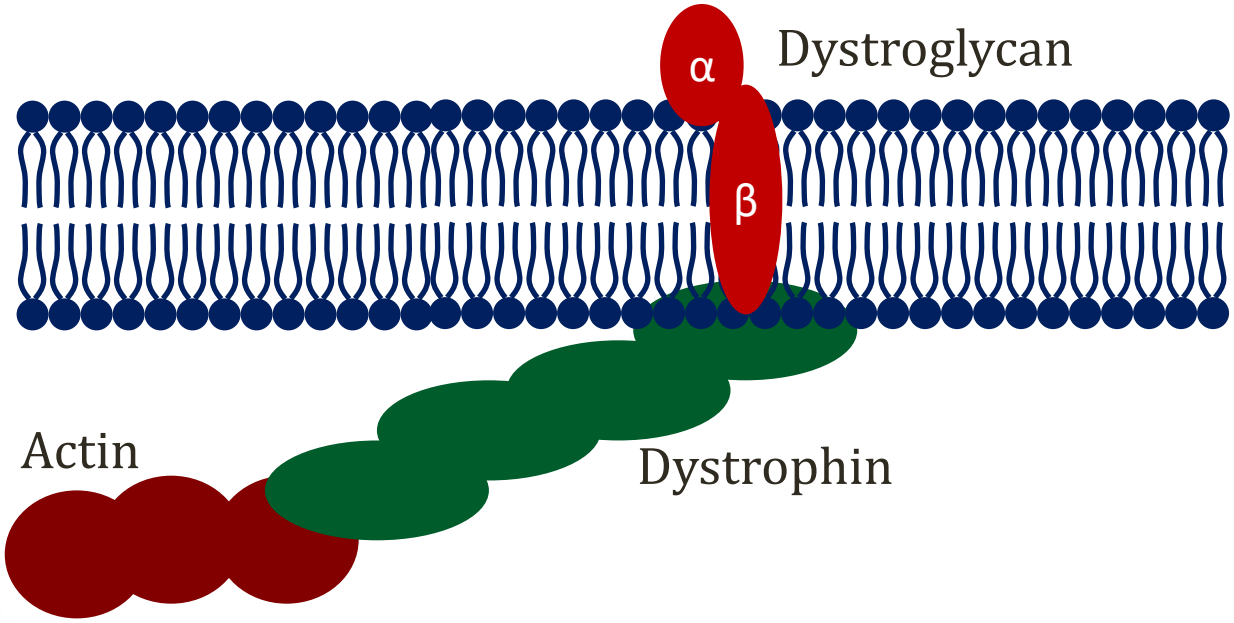
DMD

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**

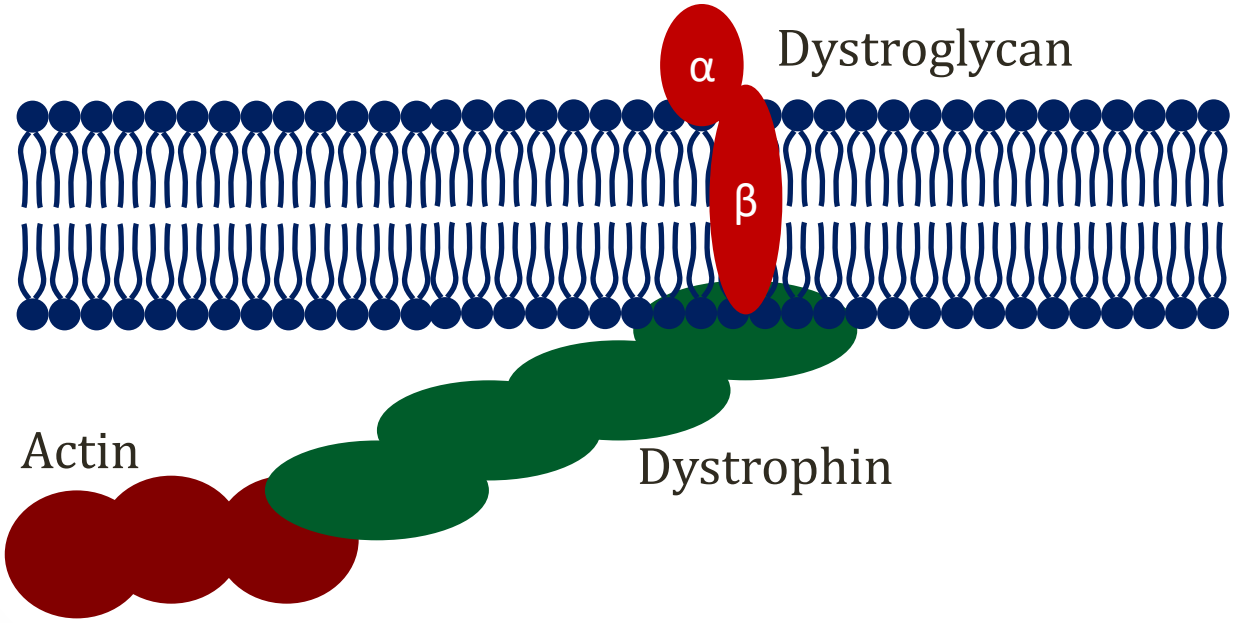
Dystrophin

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



Dystrophin

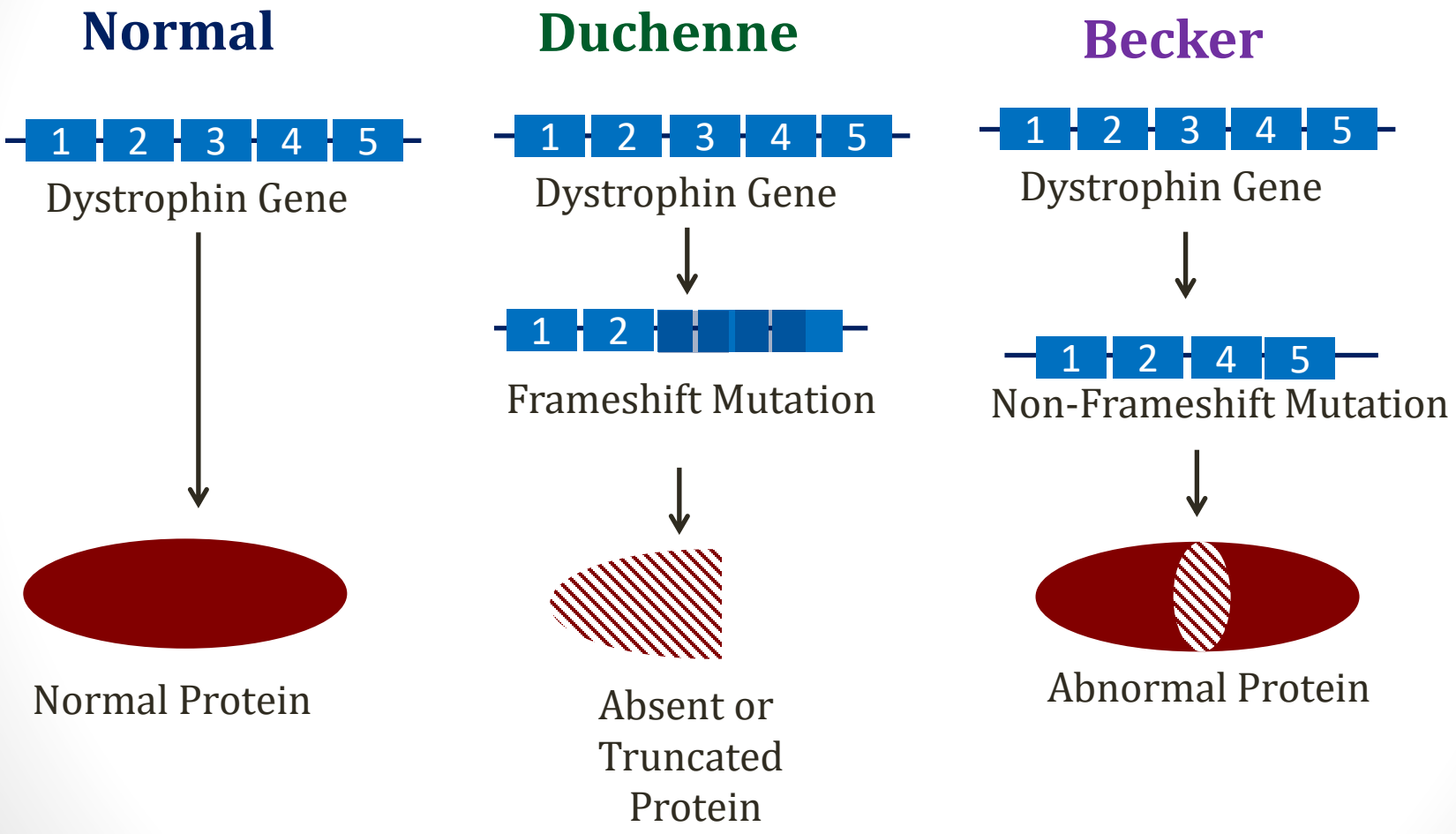
- Also found in cardiac and smooth muscle
- Also found in some brain neurons



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



