Lecture 4A:
Abnormalities in Chromosome Number
Abnormalities in Chromosome Structure

Genetic Disorders

- **Congenital disorder**-a disorder that is present at birth, whether it is due to a genetic (inherited) condition, environmental effects or a combination of both.
- About 30-40% of congenital malformations are due to inherited genetic defects:
  - About 6% of those defects are due to **chromosomal abnormalities.**
  - About 8% of those defects are due **single gene defects.**
  - The remaining defects are **multifactorial,** due to multiple gene defects.

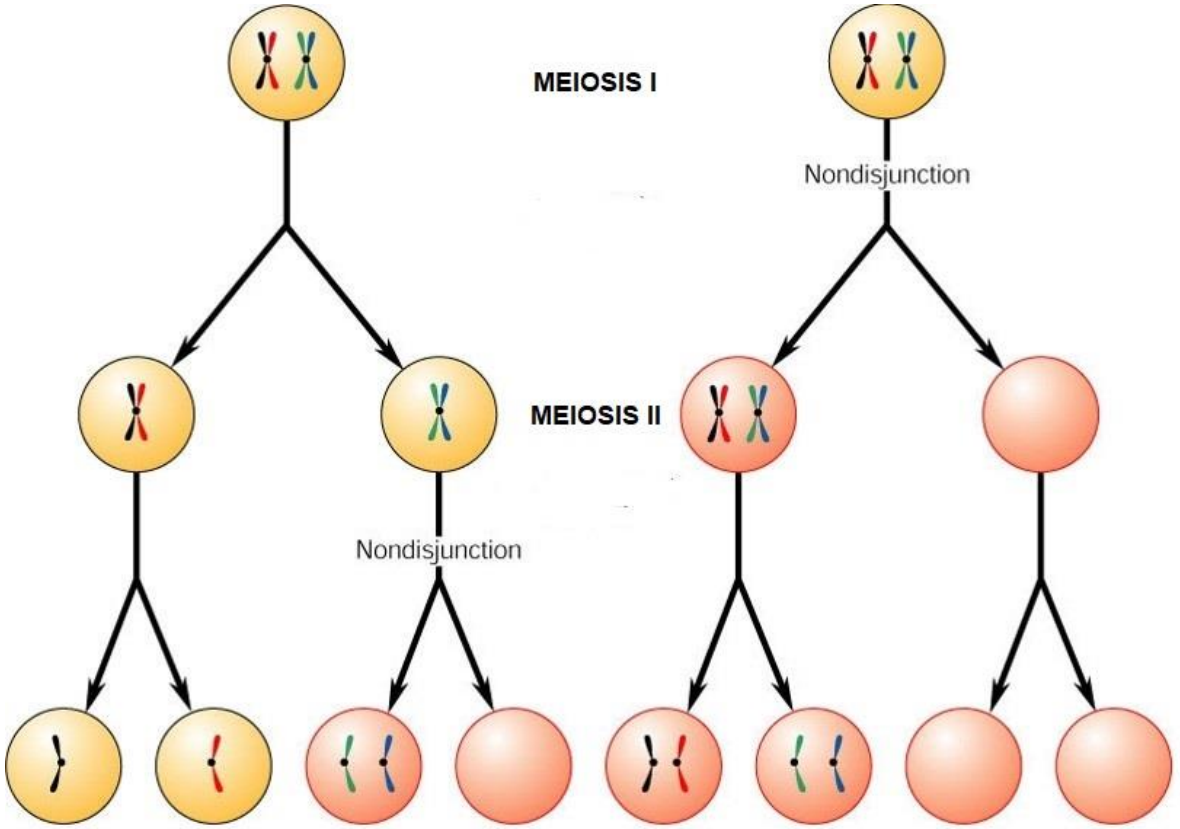
Genetic Disorders 1

- Chromosome Abnormalities
- Mendelian Single-Gene Disorders
- Non-Mendelian Single-Gene Disorders
- Multifactorial (Polygenic) Disorders

Genetic Disorders: Abnormalities in Chromosome Number

- Abnormalities in chromosome number (**aneuploidy**) are the result of **nondisjunction**, the failure of chromosomes to properly separate into daughter cells at the end of either meiosis I or meiosis II.
  - Normally, the 46 chromosomes align at the metaphase plate as **23 paired dyads during meiosis I**. If nondisjunction occurs for a pair of dyads, both dyads will enter the same daughter cell, rather than one dyad entering each of the two daughter cells. All four gametes will be abnormal.
  - Normally, the chromosomes align as **23 unpaired dyads during meiosis II**. If nondisjunction occurs for an unpaired dyad, the dyad fails to separate into two monads, and enters just one of the two daughter cells. Half of the gametes are abnormal.

Nondisjunction During Meiosis



A nondisjunction event during meiosis II produces 2 normal gametes and 2 abnormal gametes

A nondisjunction event during meiosis I produces 4 abnormal gametes

Genetic Disorders: Abnormalities in Chromosome Number 1

- A nondisjunction event leads to gametes that carry one more or one less chromosome than a normal gamete.
- If a gamete that has two copies of a particular chromosome (instead of the normal one copy) forms a zygote with a gamete having a normal haploid set of chromosomes, the diploid zygote will have three copies of the particular chromosome. This condition known as **trisomy**.
- If a gamete that has zero copies of a particular chromosome (instead of the normal one copy) forms a zygote with a gamete having a normal haploid set of chromosomes, the diploid zygote will have just one copy of the particular chromosome. This condition known as **monosomy**.

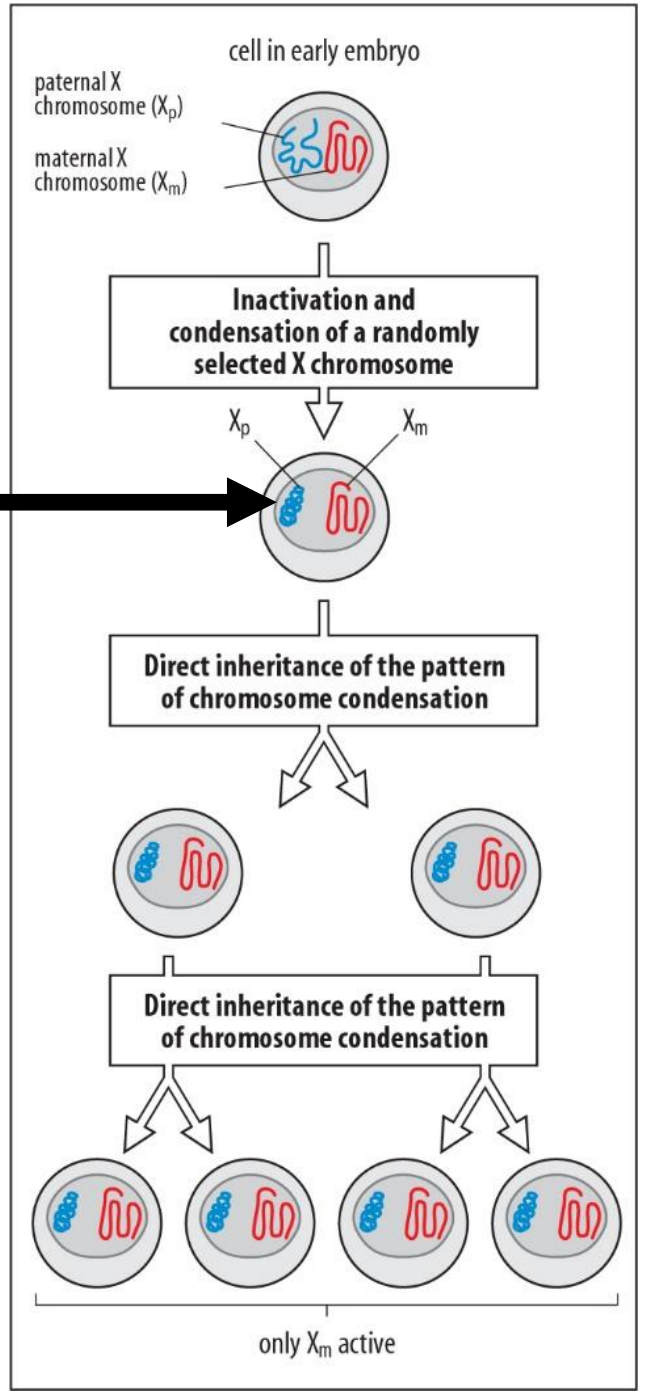
Genetic Disorders: Abnormalities in Chromosome Number 2

- Nondisjunction is associated with **advanced maternal age**. At about age 35 the chances of aneuploidy due to nondisjunction increase dramatically.
- Nondisjunction of either sex chromosomes or autosomes may occur, and the gametes produced may be fertilized.
- Monosomy for an autosome is not compatible with life. The pregnancy ends in early miscarriage.
- Monosomy for the X chromosome is more common and less debilitating. In normal females only one active X chromosome is required for most of the life span. Early in the fetal stage, one of the X chromosomes is inactivated (becomes a **Barr body**). Still, the XO sex chromosome constitution is not without consequences due to lack of the second X between fertilization and Barr body formation.

X Inactivation

In this example, the paternal X chromosome is inactivated to form a Barr body (structure shown in blue). **The genes on that paternal X are expressed before Barr body formation, but not afterward.**

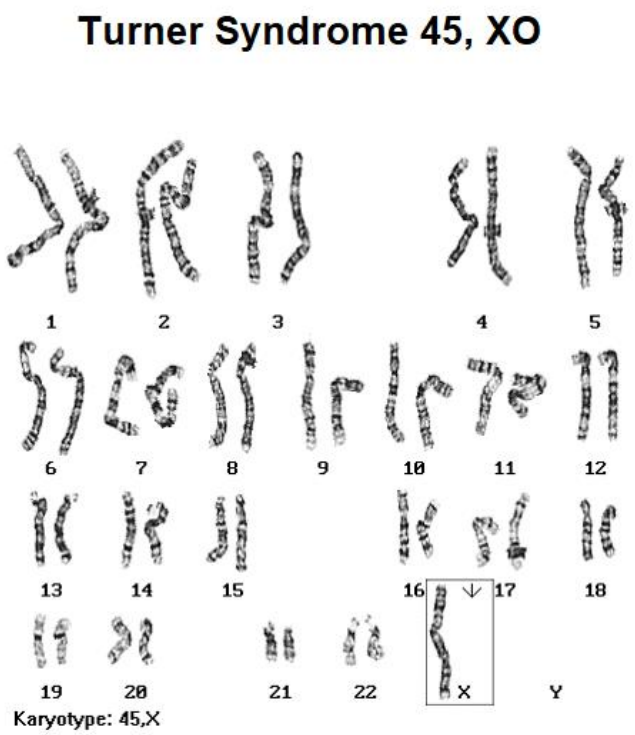
Paternal vs maternal X inactivation occurs at random.

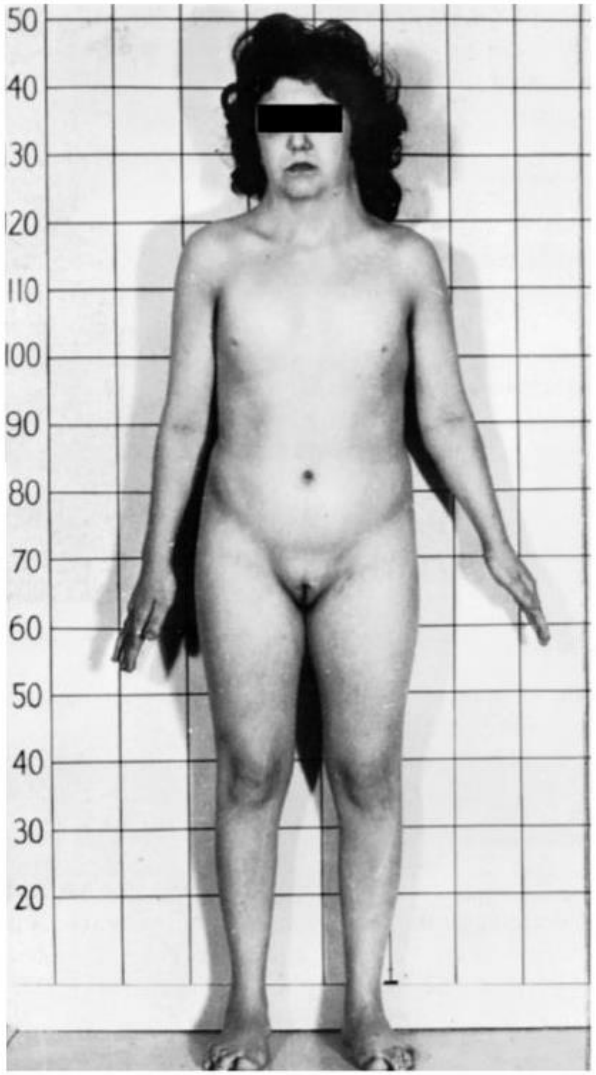


Genetic Disorders:
Abnormalities in Chromosome Number 3

- **Turner Syndrome (XO)**
  - Monosomy for the X chromosome
  - Occurrence: 1 in 3000 live births
  - 97% of XO embryos do not survive to birth
  - Female phenotype
  - Short stature, webbed neck, wide chest
  - Fibrous ovaries, sterility, amenorrhea
  - Congenital heart defects
  - Average life-expectancy is reduced by up to 13 years.

Genetic Disorders:
Abnormalities in Chromosome Number 4

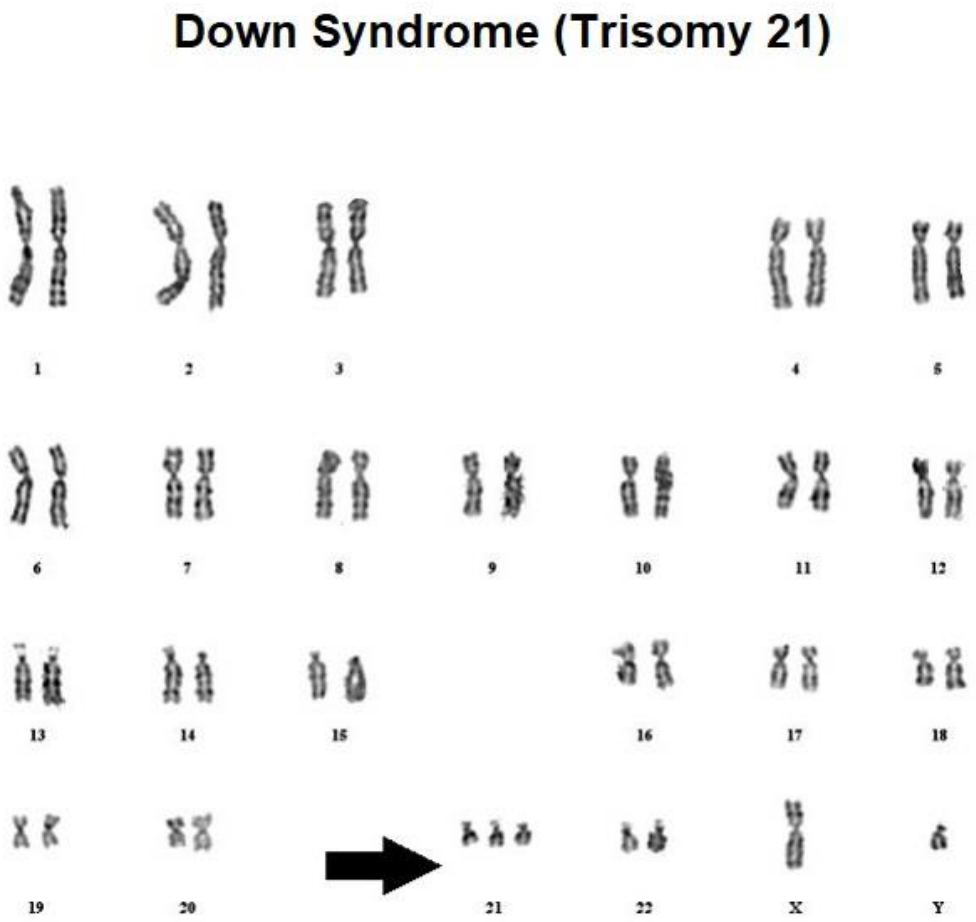


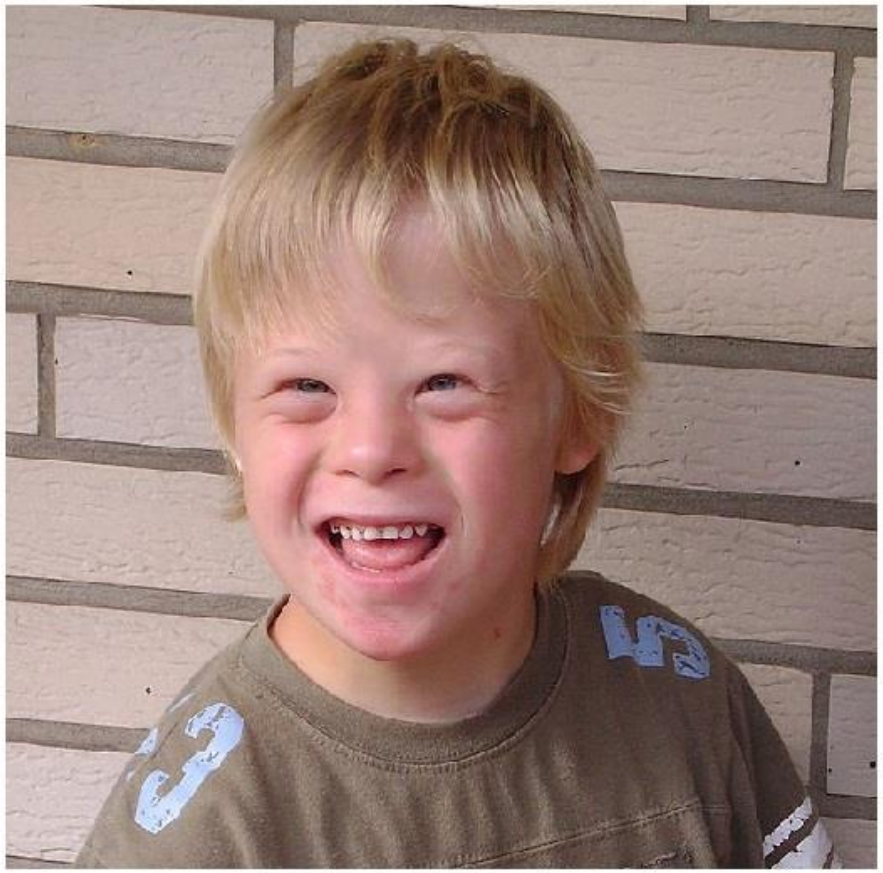


Genetic Disorders: Abnormalities in Chromosome Number 5

- **Autosomal polysomy** is having more than 2 copies of a particular autosome.
- **Trisomy 21 (Down Syndrome)**
  - 3 copies of chromosome #21
  - 1 in 700 live births
  - Most trisomy 21 fetuses are stillborn or aborted.
  - Average life expectancy is 60 years.
  - Mental retardation, but a sunny disposition
  - Protruding tongue, low-set ears, epicanthal eye folds
  - Short stature
  - Heart deformities
  - Respiratory infections
  - Increased risk of leukemia

Genetic Disorders: Abnormalities in Chromosome Number 6





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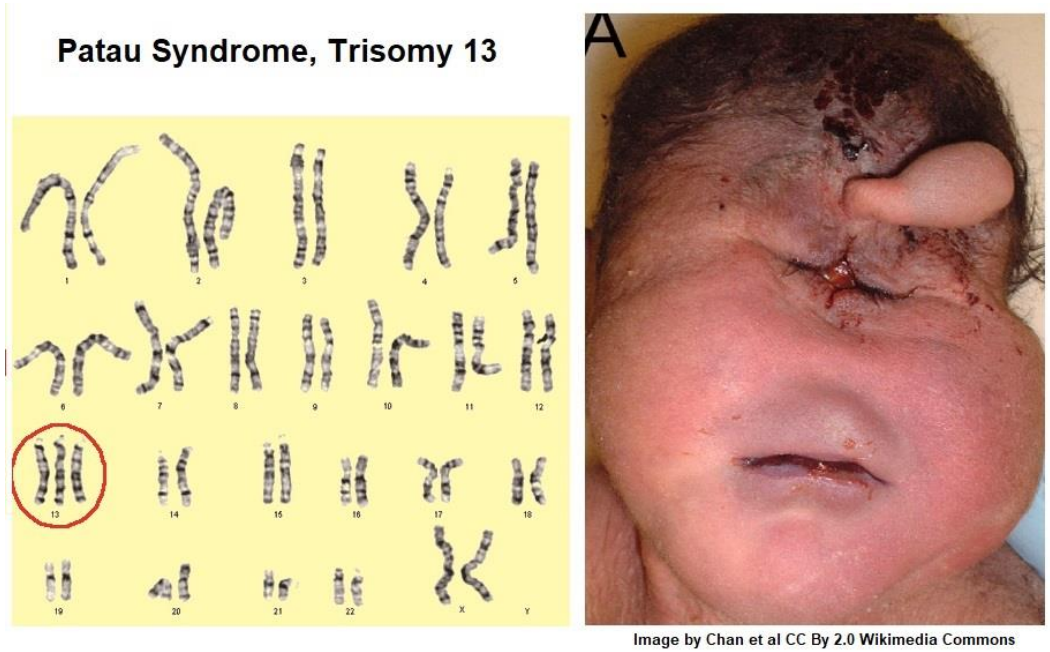
Genetic Disorders: Abnormalities in Chromosome Number 7

Trisomy for larger autosomes have more serious effects, both mental and physical. (Autosomes are numbered from largest to smallest.)
Trisomy 13, Patau Syndrome, has an average life expectancy of just 7 to 10 days.
Trisomy 18, Edwards Syndrome, has an average life expectancy of 3 to 14 days.