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

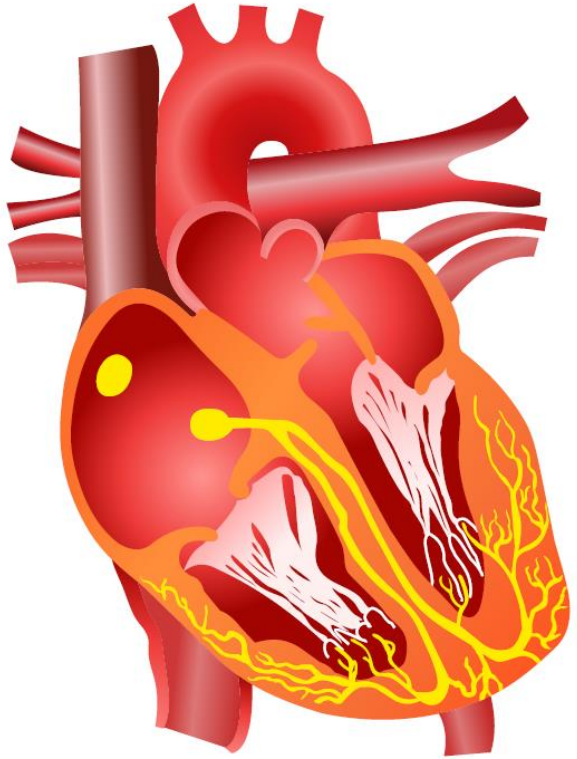
Duchenne Muscular Dystrophy

- 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

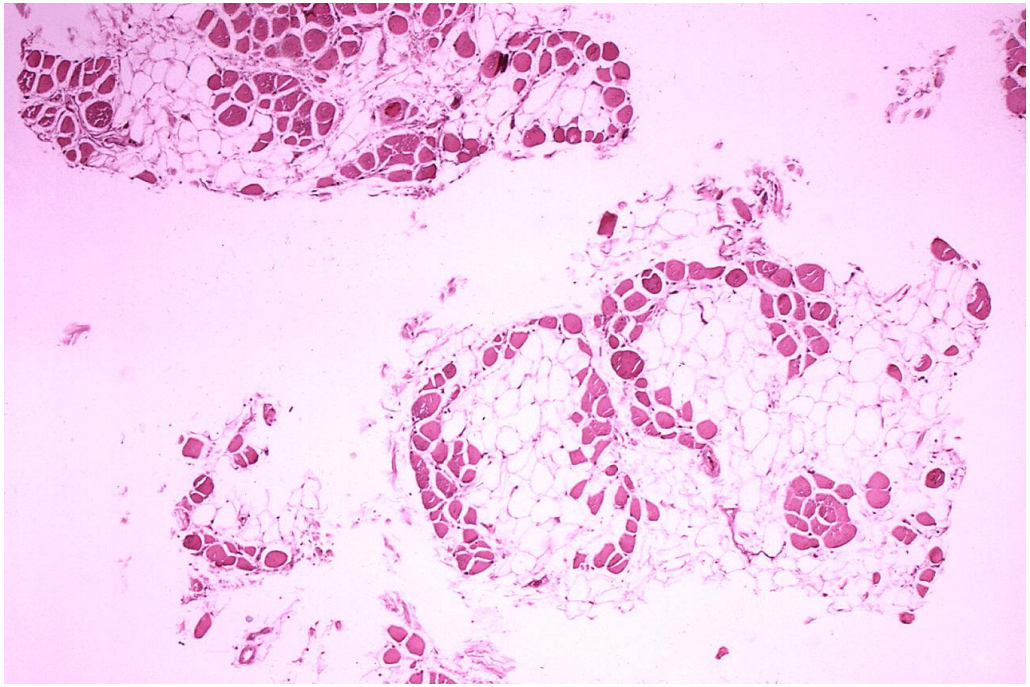
- **Cardiomyopathy**
  - Depressed LVEF
  - Systolic heart failure
  - Myocardial fibrosis
- Conduction abnormalities
  - AV block
  - Arrhythmias