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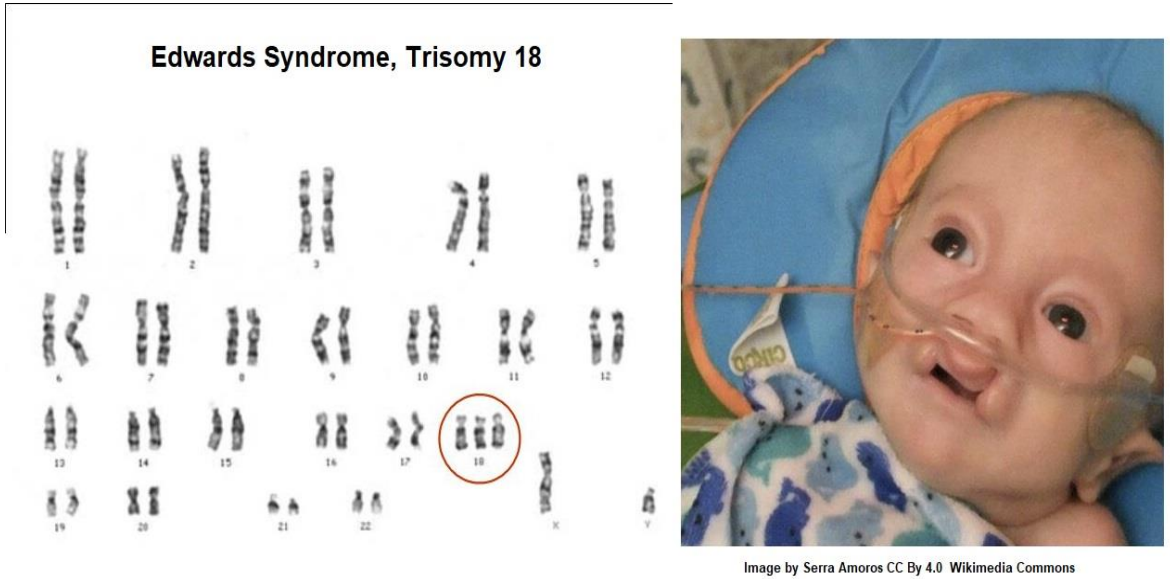

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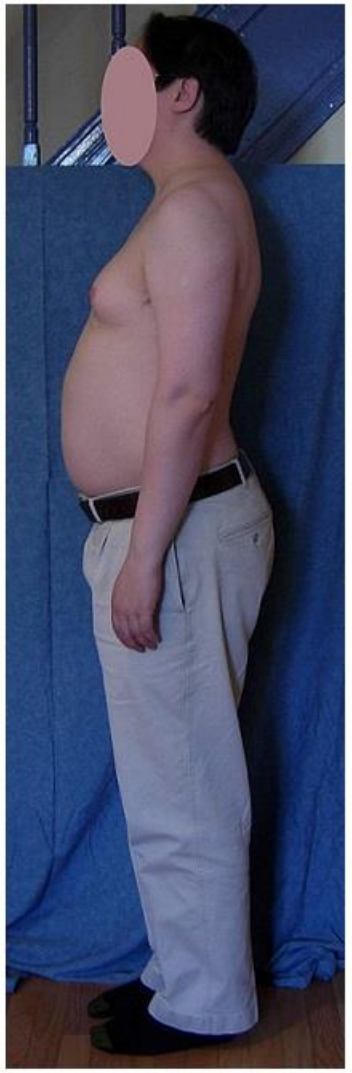
Genetic Disorders: Abnormalities in Chromosome Number 8

- **Polysomy for Sex Chromosomes:**
- **Klinefelter Syndrome (XXY)**
  - Occurrence: 1 in 500-1000 live births
  - Phenotype is male.
  - The Y chromosome determines maleness. The phenotype will be male if a Y chromosome is present, regardless of the number of X chromosomes present.
  - One of the X chromosomes will form a Barr body.
  - Testicular atrophy, infertility, gynecomastia (breast tissue)
  - High-pitched voice
  - Impaired intelligence
  - Life expectancy is reduced by 2 years.
  - Testosterone therapy reduces feminine characteristics.

Genetic Disorders: Abnormalities in Chromosome Number 9



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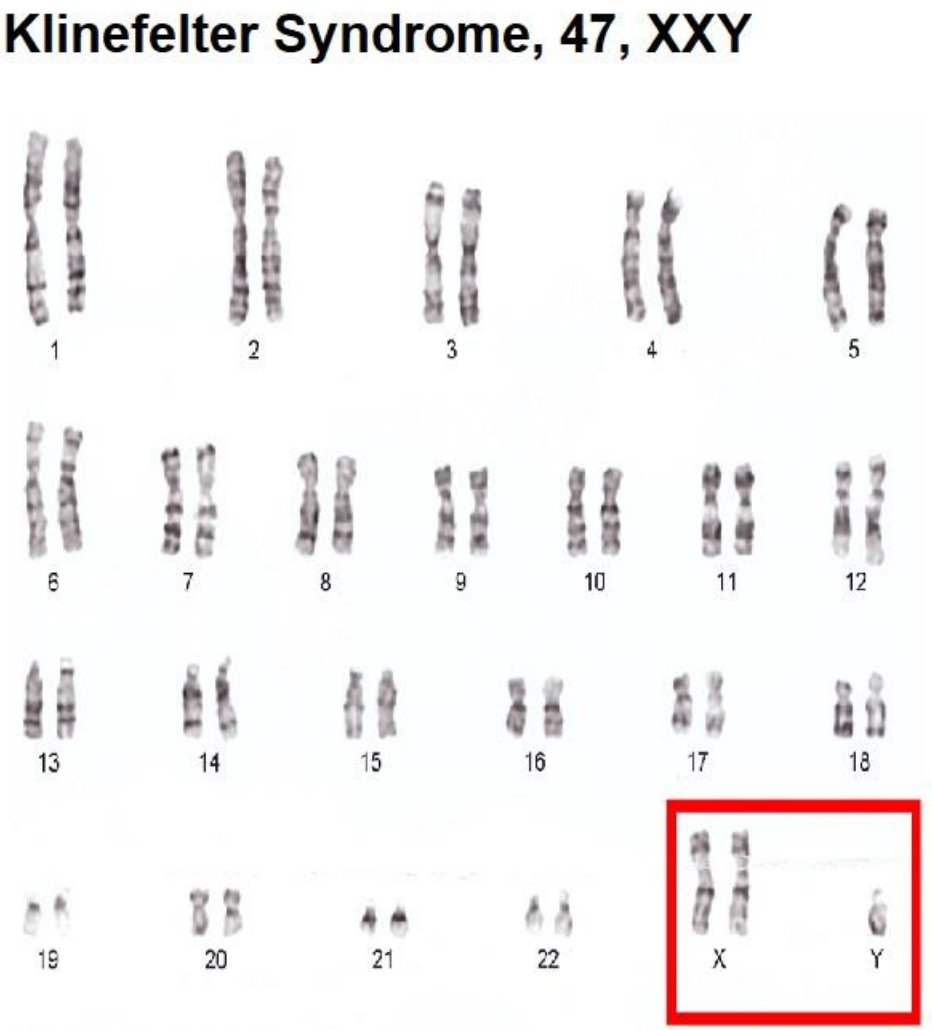
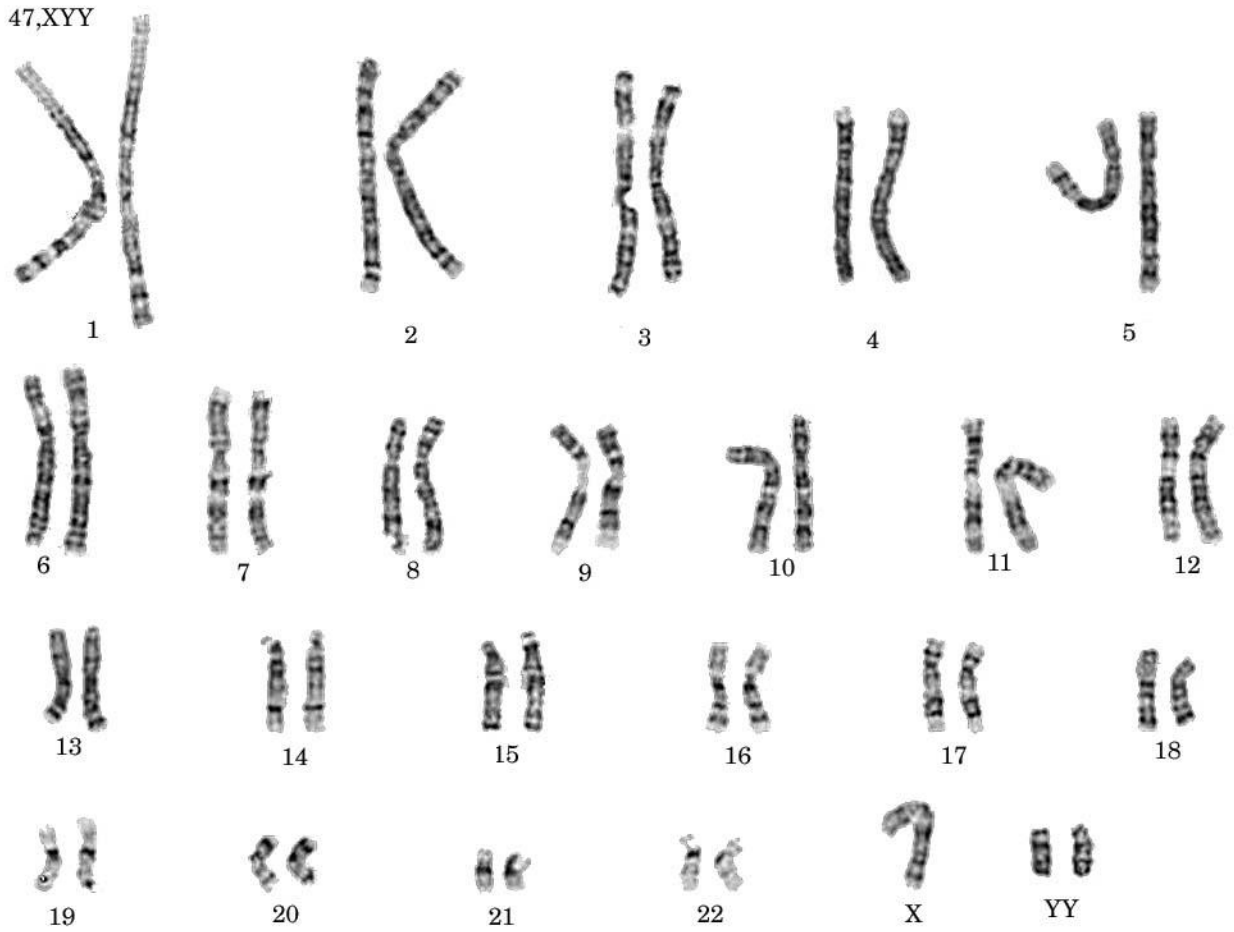


Genetic Disorders: Abnormalities in Chromosome Number 10

- **Polysomy for Sex Chromosomes, cont.**
- **Multiple X Female (XXX or XXXX)**
  - XXX occurs in about 1 in 1000 births, XXXX is very rare.
  - These females tend to be taller than average, but have no other physical differences. They usually have normal sexual development and normal fertility.
  - Life expectancy is normal.
  - The effect of disorders involving one or two extra X chromosomes is lessened by the fact that all but one X chromosome is inactivated (become **Barr bodies**) in somatic cells early in embryonic development.
  - More than 4 X chromosomes has been documented and causes mental retardation.
- **Jacob Syndrome (XYY)**
  - Occurs in about 1 in 1000 births
  - Life expectancy reduced by 10 years
  - Taller than normal, normal sexual development and fertility
  - Risk of delayed communication and motor skills
  - Learning disabilities
  - Increased risk of cancer, neurological disorders and pulmonary disease

Genetic Disorders:
Abnormalities in Chromosome Number 11

XYY Karyotype

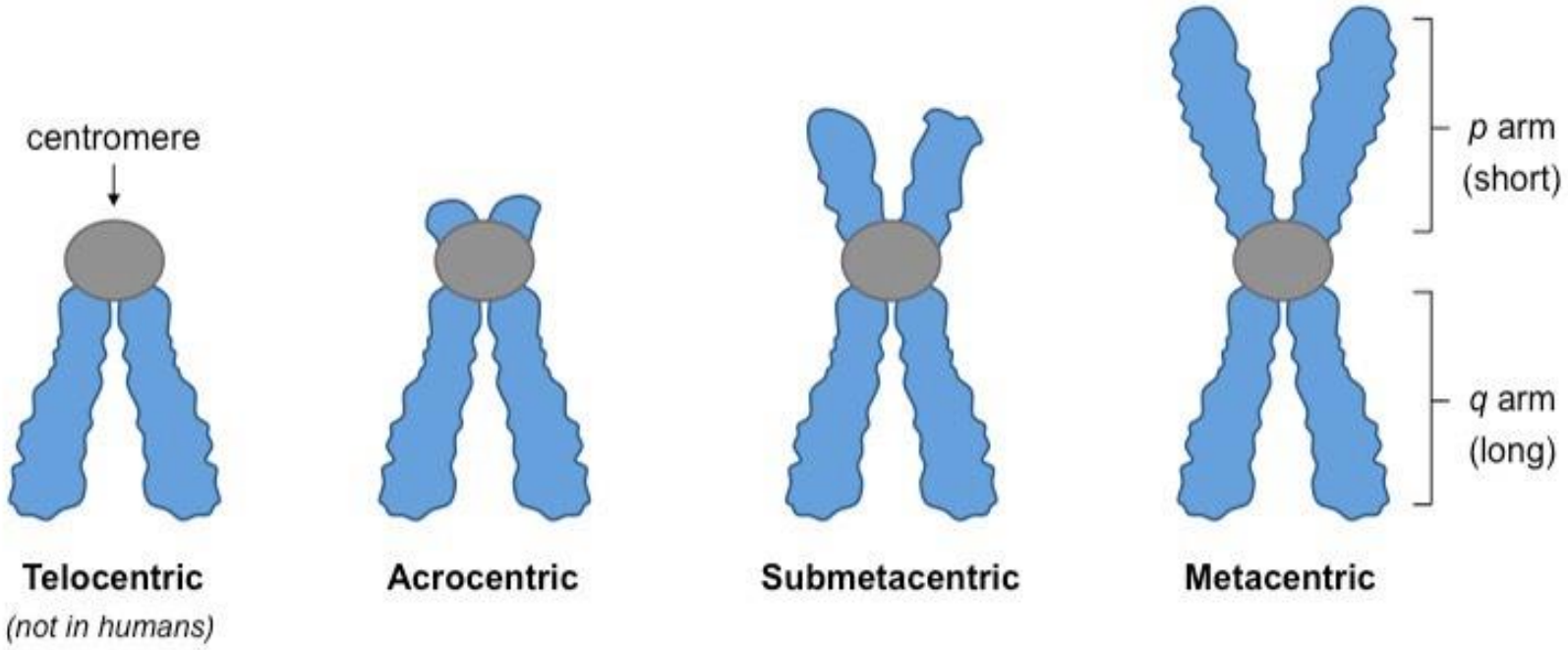


Genetic Disorders: Abnormalities in Chromosome Structure

- Caused by the rare loss or rearrangement of a piece of chromosome that occurred during gamete formation (usually during crossing over in Prophase I) in one parent. **The other parent contributes a normal gamete to the zygote.** Thus chromosome structure abnormalities are **heterozygous**.
- Locations of defects are described in terms of chromosome "arms". The length of chromosome arms is determined by the location of the centromere.
  - **p=short arm**
  - **q=long arm**
- Chromosome banding patterns produced by staining techniques facilitate detection of structural abnormalities by inspection of karyotypes.
- Diagnosis by DNA fingerprinting is also a diagnostic tool.

Genetic Disorders:
Abnormalities in Chromosome Structure 1

Types of Chromosomes Based on Centromere Locations



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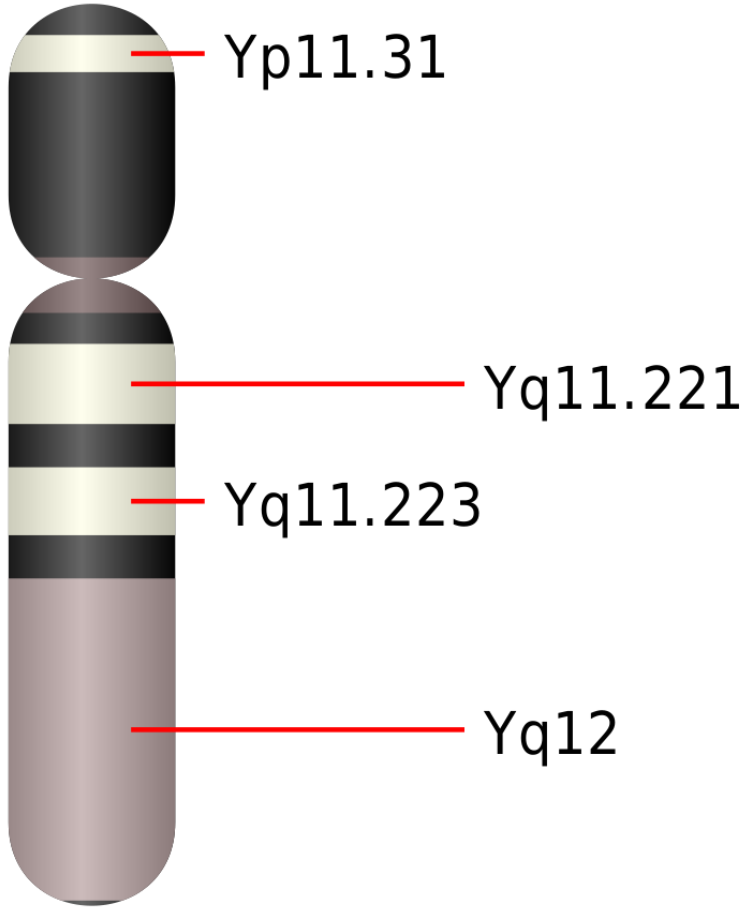
Genetic Disorders:
Abnormalities in Chromosome Structure 2

Standardized staining methods are used to produce distinct banding patterns on metaphase chromosomes. The bands are numbered and used to describe gene locations.



Genetic Disorders:
Abnormalities in Chromosome Structure 3

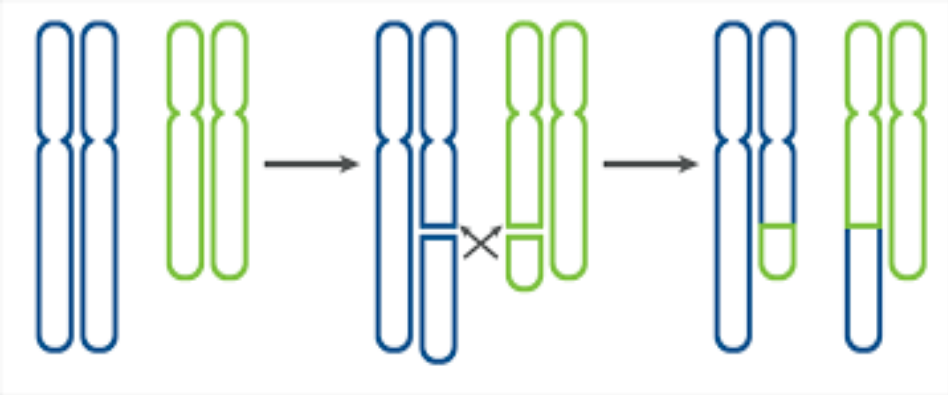
- **Classes of Abnormalities in Chromosome Structure**
  - **Translocations**- a piece of one chromosome becomes attached to a different chromosome.
  - **Inversions-**a section of a chromosome is flipped end-to-end, so the genes in the flipped section are in reverse order.
  - **Deletions-**a section of a chromosome is lost.
  - **Duplications**-a section of a chromosome is repeated.
- Typically, a **translocation or an inversion** produces a zygote that has no extra or missing genetic material. The individual will be normal except that he or she will have problems producing normal gametes as an adult. **The chromosome with the abnormal arrangement of genetic material will be unable to synapse properly with its homologous normal chromosome during meiosis I**. This leads to reduced fertility.

Genetic Disorders: Abnormalities in Chromosome Structure 4

Types of Translocations

- **Reciprocal Translocation**
  - No genetic material is lost. Chromosomes trade pieces.
  - Individuals are normal but their gamete formation is abnormal.
- **Centric Fusion (aka Robertsonian Translocation)**
  - The long arms of two **acrocentric** (eg. #13, #14, #15, #21, #22) chromosomes fuse and the tiny short arms are lost.
  - **9% of Down Syndrome** cases are due to centric fusion of chromosome 21. This form of Down Syndrome is **not related to maternal age**.
  - Depending on the chromosome involved the individual may be nearly normal, but their gamete formation is abnormal.
- **Isochromosomes**
  - Sister chromatids of a dyad fail to separate properly at meiosis II such that the centromere area splits along the wrong plane. As a result the two short arms form one monad chromosome and the two long arms form another monad chromosome.
  - Most commonly occurs with the X chromosome
  - Females with an iso X chromosome have a **Turner Syndrome-like** phenotype.

Genetic Disorders: Abnormalities in Chromosome Structure 5



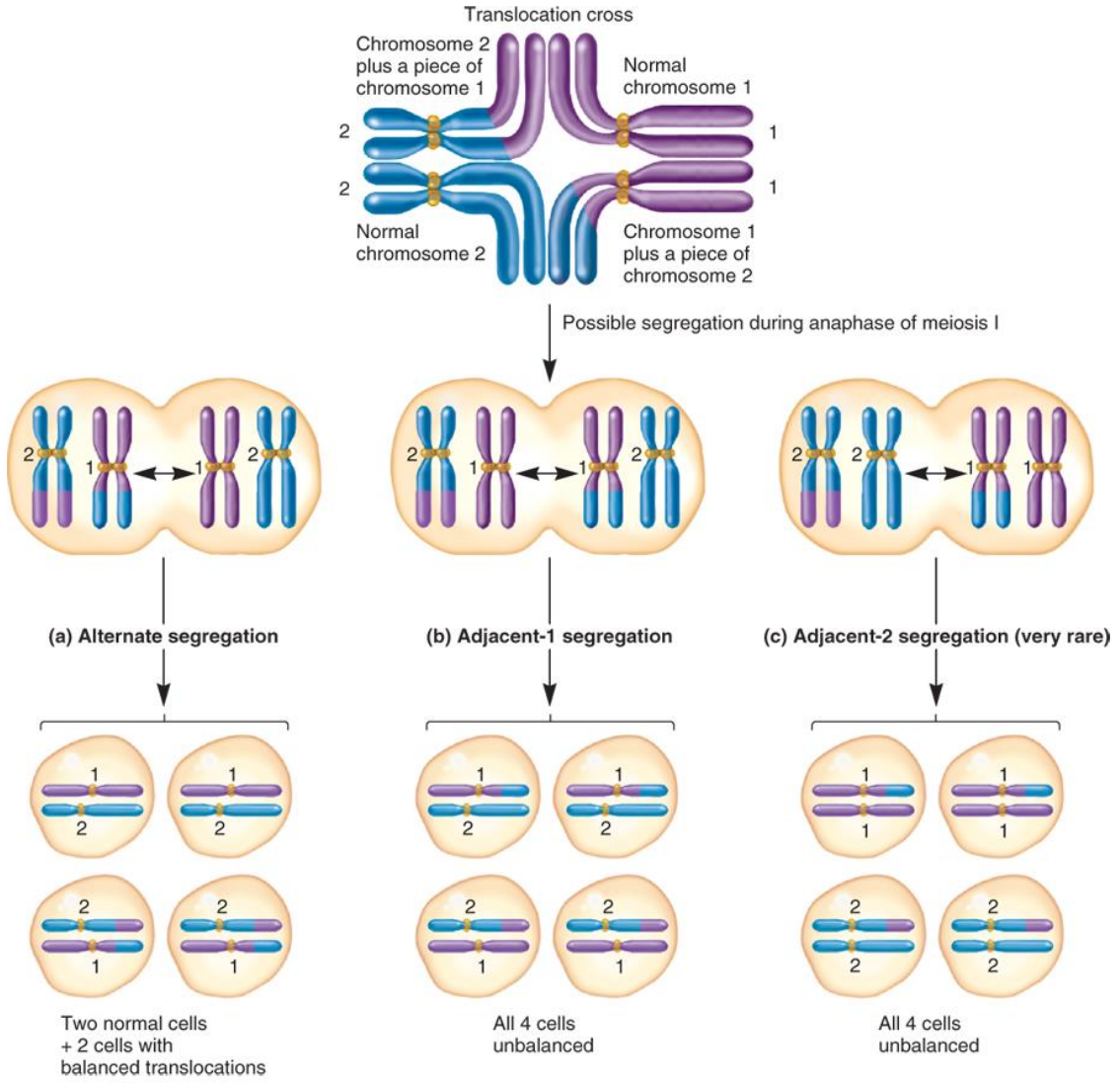
Reciprocal (Balanced) Translocation

- This individual is heterozygous for a reciprocal translocation.
- Although this individual has lost no genetic material, he or she will produce some abnormal gametes because chromosomes will have to contort themselves in order to synapse during Prophase I.
- **Most gametes will have some missing genes and some duplicated genes**. Fertility will be negatively affected.

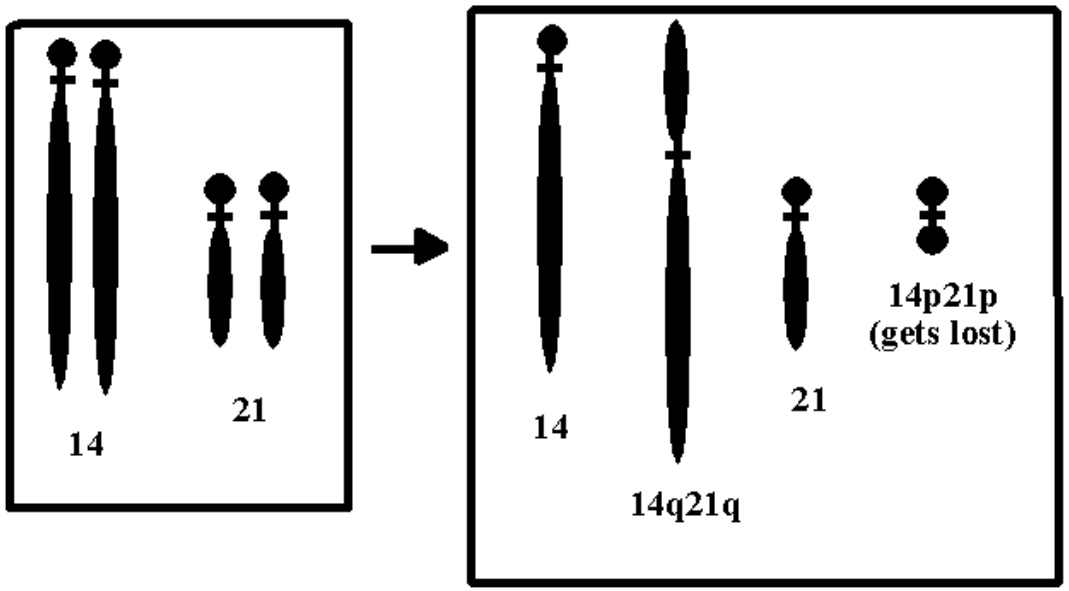
Synapsis
Reciprocal Translocation

Meiosis I: In a Person with a Balanced Translocation

- A **cross-shaped figure** is produced when the reciprocal translocation chromosomes synapse with the normal chromosomes during meiosis I.
- The four dyad chromosomes will segregate into gametes in one of three ways.
- Two of the three ways (Adjacent-1 segregation and Adjacent-2 segregation) will produce 100% abnormal gametes each with a mix of duplicate genes and likely not be viable.
- Alternate segregation (far left) will produce 50% normal gametes and 50% reciprocal translocation gametes. Those gametes will be viable.
- So two thirds of gametes, on average, will not survive.



Genetic Disorders: Abnormalities in Chromosome Structure 6



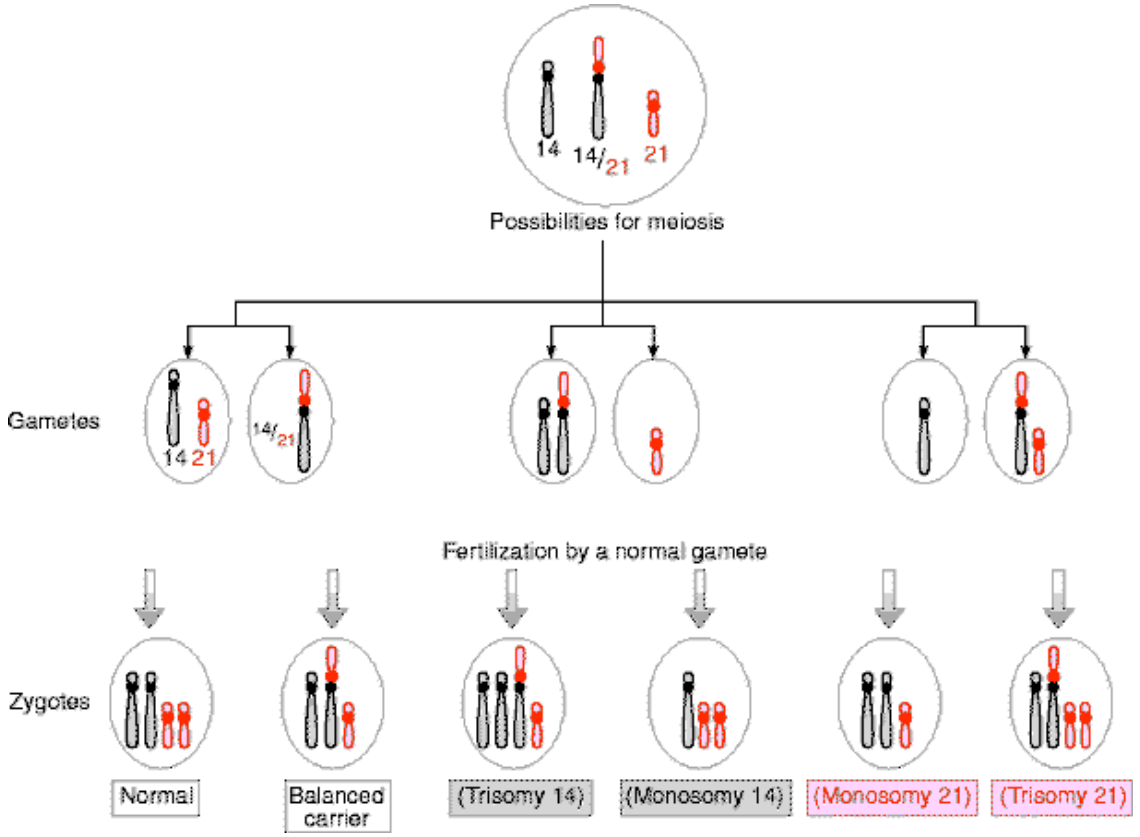
Centric Fusion

(Robertsonian Translocation)

- In this form of translocation the long arms and short arms of two acrocentric chromosomes (centromere near the end of the chromosome) fuse and the tiny chromosome formed by the short arms is usually lost.
- This individual has lost some genetic material (14p21p). During synapsis in meiosis I the short arms of the normal 14 and 21 chromosomes will have nothing to synapse with.

Genetic Disorders:
Abnormalities in Chromosome Structure 7

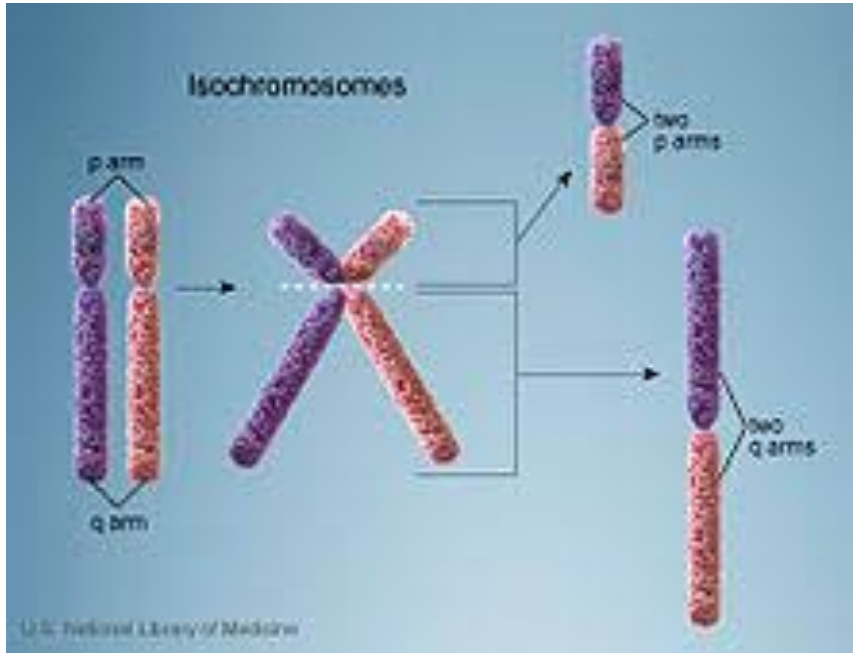
Gametes: Robertsonian Translocation of 14/21



- As in a reciprocal translocation, most (two-thirds) of the gametes formed will contain lost or extra DNA. If they survive to be fertilized (unlikely), the resulting zygotes are shown.
- Monosomy zygotes and trisomy 14 zygotes will most likely not be viable.
- Some gametes will contain BOTH the 14/21 translocation chromosome AND a normal 21 chromosome (far right). If fertilized, such a gamete will produce a individual with a Down Syndrome phenotype **(trisomy 21).**

Genetic Disorders:
Abnormalities in Chromosome Structure 8

Isochromosomes



Iso X chromosomes are produced by an abnormality during meiosis. A dyad X separates along the wrong plane. The resulting gametes will receive a monad with either an iso Xp (fused short arms) or an iso Xq (fused long arms). Either gamete will produce a zygote that will be missing one arm of an X chromosome. In a female this results in symptoms similar to **Turner Syndrome**.