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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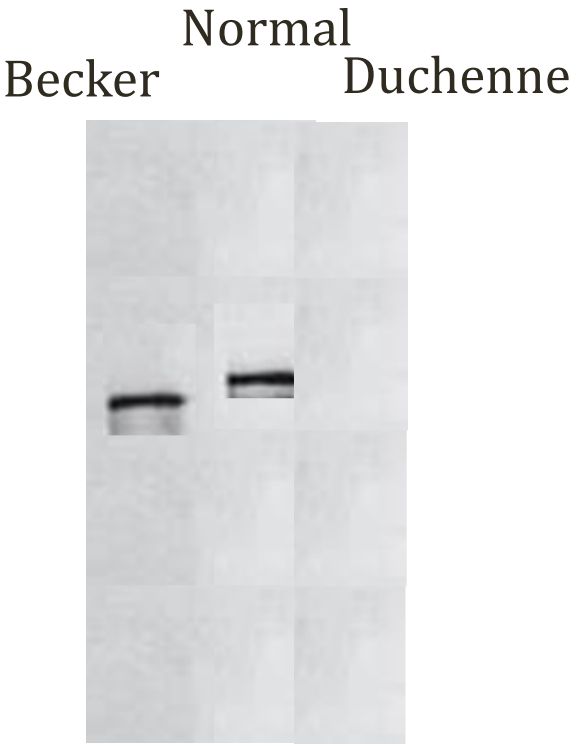
DMD

Duchenne Muscular Dystrophy

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



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

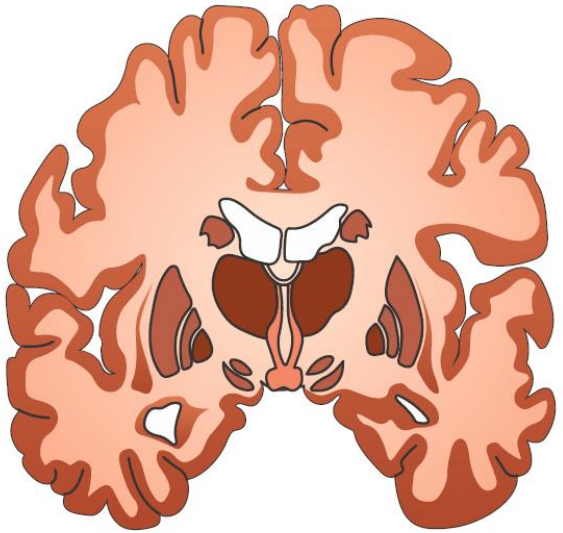
- Begins in adolescence with progressive symptoms
- Cerebellar and spinal cord degeneration
  - Loss of balance
  - Weakness
- Associated with **hypertrophic cardiomyopathy**
- Physical deformities:
  - Kyphoscoliosis
  - Foot abnormalities

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

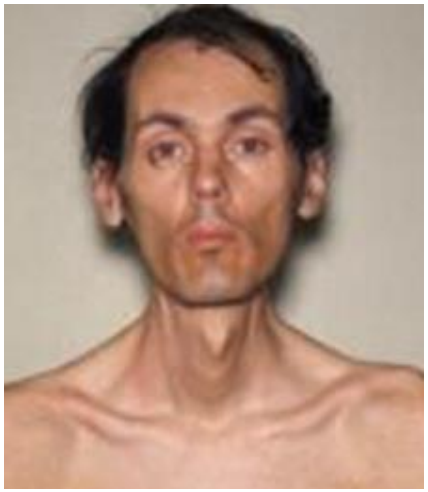
- Type I (most common)
  - Abnormal **DMPK gene** (chromosome 19)
  - Dystrophia myotonica protein kinase
  - CTG expansion
  - Codes for **myotonic dystrophy protein kinase**
  - Abnormal gene transcribed to mRNA but not translated
- Type 2: abnormal CNBP gene
  - Rare type
  - Usually less severe than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

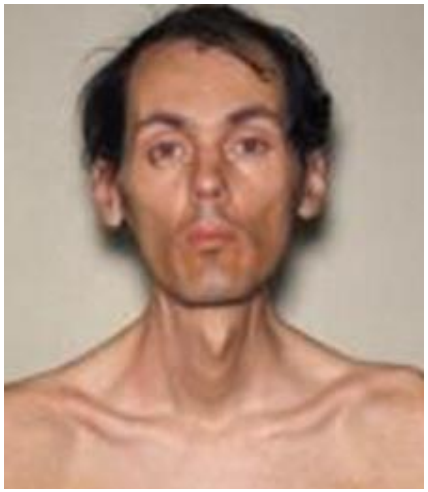
- **Facial muscles** often affected
- Characteristic facial appearance
- Caused by muscle weakness and wasting
- Long and narrow face
- Hollowed cheeks



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

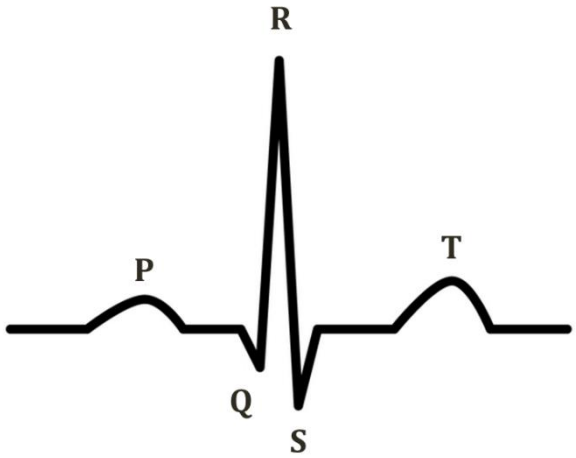
Endocrine Involvement

- 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

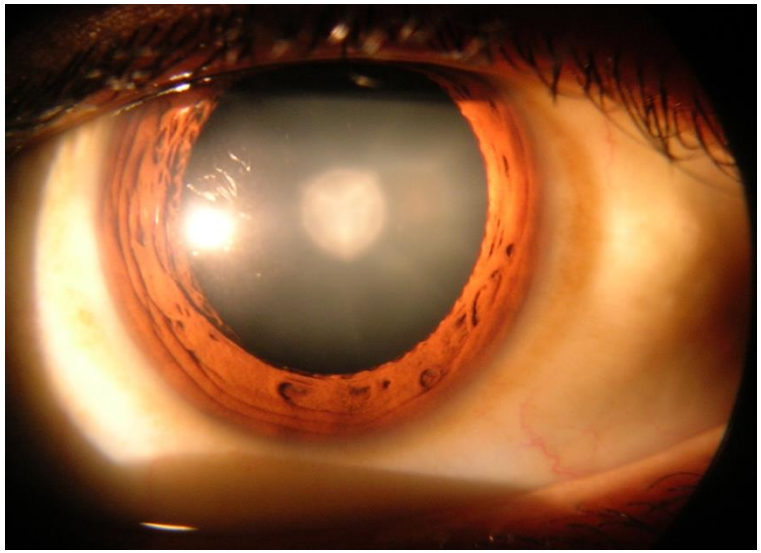
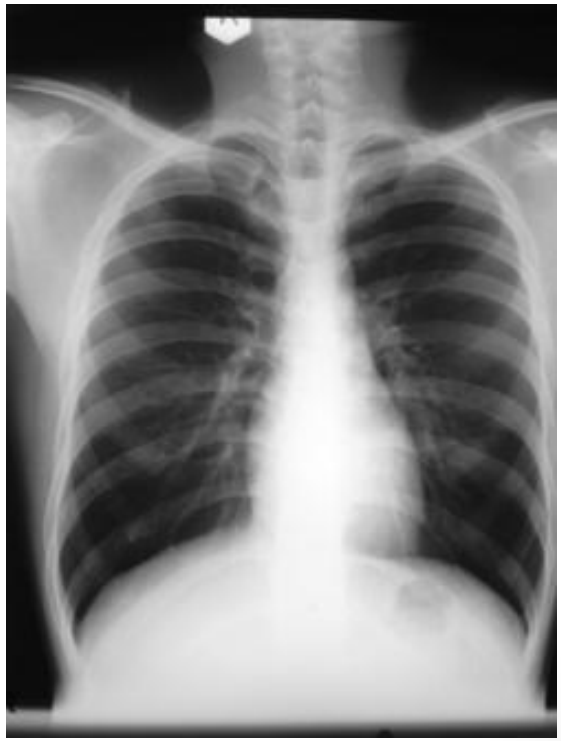


Image courtesy of Rakesh Ahuja, MD

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

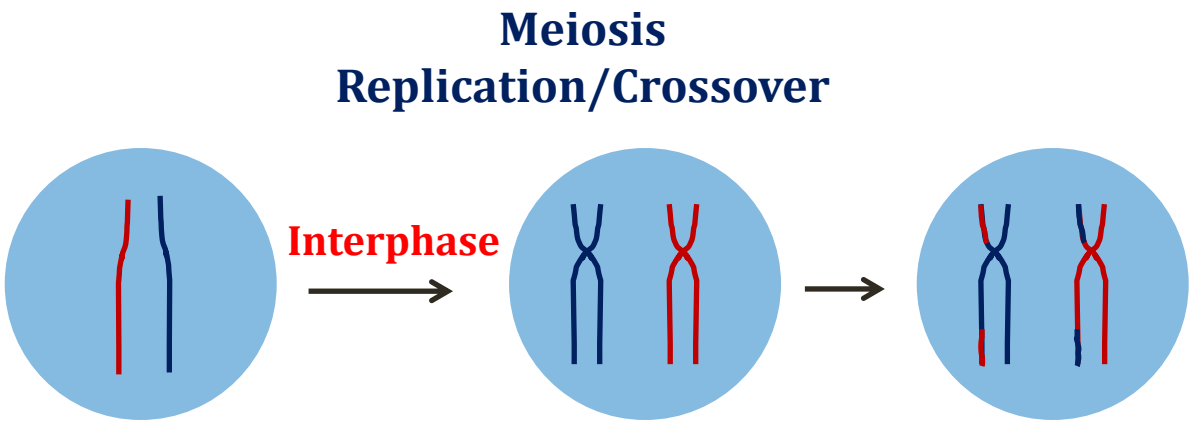
Jason Ryan, MD, MPH

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

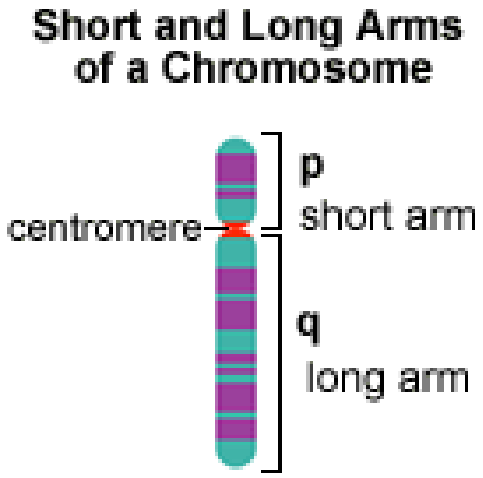


Deletion Syndromes

- 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"



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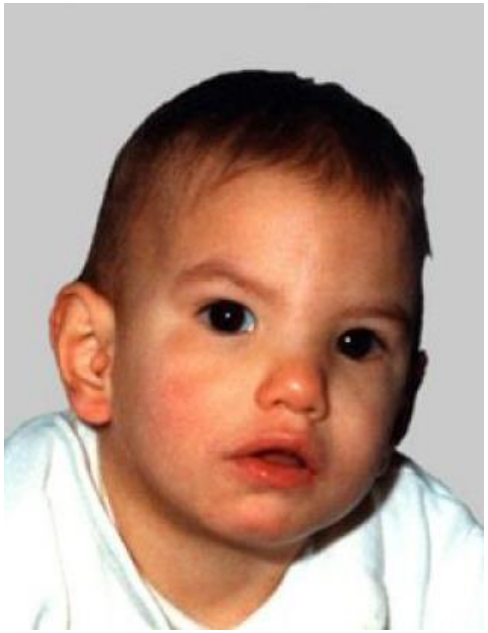
Cri-du-chat Syndrome

- 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

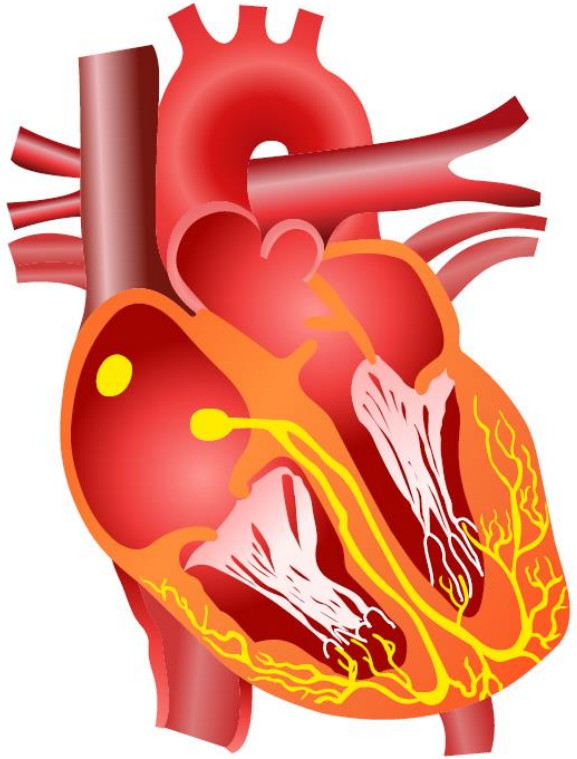
- Microcephaly (small head)
- Characteristic facial features
  - Widely set eyes (hypertelorism)
  - Low-set ears
  - Small jaw
  - Rounded face



Paola Cerruti Mainardi.