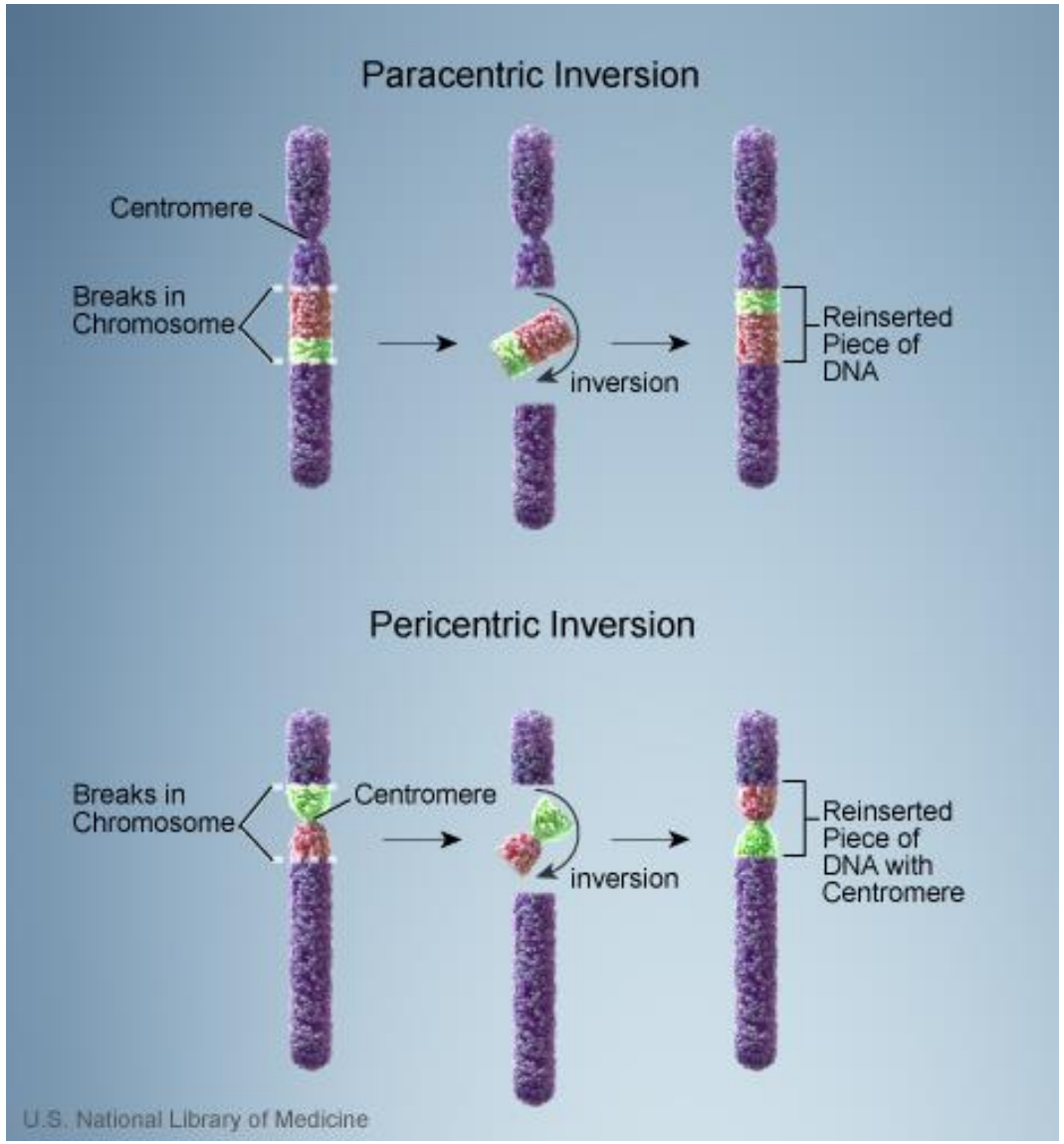
Genetic Disorders: Abnormalities in Chromosome Structure 9

- **Types of Inversions**
- There are two types of inversions. In both types there is no loss of genetic information, but the individual that carries the inversion will form abnormal gametes due to abnormalities in synapsis.
  - **Paracentric inversion**-inverted segment **does not** include the centromere
  - **Pericentric inversion**-inverted segment **does** include the centromere

Genetic Disorders: Abnormalities in Chromosome Structure 10

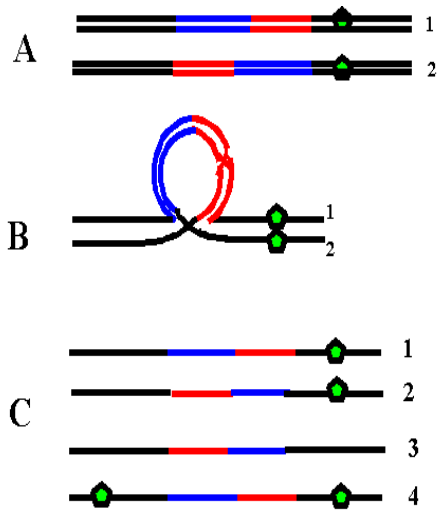
Centromere IS NOT in the inverted segment.

Centromere IS in the inverted segment.



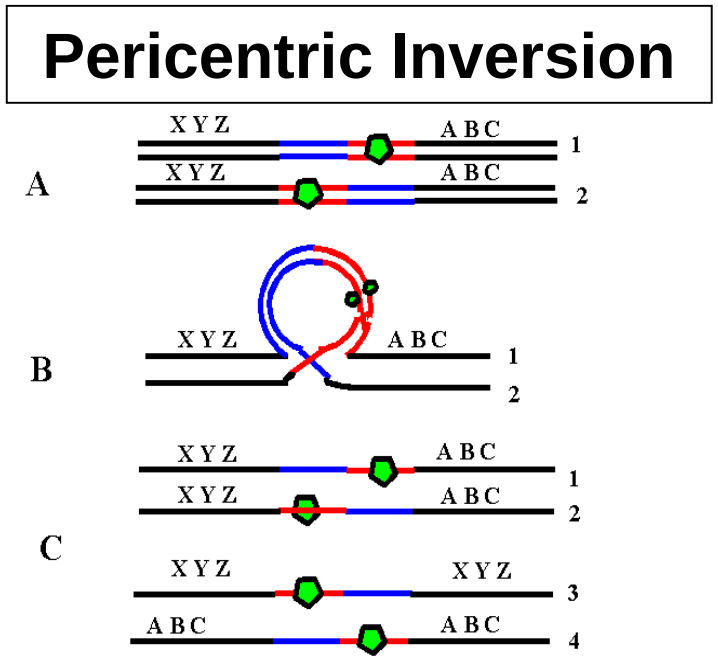
Genetic Disorders: Abnormalities in Chromosome Structure 11

Paracentric Inversion



- Although this individual has lost no genetic material, he or she will produce abnormal gametes having either extra DNA or missing DNA**.**
- **Inversion loops** (part B) will form during meiosis I as chromosomes synapse.
- If the inverted DNA is long enough, crossing over will occur within the loop leading to **abnormal gamete formation.** Some (25%) chromosomes lose their centromeres (part C #3) some (25%) have two centromeres (part C #4). Gametes with such chromosomes die.
- Double centromeres cause chromosomes to break. Spindle fibers pull them apart.
- Lack of a centromere causes chromosomes to be lost. Spindle fibers cannot bind to them.

Genetic Disorders: Abnormalities in Chromosome Structure 12



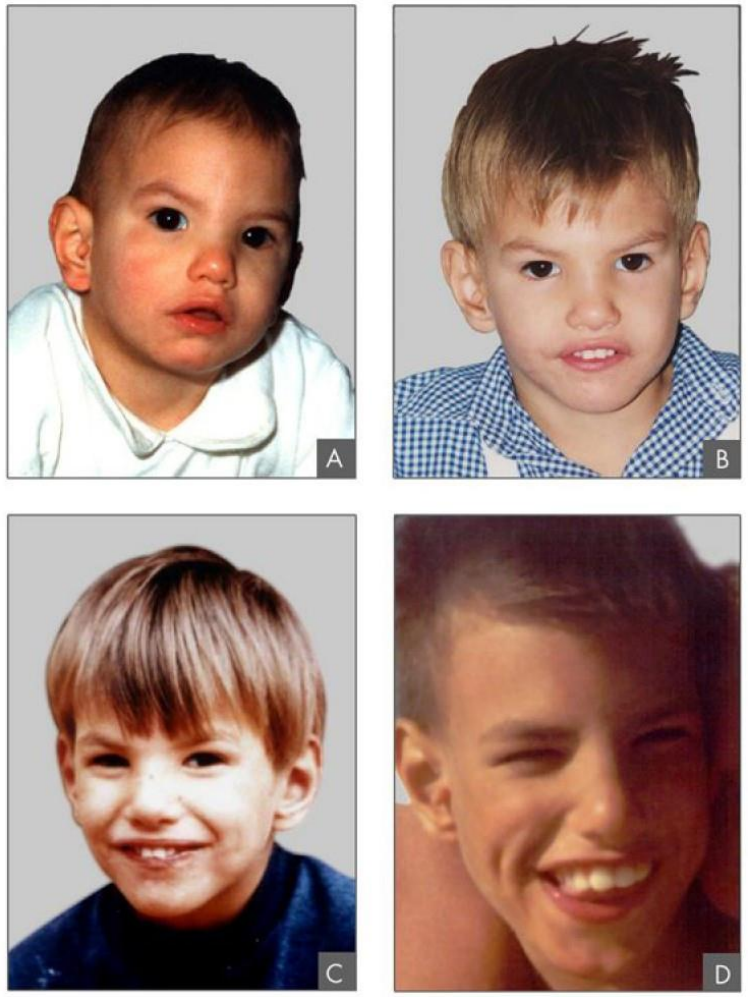
- Although this individual has lost no genetic material, he or she will produce abnormal gametes having either extra DNA or missing DNA**.**
- **Inversion loops** (part B) will form during meiosis I as chromosomes synapse.

Genetic Disorders: Abnormalities in Chromosome Structure 13

- **Deletions**
  - A chromosome break leaving a piece of DNA with no centromere.
  - That piece is lost at the next cell division because it cannot attach to a spindle fiber. When the nucleus reforms, the piece is not included. It stays in the cytoplasm where it has no function and is destroyed by enzymes.
  - **Cri du Chat (French for "Cry of the Cat") Syndrome (5p-)**
    - 1 in 20,00-50,000 live births
    - If survival past age 1 year occurs, the life expectancy is normal.
    - Deletion of the short arm of chromosome 5
    - Severe mental retardation, round face, congenital heart anomalies, unusual cat-like cry

Genetic Disorders:
Abnormalities in Chromosome Structure 14

Cri du Chat syndrome 5p-



Lecture 4B:

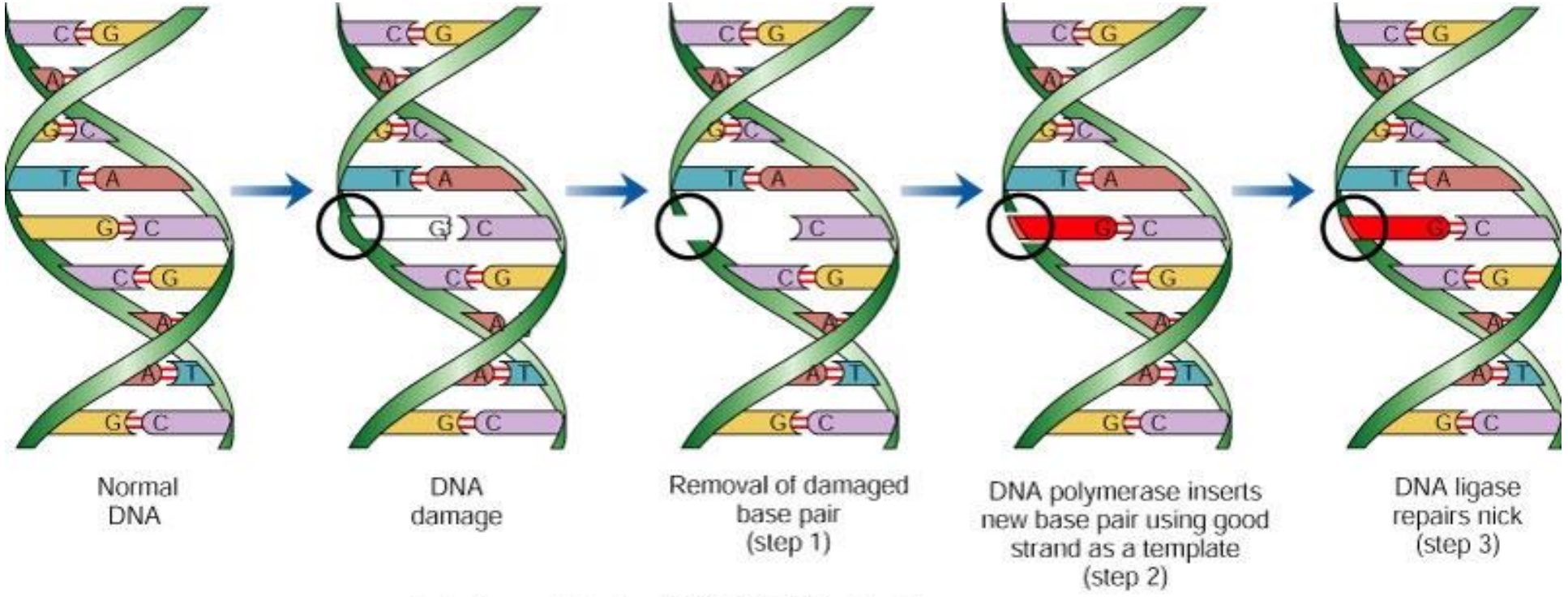
Mendelian Single Gene Disorders
Sex-Linked Single Gene Disorders
Non-Mendelian Single Gene Disorders
Polygenic Disorders
Environmentally Induced Congenital Disorders
Gene Therapy

Genetic Disorders: Mendelian Single-Gene Disorders

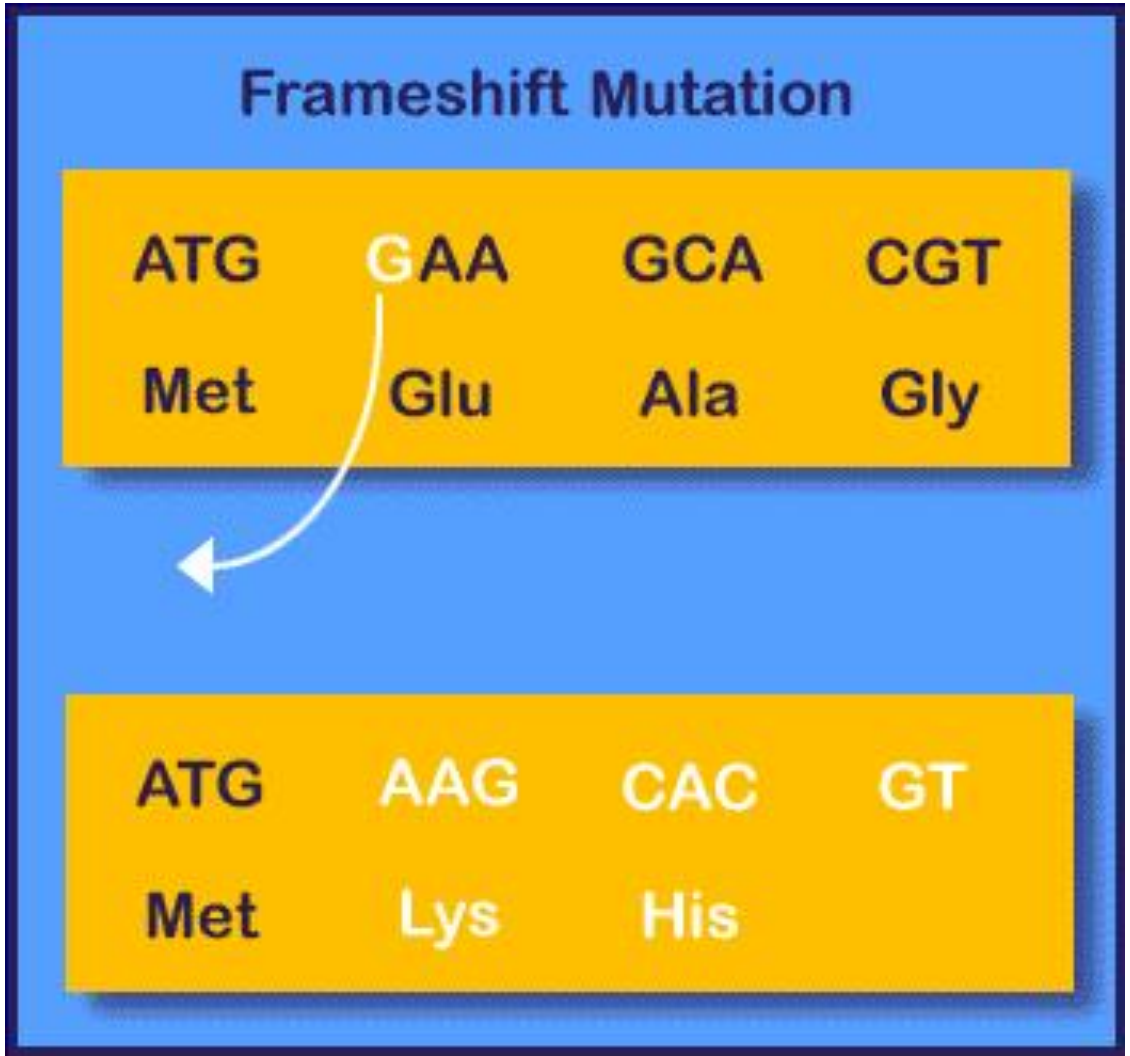
- Most are inherited, but about 15% are due to new germ line mutations (mutation in a pre-gametic or gametic cell in the ovaries or testes).
- DNA repair mechanisms prevent many, but not all, DNA changes from being passed on to offspring.
- **Point mutation**
  - Change in a single DNA base; usually occurs **during DNA replication when the wrong nucleotide is added opposite the template strand.**
  - The resulting mRNA codon may (or may not) cause a different amino acid to be inserted into the protein gene product. A single amino acid change may effect protein function. Sickle cell anemia is an example.
- **Frameshift mutation**
  - A single nucleotide base is deleted or added; usually occurs **during DNA replication when an extra nucleotide is added or a nucleotide fails to be added opposite the template strand.**
  - The reading frame of the DNA is shifted. All downstream codons are affected. The protein product will likely have many amino acids that are different from those produced by the non-mutated gene. Thus, frameshift mutations are **much more serious than point mutations.**

Genetic Disorders:
Mendelian Single-Gene Disorders 1

DNA Repair: Removal of a Point Mutation



Genetic Disorders:
Mendelian Single-Gene Disorders 2

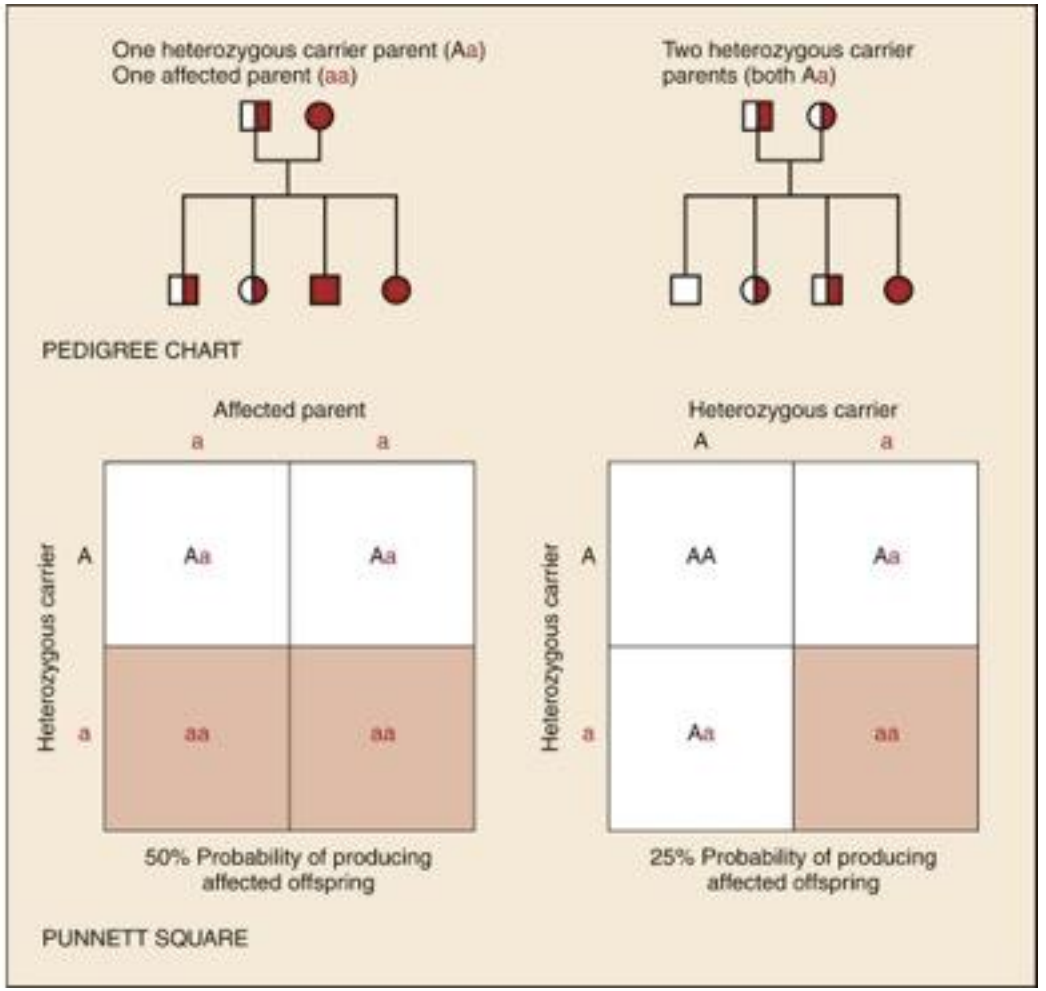


Genetic Disorders: Autosomal Single-Gene Disorders 3

- A single gene disorder may affect either a **protein** (enzyme, structural protein, hormone, etc.) or it may affect a **regulatory RNA** molecule that isn't translated.
- Most harmful single gene mutations are **recessive** to a functional normal allele. Two copies of the abnormal allele are required to affect the phenotype of the individual.
- A **heterozygous (Aa)** individual for a recessive single gene disorder is said to be a **"carrier"** of the disorder. Carriers have a normal phenotype. The genotype must be **homozygous recessive (aa)** in order for the abnormal phenotype of the disorder to be expressed.
- Some disorders are due to **dominant** genes. Just one abnormal allele is required for the disorder to be expressed. The abnormal phenotype will be present in the case of a genotype that is either a **heterozygous (Aa)** or a **homozygous dominant (AA).**

Genetic Disorders:
Autosomal Single-Gene Disorders 4

If one parent is affected (**aa**) by an autosomal recessive disorder and one parent is a heterozygous carrier (A**a**) they have a 50% chance of producing an affected child. If both parents are heterozygous carriers they have a 25% chance of producing a child with the disorder.