Cri-du-chat Syndrome

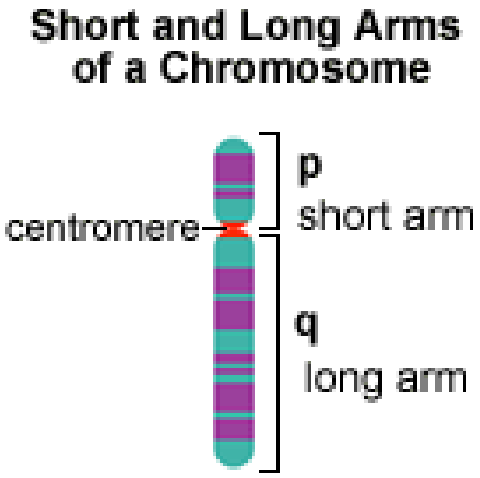
- **Congenital heart defects**
  - Ventricular septal defect (VSD)
  - Patent ductus arteriosus (PDA)
  - Tetralogy of Fallot (TOF)
  - Others



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 "haploinsufficency"



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Williams Syndrome

Williams-Beuren syndrome

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

Williams Syndrome

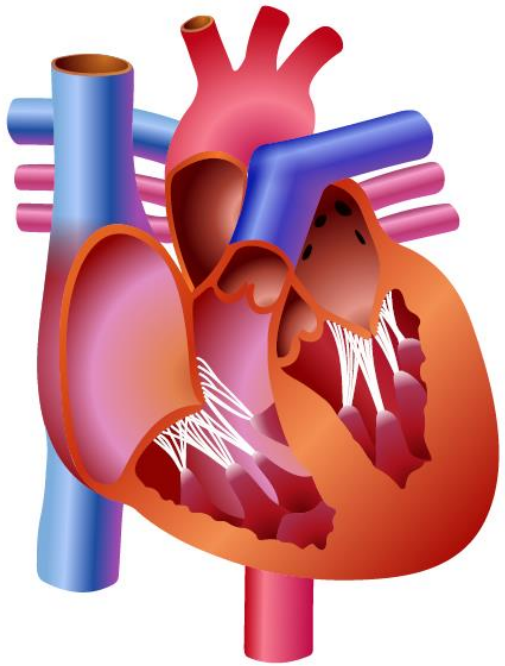
Williams-Beuren syndrome

- 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 prevalance among children with WS
- Pulmonary artery stenosis
- Renal artery stenosis



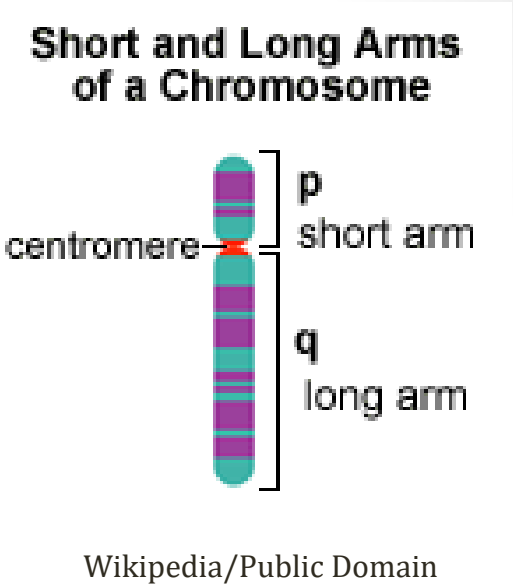
Williams Syndrome

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



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- 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

Klinefelter and Turner Syndromes

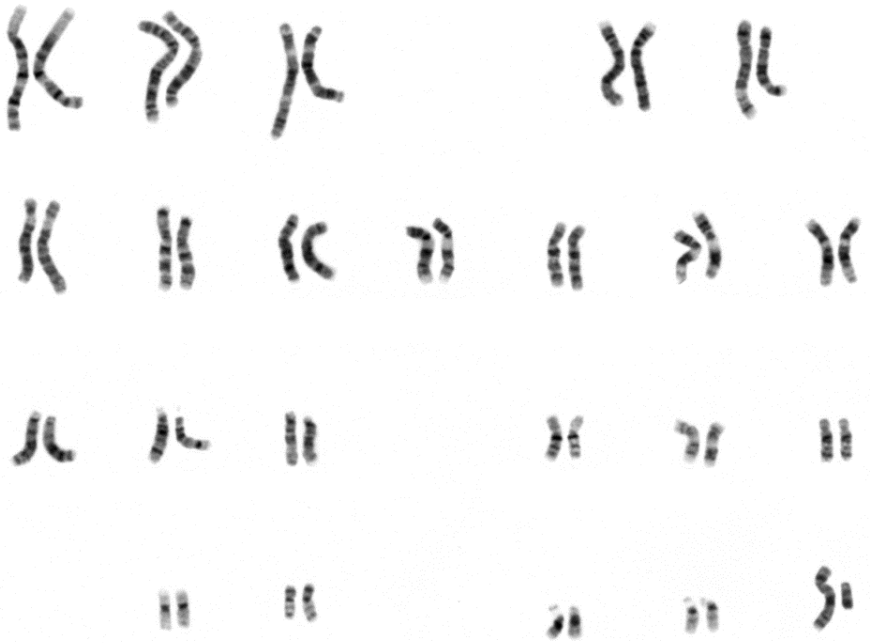
Jason Ryan, MD, MPH

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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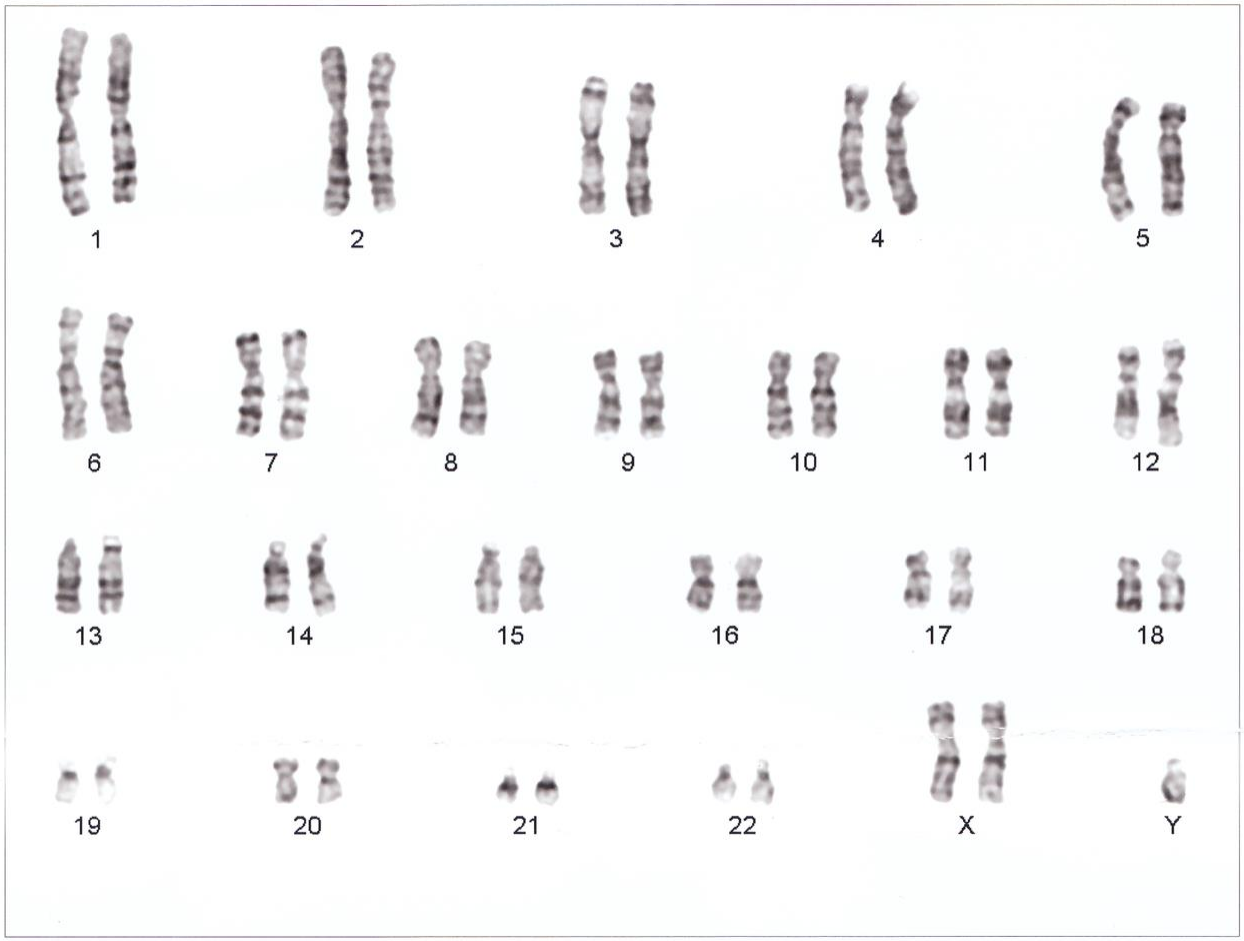
Klinefelter Syndrome

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

Klinefelter Syndrome



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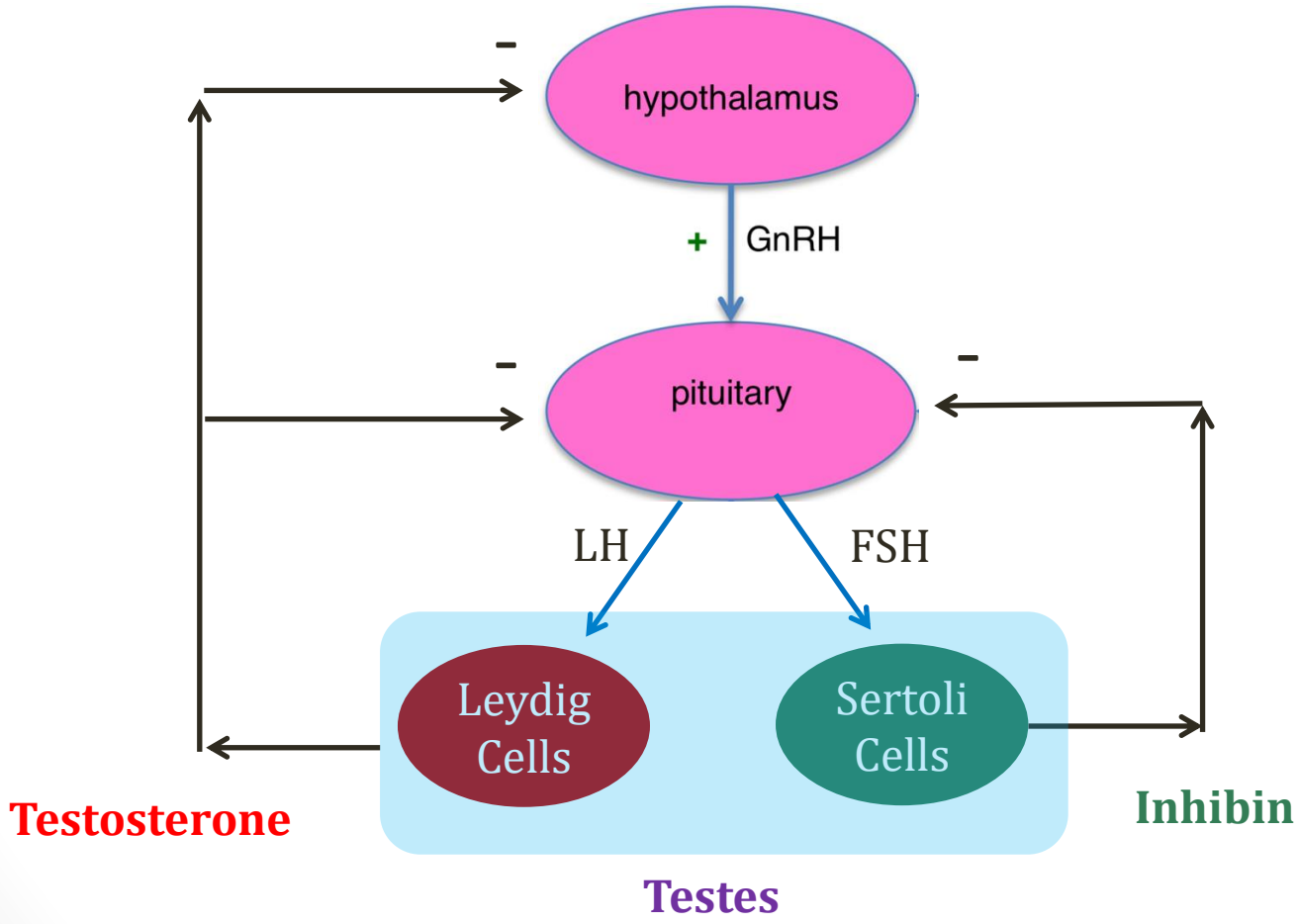
Klinefelter Syndrome