Genetic Disorders:
Autosomal Single-Gene Disorders 5

Autosomal Recessive:

Oculocutaneous Albinism (OCA)

- In one form, the tyrosinase gene on chromosome #11 is defective.
- The enzyme, tyrosinase, converts the amino acid, tyrosine, into DOPA (dihydroxyphenylalanine).
- DOPA is a precursor of the pigment, melanin.
- Melanin
  - protects skin cells from uv light.
  - is required for proper development of the fovea region of the retina.
- Albinism carries an increased risk of sunburn, skin cancers, and impaired vision.
- Life expectancy is not affected.

Genetic Disorders: Autosomal Single-Gene Disorders 6

Autosomal Recessive:

PKU (Phenylketonuria)

- Phenylalanine hydroxylase gene (on chromosome #12) is abnormal.
- Phenylalanine (an amino acid) cannot be broken down, so it builds up causing neurotoxicity.
- Phenylalanine is excreted in the urine as phenylketones. The chemicals emit a musty odor in urine.
- Phenylalanine is normally broken down into tyrosine; PKU means low melanin pigment, because tyrosine is a precursor of melanin.
- PKU can be detected at birth by a simple blood test.
- A diet devoid of phenylalanine prevents symptoms.
- No meat
- No dairy products
- Tyrosine and other amino acids must be supplemented.
- Untreated infants are irritable, exhibit tremors and slowly developing mental retardation.
- With treatment, life expectancy is not affected.

Genetic Disorders:
Autosomal Single-Gene Disorders 7

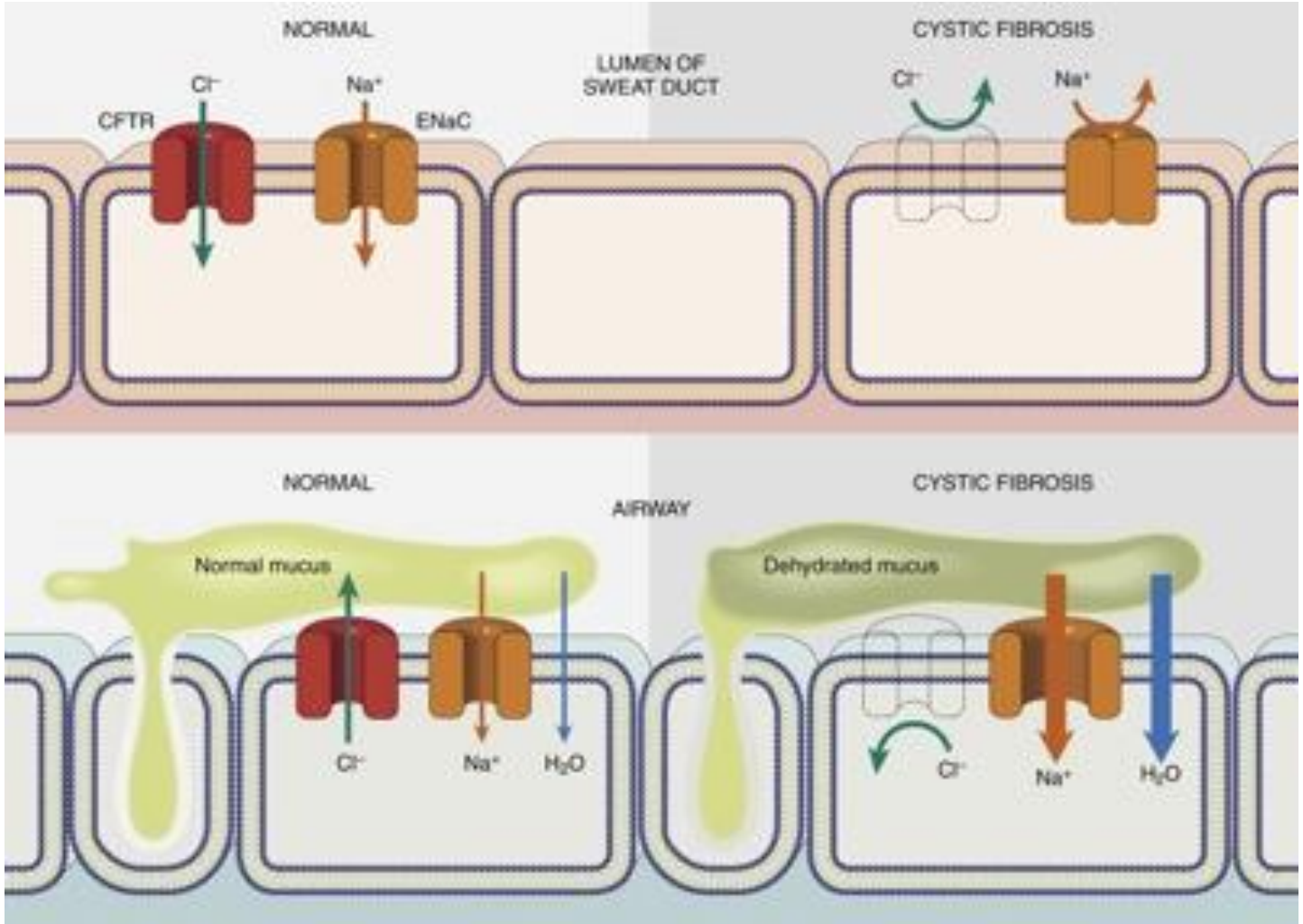
Autosomal Recessive:

Cystic Fibrosis

- CFTCR-(cystic fibrosis transmembrane conductance regulator) gene on chromosome #7 is defective. Multiple CF alleles exist.
- The gene product is a membrane transporter protein for chloride ions. Failure of chloride transport causes CF patients to have **high amounts of NaCl in sweat**, and to produce very **thick, sticky mucus** secretions in body tracts. (Mucus does not contain enough water.) See diagram.
- Obstruction of the **bronchioles** occurs causing dyspnea and frequent respiratory infections.
- Obstruction of the **hepatopancreatic sphincter** occurs, restricting the flow of bile and pancreatic juice into the small intestine. **Fat digestion** is most seriously affected because it requires both bile and the lipase enzyme in pancreatic juice, but digestion of other macronutrients is also defective.
- Prenatal screening for the common form of CF is readily available. About 4% of Caucasian Americans are carriers for CF.
- Average life expectancy is 37.5 years, but some live much longer with careful treatment.

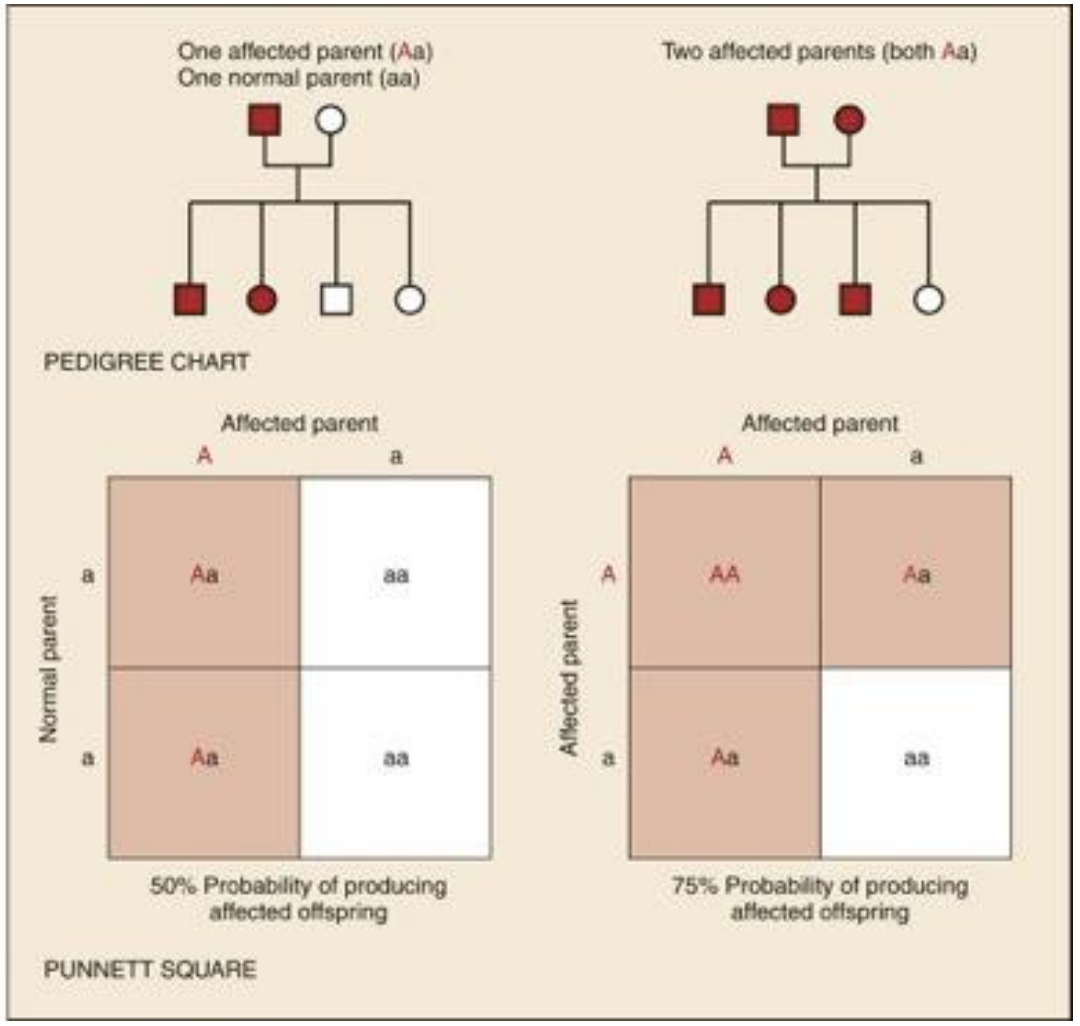
Genetic Disorders:
Autosomal Single-Gene Disorders 8

Cystic Fibrosis



Genetic Disorders:
Autosomal Single-Gene Disorders 9

In the case of a genetic disorder produced by a **autosomal dominant** gene, a union between one affected parent (Aa) and one normal parent (aa), has a 50% chance of producing an affected child. If both parents are affected (Aa) the chance of producing an affected child is 75%.

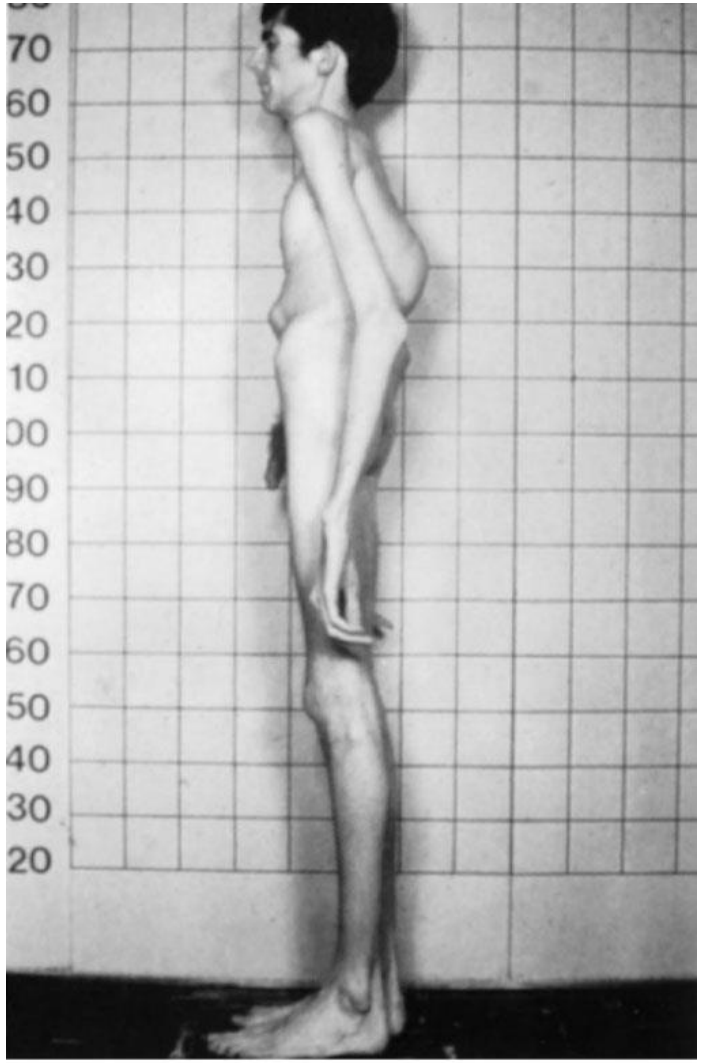


Genetic Disorders: Autosomal Single-Gene Disorders 10

Autosomal Dominant:

Marfan Syndrome

- Defect in the fibrillin 1 gene on chromosome #15.
- Fibrillin is a glycoprotein important in the structure of connective tissues.
- Tall, slender with long, thin extremities
- “Arachnodactyly”=very long fingers; flat feet
- Chest protrudes outward or sinks inward.
- Abraham Lincoln may have had Marfan Syndrome.
- Cardiovascular structural abnormalities
  - Aortic wall is weak and subject to rupture.
  - Heart valves are misshapen and dysfunctional.
- Life expectancy is 70 years, nearly normal.



From Connor JM, Ferguson-Smith MA. Essential medical genetics, ed 5, London, 1997, Blackwell Scientific, p 142.

Genetic Disorders:
Autosomal Single-Gene Disorders 11

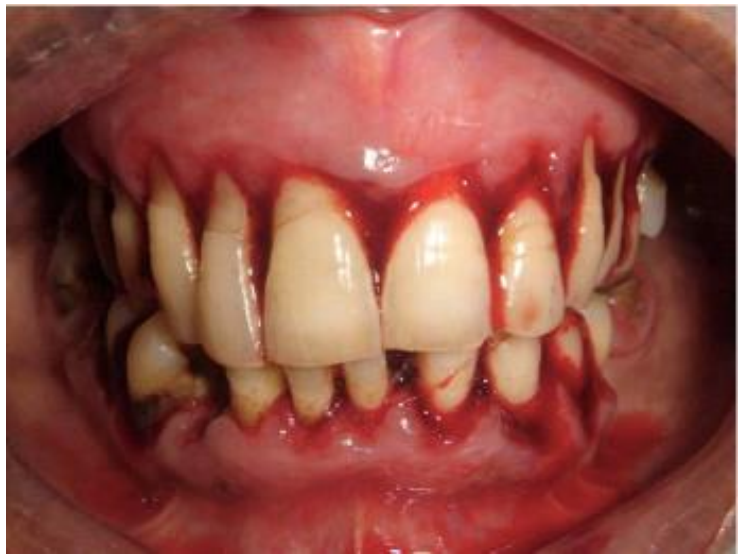
Autosomal Dominant:
Huntington Disease

•Caused by more than 39 CAG repeats in the huntingtin gene on chromosome 4.
•The normal function of huntingtin protein is unknown. Abnormal huntingtin is deposited in brain tissue.
•Mental and physical deterioration reduces life expectancy by an average of 10 to 30 years after diagnosis.
•Suicide rate is 9%.
•Involuntary skeletal muscle movements cause “chorea”, a term derived from a type of dance.
•HD is not apparent until about age 40 (after reproduction has likely already occurred).

Genetic Disorders: Autosomal Single-Gene Disorders 12

Autosomal Dominant: von Willebrand Disease

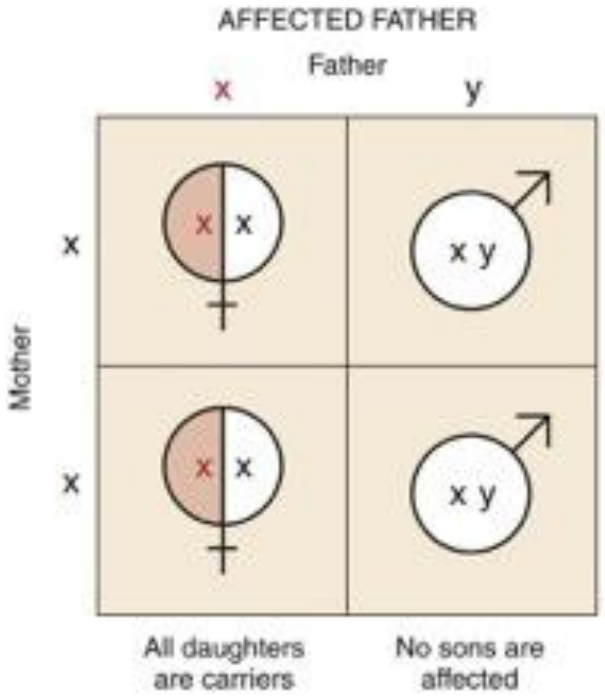
- Caused by mutation of the VWB gene on chromosome 12.
- There are three different mutant allelic forms. Two are inherited as dominant genes and one is inherited as a recessive gene.
- The normal function of von Willebrand protein was discussed previously as were the manifestations of von Willebrand disease.
- Life expectancy varies with type. With treatment a normal lifespan is possible.