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

Klinefelter Syndrome

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

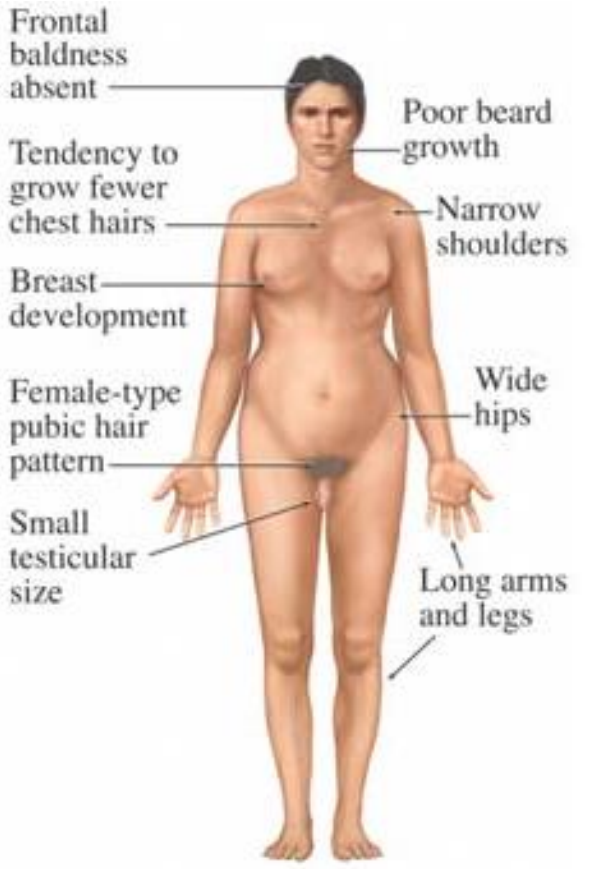
FSH and LH



Klinefelter Syndrome

Low Testosterone Features

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

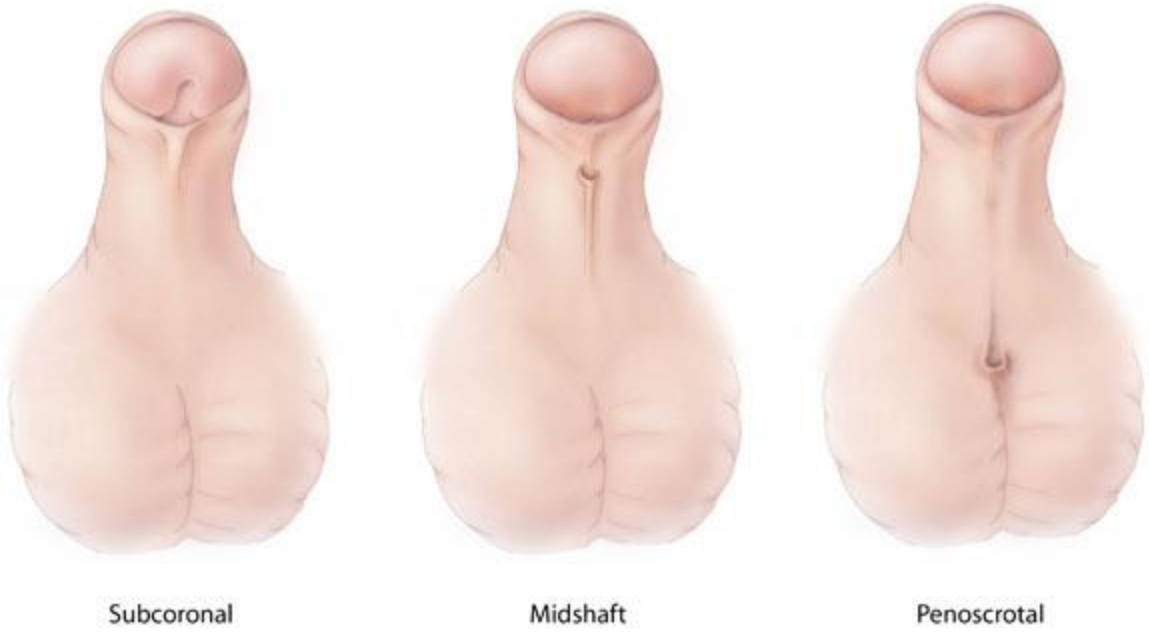


Wikipedia

Klinefelter Syndrome

Genital Abnormalities

- Cryptorchidism (undescended testes)
- Hypospadia
- Micropenis



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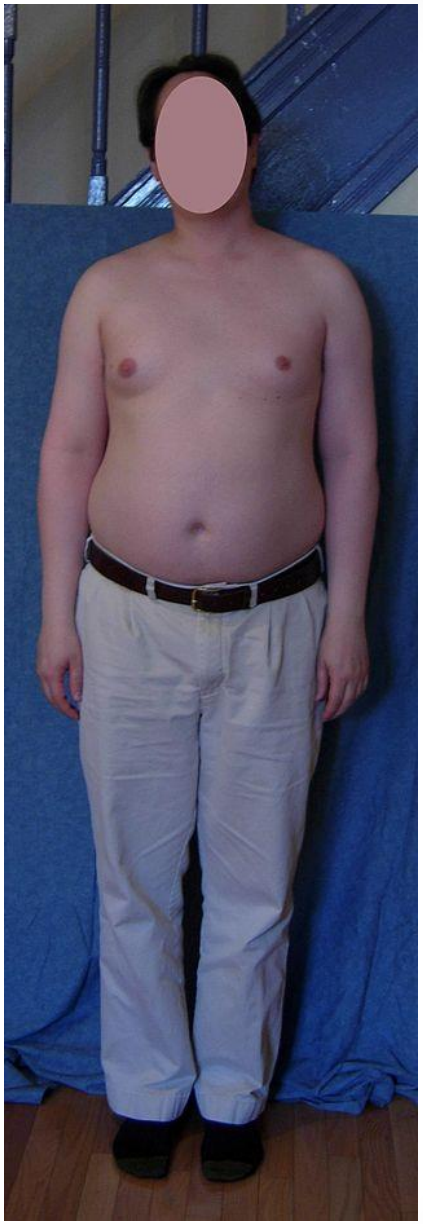
Klinefelter Syndrome