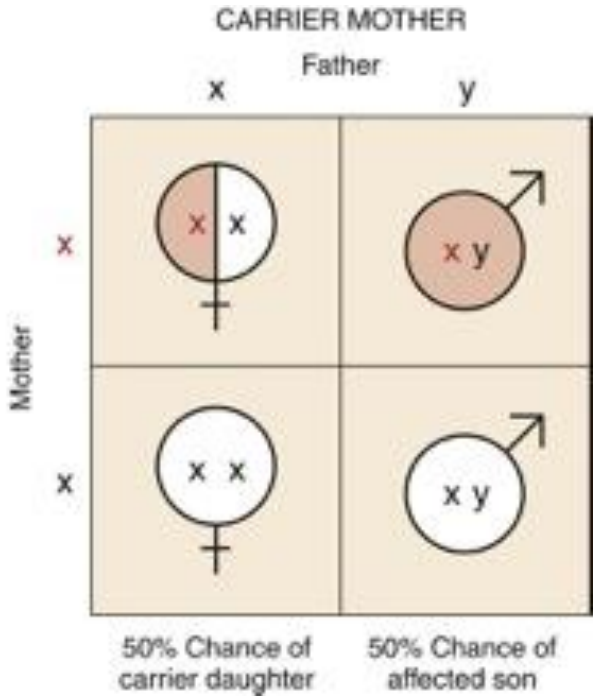


Genetic Disorders:
Sex-Linked Single-Gene Disorders

- Sex-linked disorders are due to genes located on the X chromosome. All sex-linked alleles **behave as dominant alleles** in males. Only one copy of the X-linked allele will produce the abnormal phenotype in males. The Y chromosome carries very few genes, different genes from those on the X chromosome. There are no alleles on the Y chromosome to mask alleles on the X chromosome.
- Females have two X chromosomes. A female may be heterozygous (a carrier) or homozygous for a sex-linked disorder.
- A male child always receives his X chromosome from his mother and his Y chromosome from his father. A female child receives an X chromosome from each parent.

Genetic Disorders:
Sex-Linked Single-Gene Disorders 1





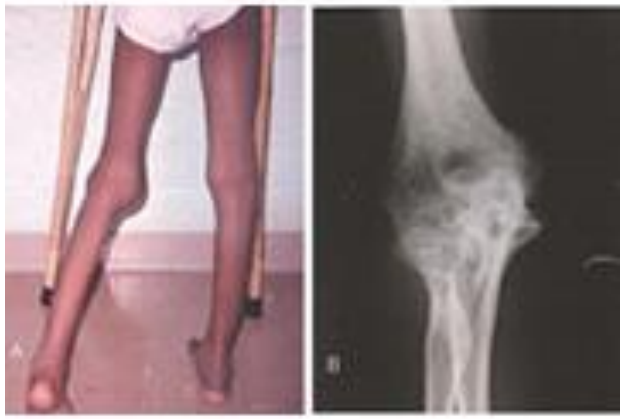
All of the daughters of an affected father and a normal mother will be carriers of an X-linked recessive disorder. All sons will be normal.

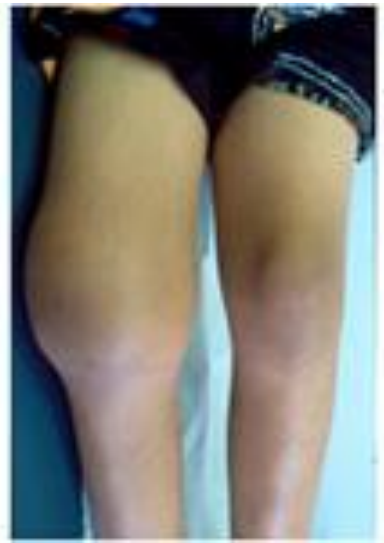
Daughters of a carrier mother and a normal father will have a 50% of being carriers. Sons will have a 50% chance of being affected by the recessive sex-linked disorder.

Genetic Disorders:
Sex-Linked Single-Gene Disorders 2

X Linked Recessive: Hemophilia A

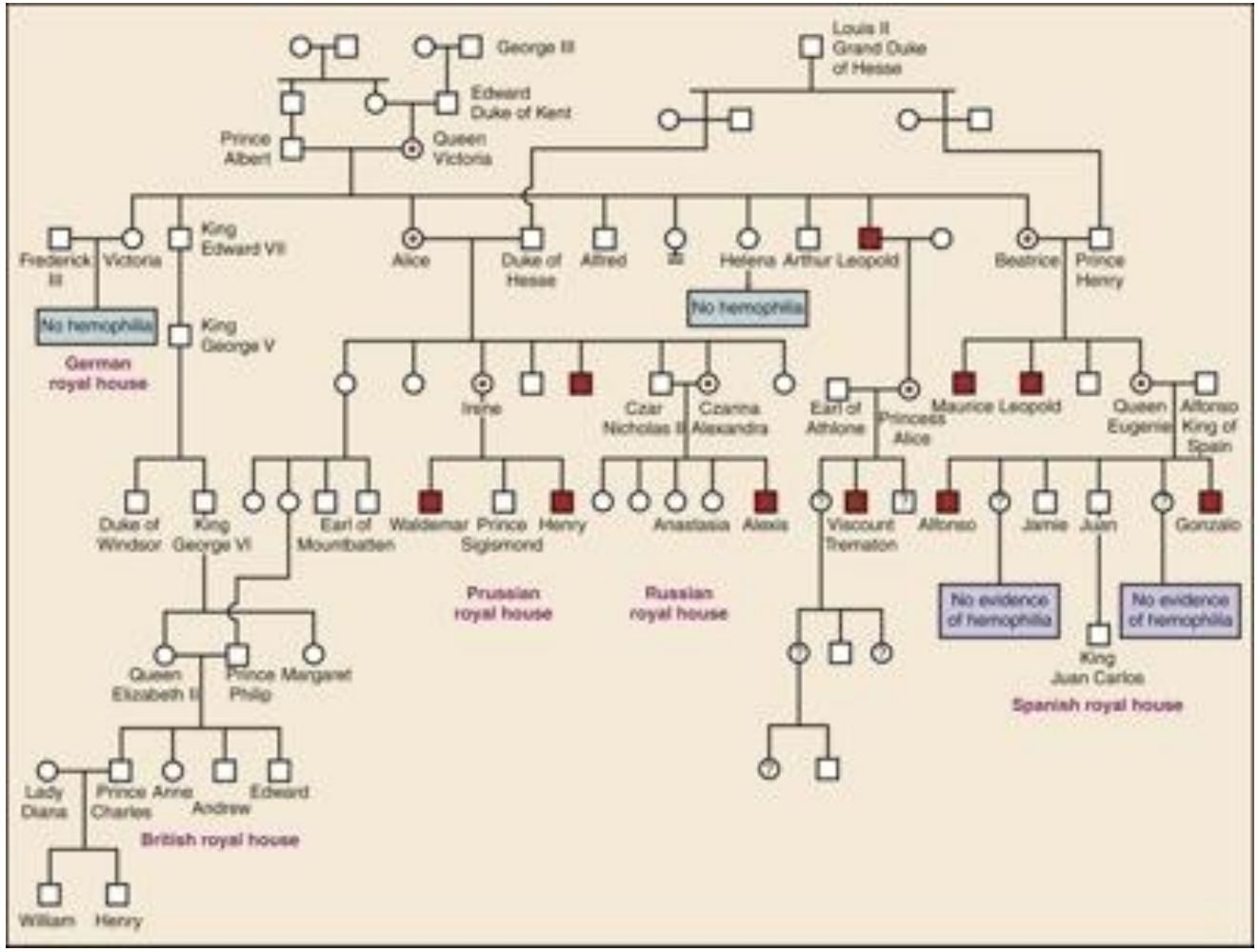
- Factor VIII gene is defective
- Factor VIII is a plasma protein required for blood clotting.
- Bleeding occurs easily and profusely from minor injuries.
- Bleeding occurs into large joints, especially knees.
- Treatment is intravenous supplementation of Factor VIII.
- With treatment average life expectancy is reduced by 10 years.
- Hemophilia A in the European royal families constitutes a well-known pedigree. See the next slide. NOTE: The children of Prince William and Prince Harry aren't shown on the pedigree.





Genetic Disorders:
Sex-Linked Single-Gene Disorders 3

Hemophilia A Pedigree



Genetic Disorders:
Sex-Linked Single-Gene Disorders 4

Other X-Linked Recessive Disorders:

Hemophilia B (Factor IX) (Symptoms and prognosis are very similar to Hemophilia A.)

Duchenne Muscular Dystrophy (a topic later in this course)

Genetic Disorders: Carrier Testing

- Using DNA analysis techniques it is possible to test prospective parents for many genetic disorders **prior to conception**. This includes recessive disorders. So called **"carrier testing"** will tell a prospective parent if he or she is heterozygous for a recessive allele (autosomal or sex-linked) that causes a single-gene genetic disorder.
- If both prospective parents are carriers, they have a 25% chance of producing a child with the disorder.
- Carrier tests exist for more than 100 different genetic disorders.

Genetic Disorders:
Non-Mendelian Single Gene Disorders

Fragile X Syndrome

•Amplification of CGG repeats (230-4000) in the FMR1 gene near the end of the long arm of the X chromosome. A constriction in the X chromosome is visible in that area on karyotypes, causing that area to appear “fragile”.

•Such long stretches of repeated triplets are “silenced” by **imprinting.**

•**Imprinting is the addition of methyl (–CH_3) groups to DNA. Imprinting is not the same as mutation. The base sequence of the DNA is not altered.**

•Imprinting decreases gene expression. That means it prevents the transcription of the FMR1 gene and thus also prevents the synthesis of a **protein (FMRP)** important in **learning and memory**.

Genetic Disorders:
Non-Mendelian Single Gene Disorders 1

Fragile X Syndrome

•The protein produced by the normal FMR1 gene is a **ribosome-associated protein expressed in neurons.**

•Fragile-X Syndrome is the most common cause of **familial mental retardation** in boys. **Autism** is also common in Fragile X patients.

•Life expectancy is normal.

•This disorder is not considered to be a Mendelian trait. What is inherited is not a defective gene per se, but the **tendency for a region of the FRM1 gene that contains CGG repeats (repeats of the DNA triplet cytosine guanine guanine) to be expanded (amplified) during gamete production.**

•This **occurs more often during oogenesis** than during spermatogenesis.

•The disorder is, therefore, **more common in males** because males receive their X chromosome from their mother.

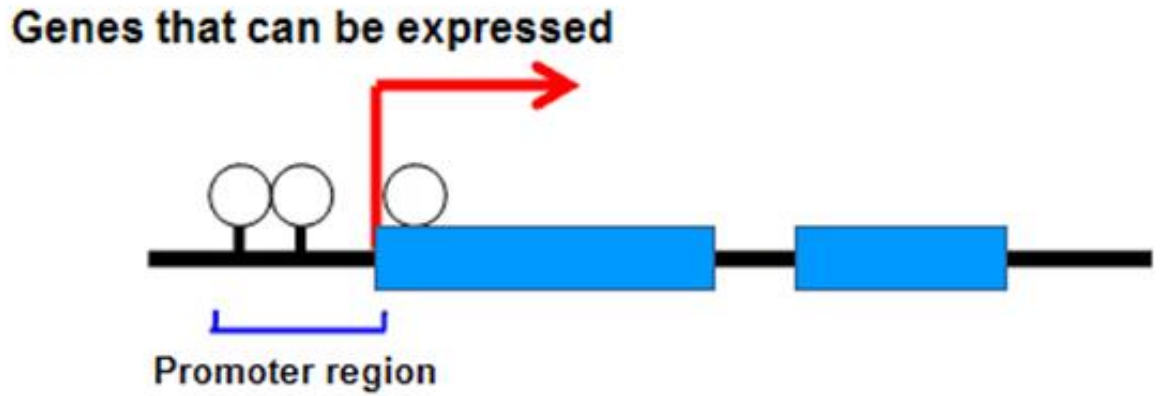
Genetic Disorders:
Non-Mendelian Single Gene Disorders 2

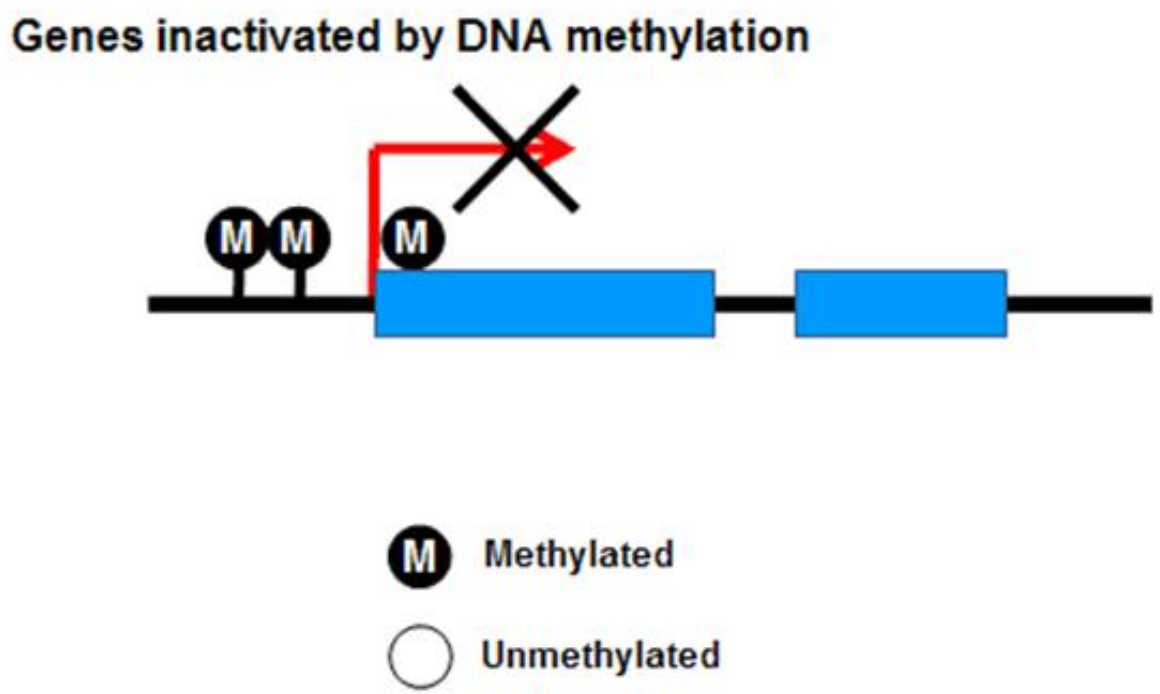
Fragile X Syndrome

•A normal X chromosome contains an average of about 30 CGG repeats in the FMR1 gene. If, during meiosis, that number is amplified beyond 60, the affected gamete will carry a Fragile X chromosome. The number of triplet repeats in the Fragile X chromosome tends to increase with each generation. The arrow below points to a Fragile X chromosome.

Methylation and Gene Expression

Recall from your Biology course that the **promoter region** is the binding site for **RNA polymerase.** If there are methylated DNA bases in the promotor region, RNA polymerase is unlikely to transcribe the associated gene.





Genetic Disorders:
Non-Mendelian Single Gene Disorders 3

Fragile X Syndrome: CGG Repeats and Imprinting of DNA

Genetic Disorders:
Non-Mendelian Single Gene Disorders 4

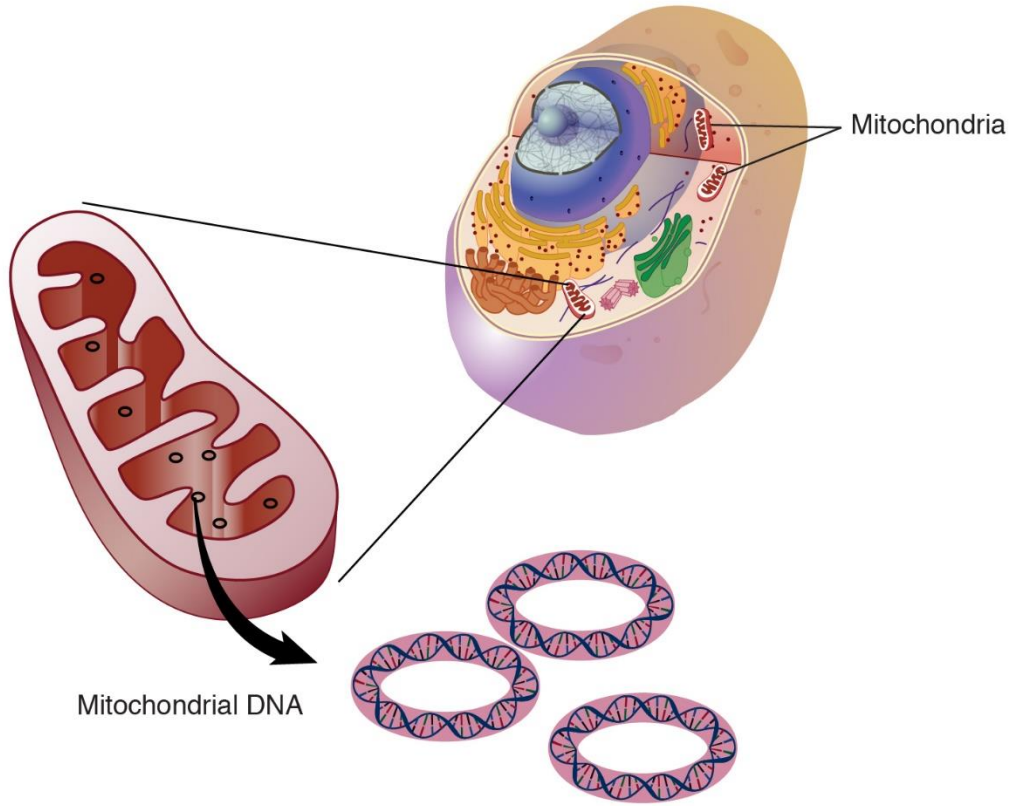
- **NARP (Neuropathy-Ataxia-Retinitis Pigmentosa**
  - **Mitochondrial** gene mutation
  - Mitochondria are cytoplasmic organelles. They are the sites of the **Kreb's Cycle and the Electron Transport Chain (Oxidative Phosphorylation).** Mitochondria have their own circular chromosomes.
  - Mitochondrial chromosomes contain just **37 genes**. Thirteen of them code for proteins. Those proteins are subunits in the molecules that support **Oxidative Phosphorylation.**
  - **The female gamete (ovum) contains a great deal of cytoplasm. During each meiotic division, there is unequal division of the cytoplasm.**
    - **In meiosis I cytoplasm goes to the primary oocyte, while the first polar body gets none.**
    - **In meiosis II the cytoplasm goes to the secondary oocyte, while the second polar body gets none.**
    - **When a sperm penetrates its surface, a secondary oocyte completes meiosis to form the ovum.**

Genetic Disorders:
Non-Mendelian Single Gene Disorders 5

- **NARP (Neuropathy-Ataxia-Retinitis Pigmentosa**
  - Only females transmit mitochondrial genes to offspring. The sperm contains very few mitochondria because most of the cytoplasm is lost during conversion of a spermatid to a sperm.
  - About 60 mitochondria are located just proximal to the flagellum in sperm, whereas the ovum contains about 100,000 mitochondria. Sperm mitochondria are destroyed in the zygote, soon after fertilization.
  - NARP is due to a mutation in the MT-ATP6 gene. It codes for a subunit of the enzyme **ATP synthase**. The enzyme is required for the last step in oxidative phosphorylation. It converts the energy in the hydrogen gradient into ATP molecules.
  - Tissues that use a great deal of ATP are most affected by NARP: muscle, nervous, liver and kidney.
  - Life expectancy is 30 to 40 years.

Genetic Disorders:
Non-Mendelian Single Gene Disorders 6

Mitochrondrial chromosomes are circular and contain just 37 genes.

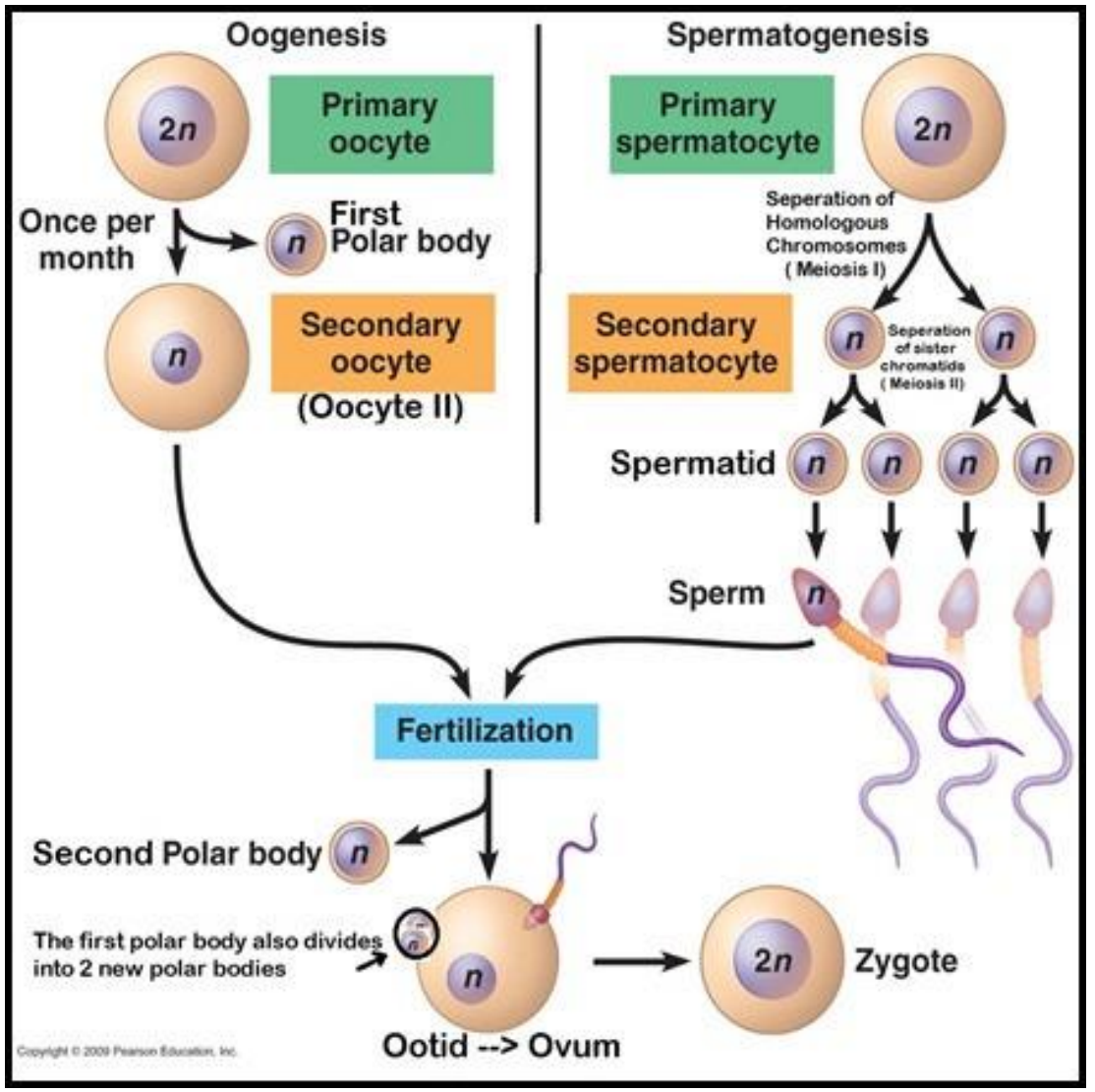


Male vs Female Gametogenesis

A sperm has very little cytoplasm (and thus very few mitochondria) compared to an ovum.

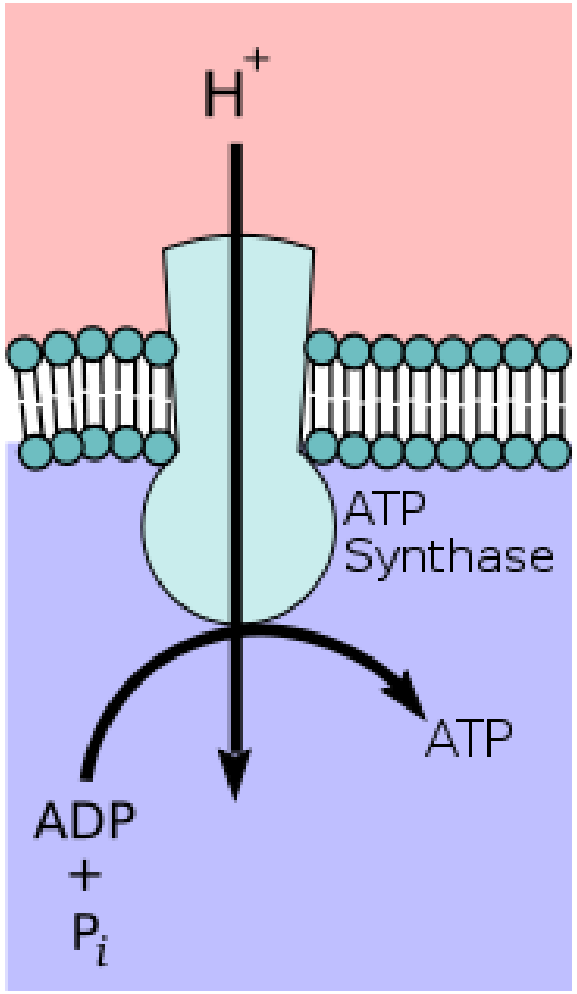
The first and second polar bodies produced during oogenesis also have very little cytoplasm.

Polar bodies never become functional gametes.



Genetic Disorders:
Non-Mendelian Single Gene Disorders 7

NARP is due to a mutation in the **mitochondrial gene** that codes for the enzyme, **ATP synthase**. ATP synthase molecules are located in the inner mitochrondrial membrane.



By Mitochondriale_Elektronentransportkette.svg: Klaus Hoffmeierderivative work: Matt(Mitochondriale_Elektronentransportkette.svg) [Public domain], via Wikimedia Commons

Genetic Disorders:
Non-Mendelian Single Gene Disorders 8

- **NARP (Neuropathy-Ataxia-Retinitis Pigmentosa**
  - **Neuropathy** affects both sensory and motor nerve impulse conduction.
  - **Ataxia** is a motor defect that affects skeletal muscle coordination.
  - **Retinitis pigmentosa** is an inflammation of the retina of the eye causing gradual degeneration of the **rods and cones, the light receptor cells of the retina,** and eventual blindness. It also causes damage to the pigmented layer of the retina and to the blood vessels that serve the retina. (Retinitis pigmentosa also may result from Mendelian inheritance of autosomal genes.)

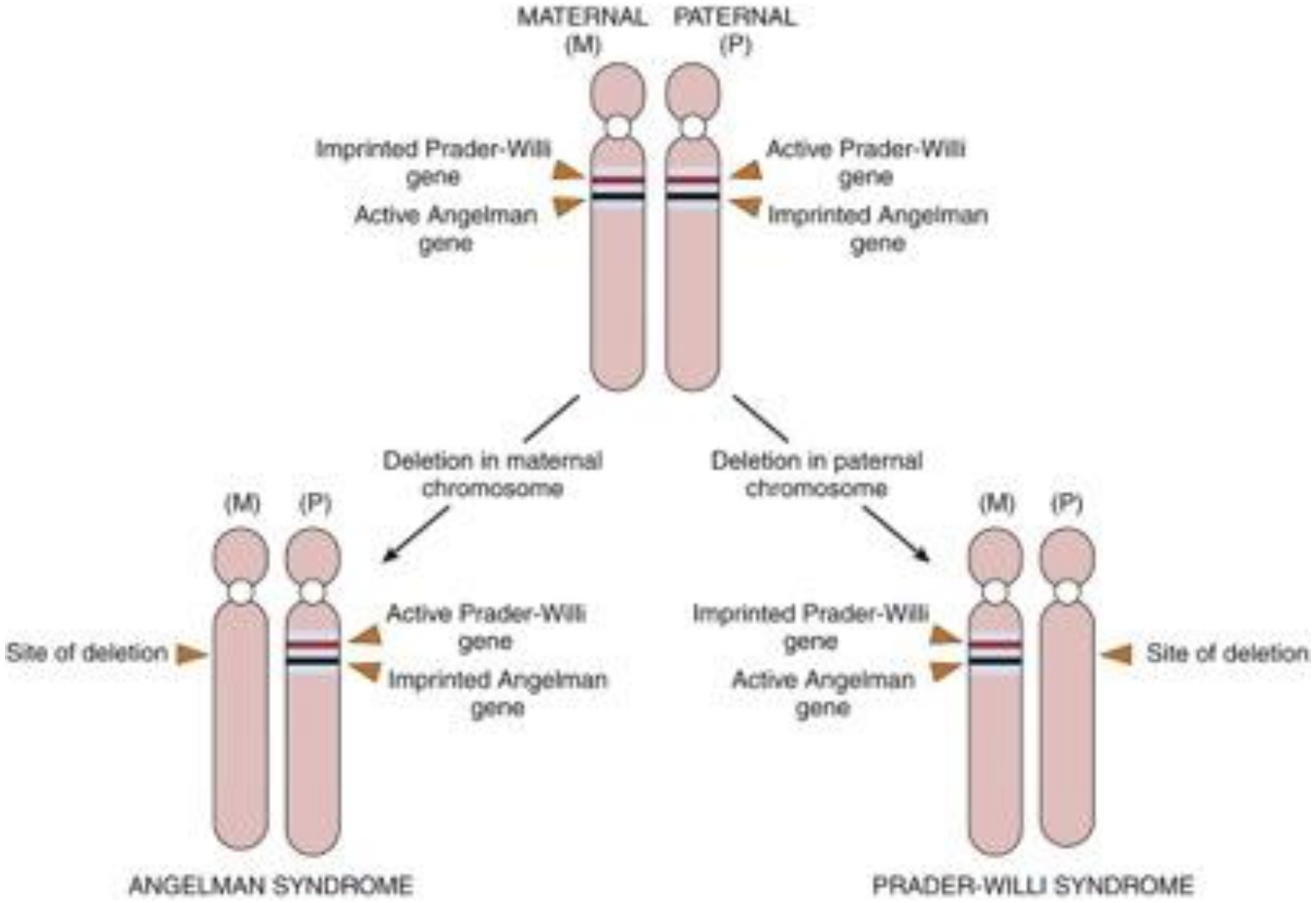
Genetic Disorders:
Non-Mendelian Single Gene Disorders 9

- **Prader-Willi Syndrome** and **Angelman Syndrome**
  - Two syndromes result from a deletion at the same location on one chromosome #15. They differ depending on whether the deletion occurs on the maternally-derived or paternally-derived chromosome.
  - The expression (transcription and translation of a gene) of Prader-Willi and Angelman syndromes involves **imprinting of DNA**. Imprinting occurs when DNA in a gamete is altered by addition of small chemical groups (methyl groups). **Imprinting suppresses gene expression.**
    - Normally, the Prader-Willi gene is imprinted on the maternally-derived chromosome, and the Angelman gene is active on the maternally-derived chromosome.
    - Normally, the Angelman gene is imprinted on the paternally-derived chromosome, and the Prader-Willi gene is active on the paternally-derived chromosome.
  - **One active allele for each gene produces a normal phenotype.**

Genetic Disorders:
Non-Mendelian Single Gene Disorders 10

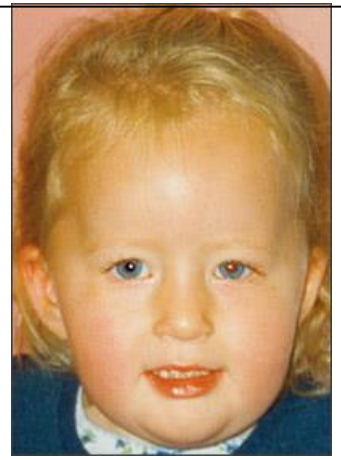
- **Prader-Willi Syndrome**
  - When the deletion occurs on **paternally-derived #15,** there will be no active Prader-Willi gene. The result is mental retardation, short stature, obesity, low muscle tone, hypogonadism, and characteristic facial features.
  - Obesity and cardiovascular effects reduce average life expectancy to middle age (late thirties to early forties).
- **Angelman Syndrome**
  - When the deletion occurs on the **maternally-derived #15**, there will be no active Angelman gene. The result is mental retardation, ataxia (uncoordinated muscle movement), tendency to laugh inappropriately, and characteristic facial features.
  - Average life expectancy is 60 to 65 years.
- Imprinting is an aspect of **epigenetics,** the study of factors other than the base sequence of DNA that affect gene expression.

Genetic Disorders:
Non-Mendelian Single Gene Disorders 11



Genetic Disorders:
Non-Mendelian Single Gene Disorders 12

Prader-Willi Syndrome (paternal chromosome 15 deletion + maternal chromosome imprinting)



Angelman Syndrome (maternal chromosome 15 deletion + paternal chromosome imprinting)

Multifactorial (Polygenic) Disorders

- When **two or more genes** act together in the production of a trait, that trait is termed multifactorial or polygenic.
- The expression of multifactorial traits tends to be **affected by the environment.**
- Multifactorial disorders are much **more common** than single gene disorders.
- Examples of polygenic disorders:
  - high blood pressure
  - predisposition to cancer
  - diabetes mellitus
  - cleft lip
  - congenital heart defects

Environmentally-Induced Congenital Disorders

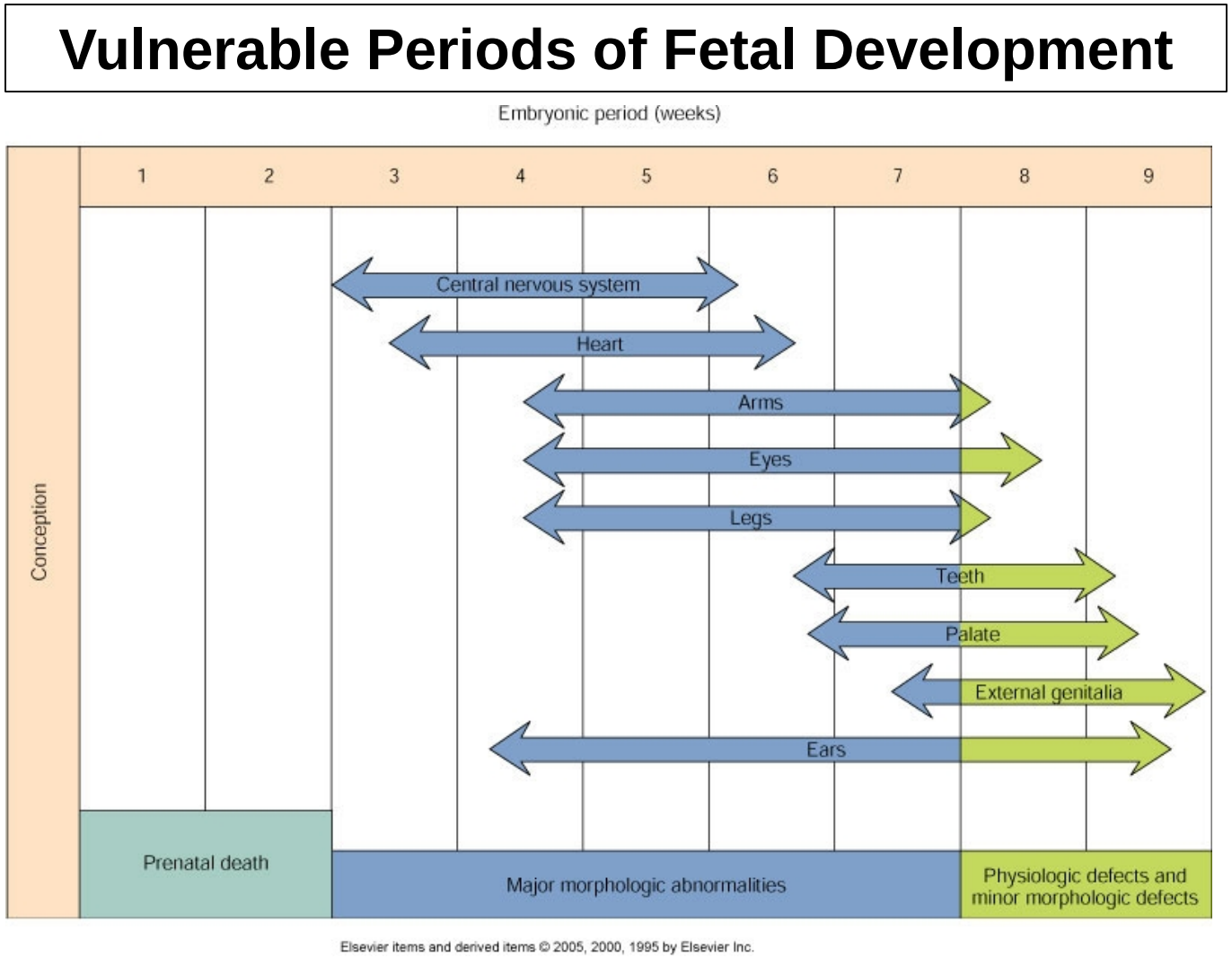
- In some congenital disorders the zygote is normal at fertilization, but abnormal at birth due to exposure to damaging environmental conditions during pregnancy.
- **Teratology**-the study of developmental anomalies (from the Greek *teras,* or “monster”
- **Teratogens**-environmental factors that cause harm to the embryo *in utero*.
- Effects of teratogens are usually limited to **somatic cells of the embryo** and thus are **not heritable.**

Environmentally-Induced Congenital Disorders 1

Periods of Fetal Vulnerability to Teratogens

- There are two broad stages of prenatal development:
  - **Embryonic period**: conception to 9 weeks gestation
  - **Fetal period**: 9 weeks gestation to birth
- **Prior to the third week of gestation** exposure to a teratogen either damages so few cells that the embryo continues to develop normally or damages so many cells that the embryo is aborted.
- **Between the third and ninth week** exposure to a teratogen is very dangerous. This is the period of **organogenesis**. Each organ has a critical period during which it is most vulnerable.
- **Between the ninth week and birth** exposure to a teratogen is less dangerous. This is a mainly a period of growth.