Physical Appearance

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



Malcolm Gin/Wikipedia

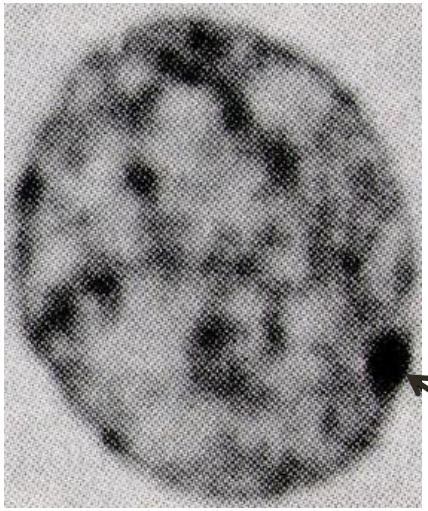
Klinefelter Syndrome

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



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

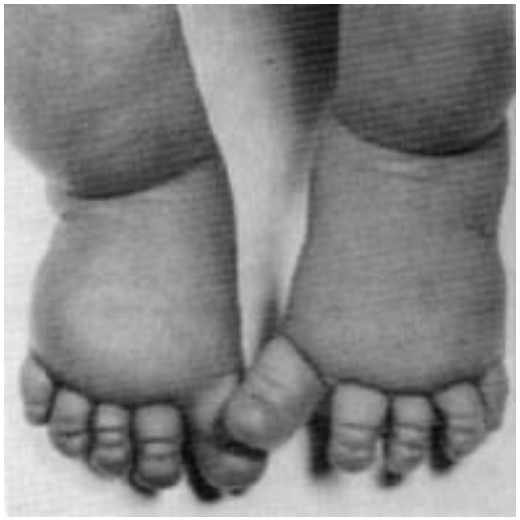
General Features

- 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)

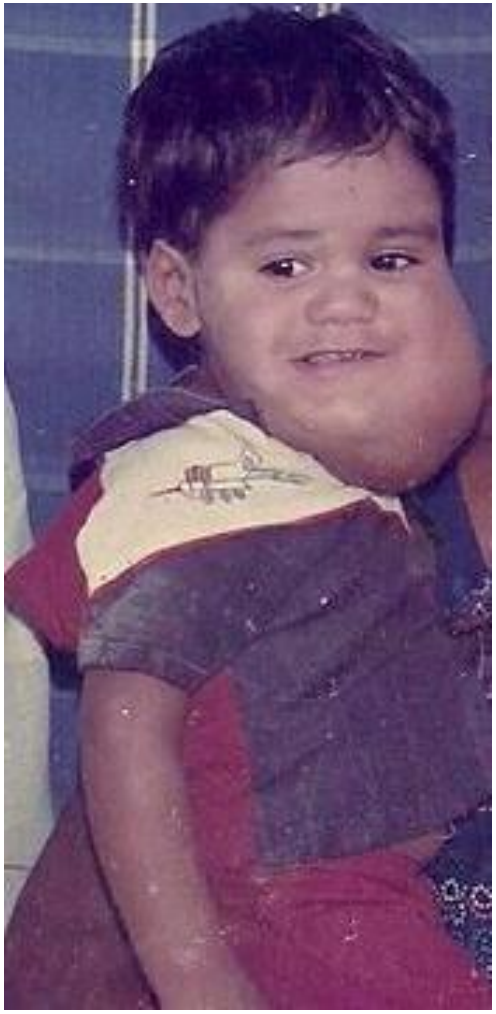


Wikipedia

Johannes Nielsen/Wikipedia

Cystic Hygroma

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

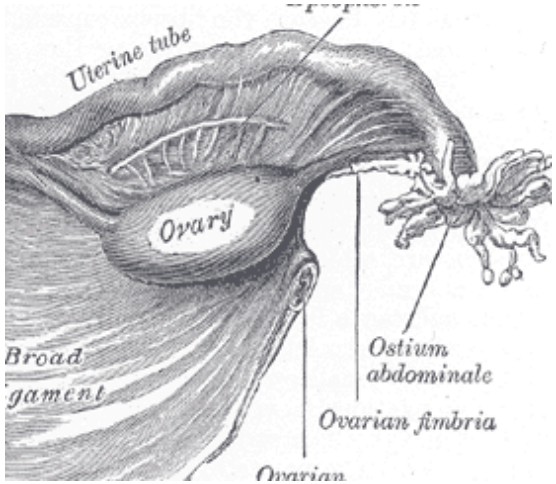


Vardhan Kothapalli

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

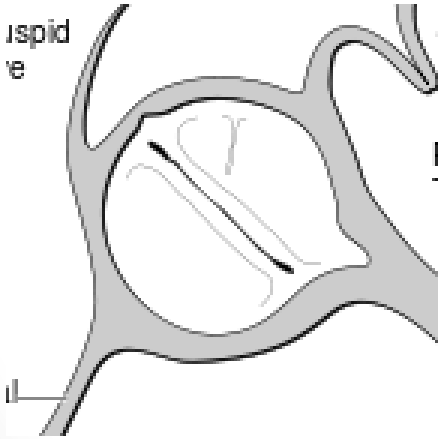
- Most women **infertile**
- Some can become pregnant with donated oocytes

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 in childhood
  - Sometimes due to coarctiaton or renal disease
  - Often primary

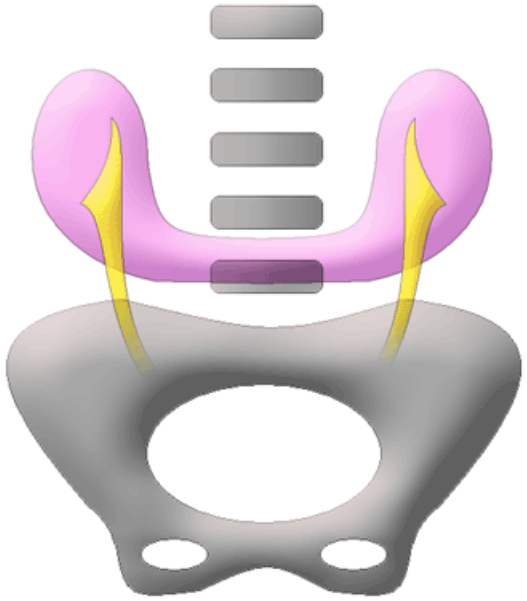


Patrick J. Lynch, medical illustrator

Turner Syndrome

Renal Manifestations

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



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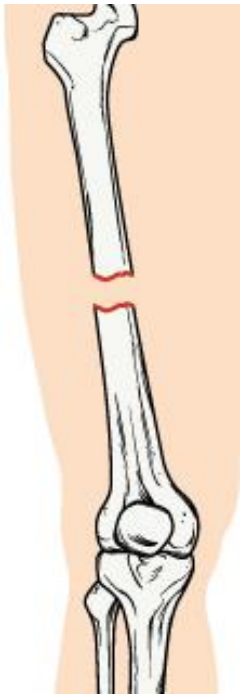
Turner Syndrome

Osteoporosis

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



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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