Environmentally-Induced Congenital Disorders 2

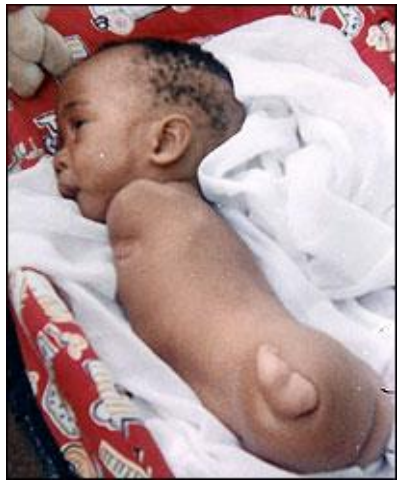


Environmentally-Induced Congenital Disorders 3

Teratogens: Chemicals/Drugs

•Proven chemical teratogens: thalidomide (tranquilizer), alcohol, anticonvulsants, warfarin, folic acid inhibitors (methotrexate), androgenic (male) hormones, ACE inhibitors (a class of diuretics), and mercury.

•**1960s-'Thalidomide babies** were born with limb malformations. Thalidomide is a drug (tranquilizer) used at the time to ease morning sickness.

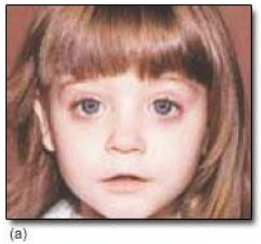


Environmentally-Induced Congenital Disorders 4

- **Fetal alcohol syndrome (FAS)**
  - FAS is due to alcohol consumption during pregnancy.
  - It affects 3 to 5 of every 1000 newborns in US. The US occurrence is more than **20 times** that in Europe!
  - FAS is due to maternal-fetal hypoxia and excessive free radical production.
  - Transient collapse of the umbilical cord is common.
  - **Complete abstinence** from alcohol during pregnancy is generally recommended.
- **FAS Phenotype**
  - Short stature, low body weight, small head
  - Small eye openings, smooth philtrum, thin upper lip
  - Poor coordination, low intelligence, behavioral problems
  - Problems with vision and hearing
  - Life expectancy is 34 years. Suicide rate is up to 15%.

Environmentally-Induced Congenital Disorders 5

Fetal Alcohol Syndrome



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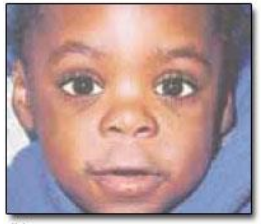

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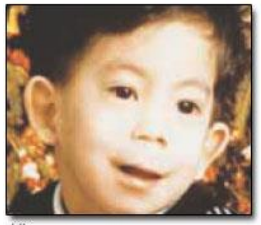

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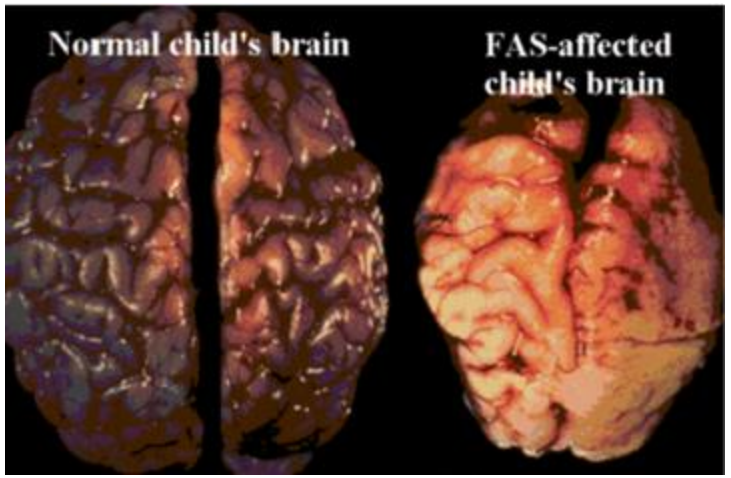
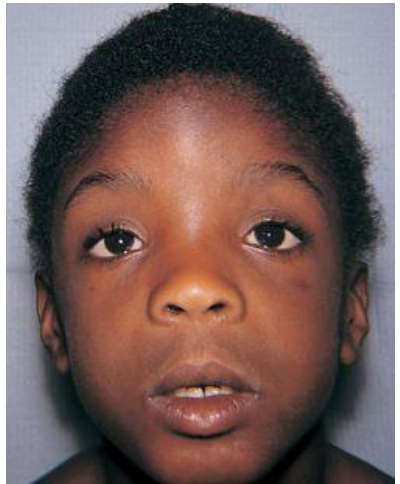




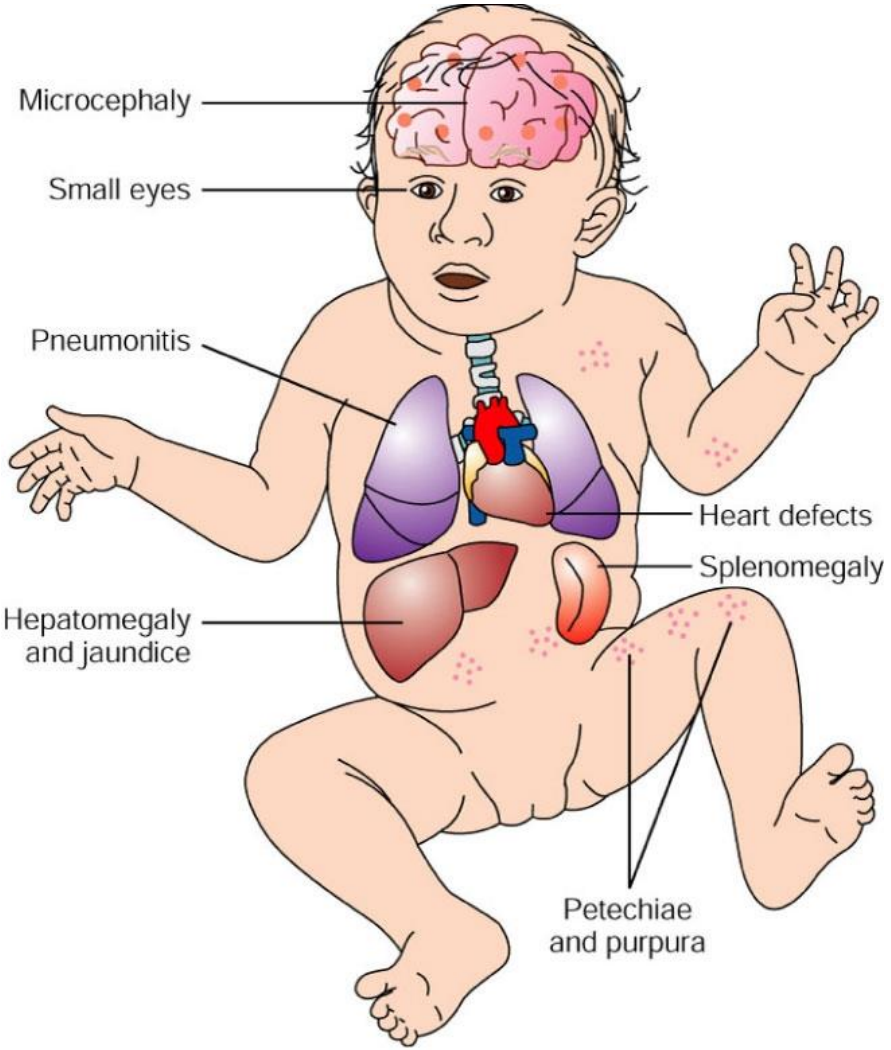
Environmentally-Induced Congenital Disorders 6

Teratogens: Infective Agents

- **Rubella virus** (German measles)
  - Risk extends from conception to 20 weeks gestation
  - Cataracts, deafness, and heart defects.
- **TORCH**
  - Refers to these infections:
    - **Toxoplasmosis, Others, Rubella, Cytomegalovirus, and Herpes virus**. (The toxoplasmosis protozoan can be transmitted in cat feces.)
  - TORCH newborns are often small, feverish, and feed poorly.
  - May have a rash, jaundice, petechiae or purpura
  - Many organs are susceptible to damage: heart, liver, spleen, lungs
- **HIV** (covered earlier)
- **Zika Virus**
  - Zika virus is transmitted by the Aedes mosquito. Maternal infection interrupts normal fetal development during the first trimester. Microcephaly may result.

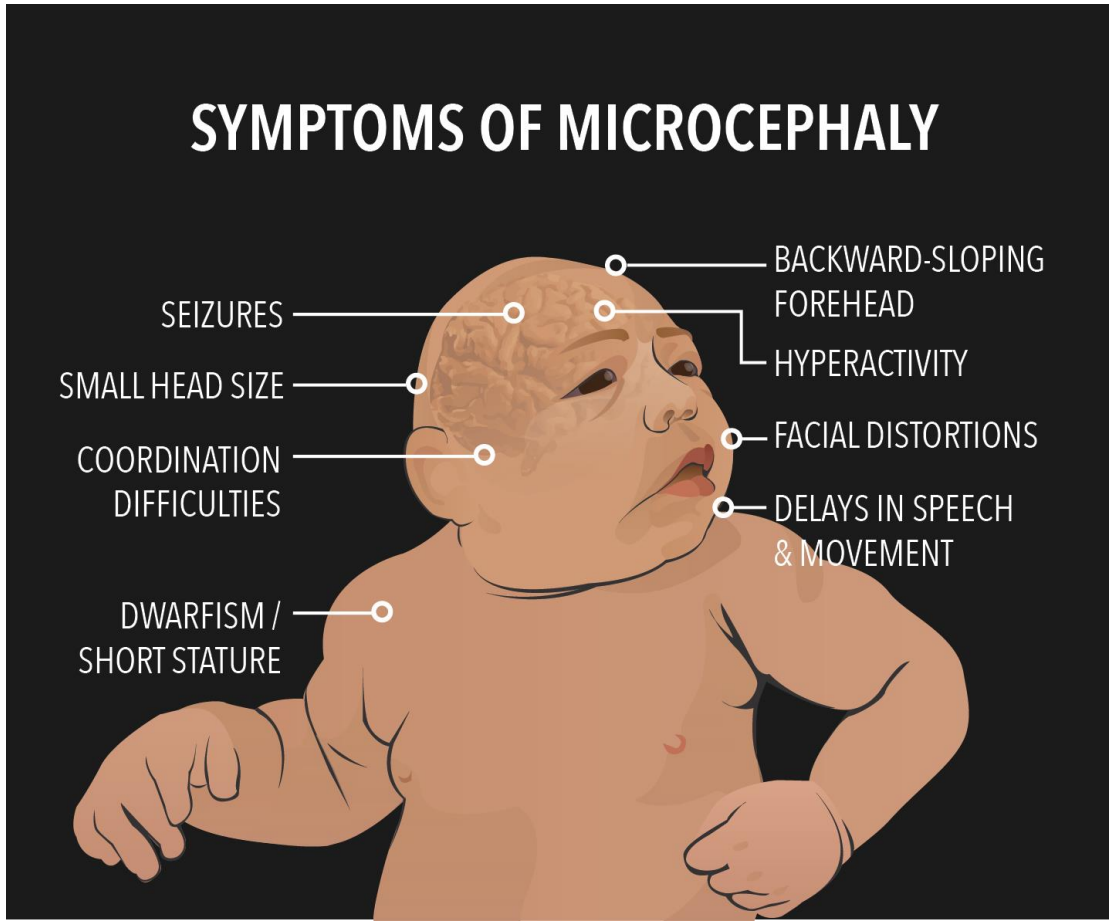
Environmentally-Induced Congenital Disorders 7

Clinical Findings of TORCH Infections



Environmentally-Induced Congenital Disorders 8

Microcephaly Caused by Zika Virus Infection



Environmentally-Induced Congenital Disorders 9

Radiation

- Ionizing radiation (X-rays or gamma rays) in high doses is both mutagenic and teratogenic.
- Ionizing radiation is capable of breaking DNA molecules.
- Early evidence for this fact:
  - Pregnant women who received irradiation of the cervix for cancer gave birth to abnormal babies.
  - Pregnant victims of atomic bombs in WW II gave birth to abnormal babies.
- Pregnant women should avoid diagnostic x-rays or use lead shielding.

Congenital Disorders Diagnosis and Counseling

Indicators for Prenatal Diagnosis and Counseling

- Maternal age of 35 years or greater
- Having borne a child with a chromosomal disorder
- Being a known carrier of a recessive genetic disorder
- Having a known family history of an X-linked or dominant disorder
- Having a family history of an inborn errors of metabolism (a metabolic pathway disorder)
- The occurrence of a neural tube anomaly in an earlier pregnancy

Postnatal Genetic Testing

- DNA from the baby's WBCs is tested for abnormalities.

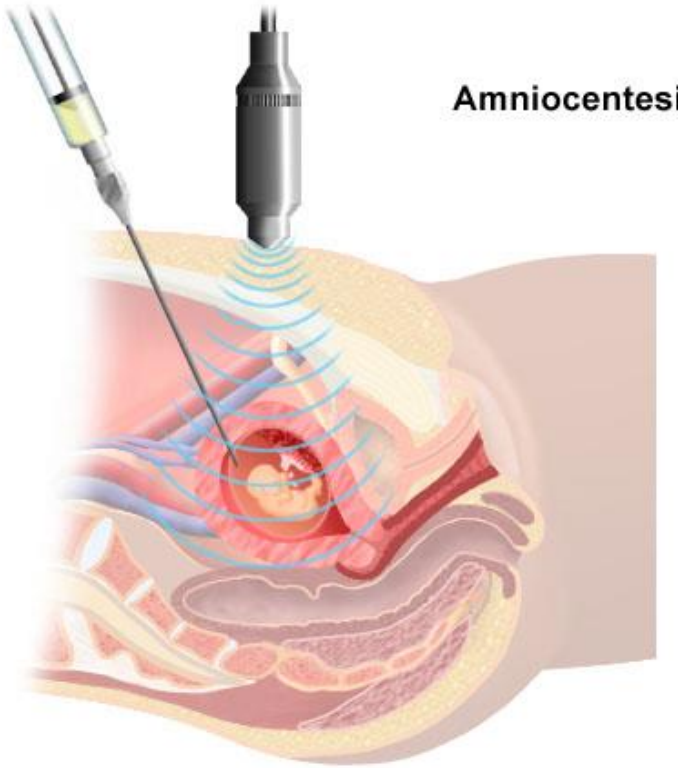
Congenital Disorders Diagnosis and Counseling 1

Prenatal Diagnostic Techniques

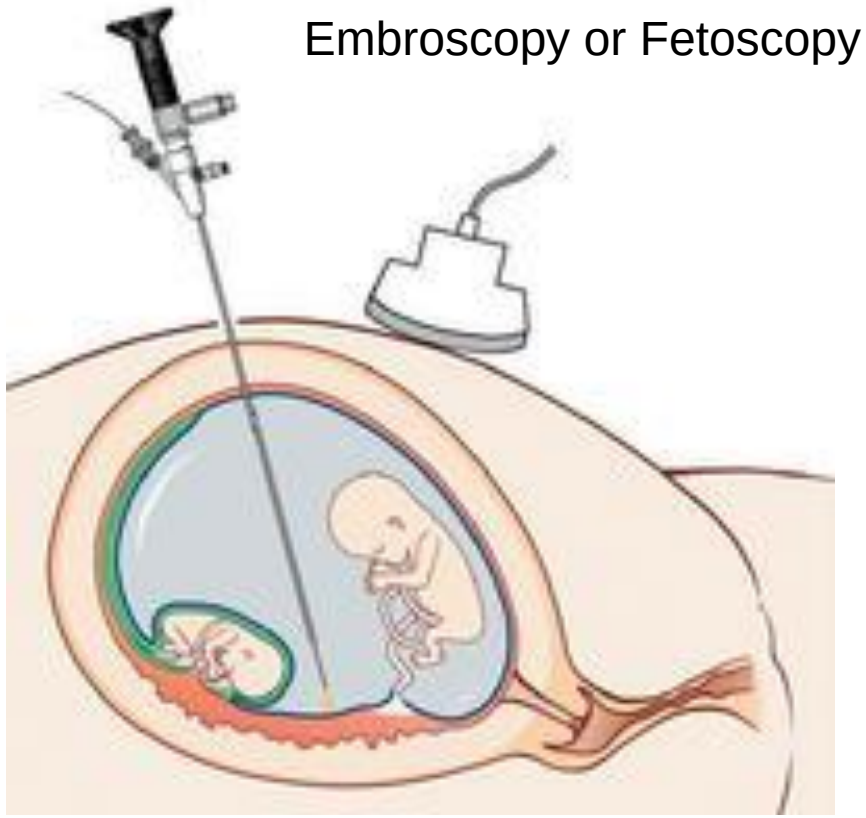
- **Ultrasound**
  - Noninvasive use of sound waves to produce an image of the fetus
  - May detect neural tube defects, heart defects, malformations of the face, head, body, limbs
- **Amniocentesis**
  - A needle inserted into the amniotic sac to extract a sample of amniotic fluid.
  - Fetal skin cells in the fluid are cultured and analyzed.
  - Fluid itself is checked for α-fetoprotein which may indicate a neural tube defect.
  - It cannot be performed until the 16th week of gestation.
  - Another 2 or 3 weeks are required for culturing skin cells for DNA analysis.
- **Chorionic Villus Sampling**
  - Removal of tissue from the chorion (outer membrane of the fetal sac)
  - Can be performed at 8 weeks gestation
  - DNA analysis results are available faster than with amniocentesis.
  - Higher rate of miscarriage than amniocentesis
  - Cannot detect neural tube defects
- **Embroscopy**
  - A scope is inserted through the cervix to allow visualization of the embryo
  - Can be performed as early as the first trimester.
  - Also used therapeutically; laser ablation of abnormal blood vessels
  - Potential to manage genetic disorders with gene therapy or stem cell therapy

Congenital Disorders Diagnosis and Counseling 2

Prenatal Diagnostic Techniques



Embroscopy or Fetoscopy



Gene Therapy

Human Genome Project

- The human genome has been sequenced. The base sequence of each chromosome is known.
- Many genes have been mapped to their locations on chromosomes.
- Many gene products have been identified.

Gene Therapy

- Treatment of genetic disease by replacing a defective gene with a normal one is called gene therapy.
  - There are moral and ethical concerns.
  - It requires splicing the normal gene into a vector (a carrier like a plasmid or a virus).
  - It requires that the vector successfully enter target cells.
  - It requires that the normal gene functions (undergoes replication, transcription and translation) in target cells.

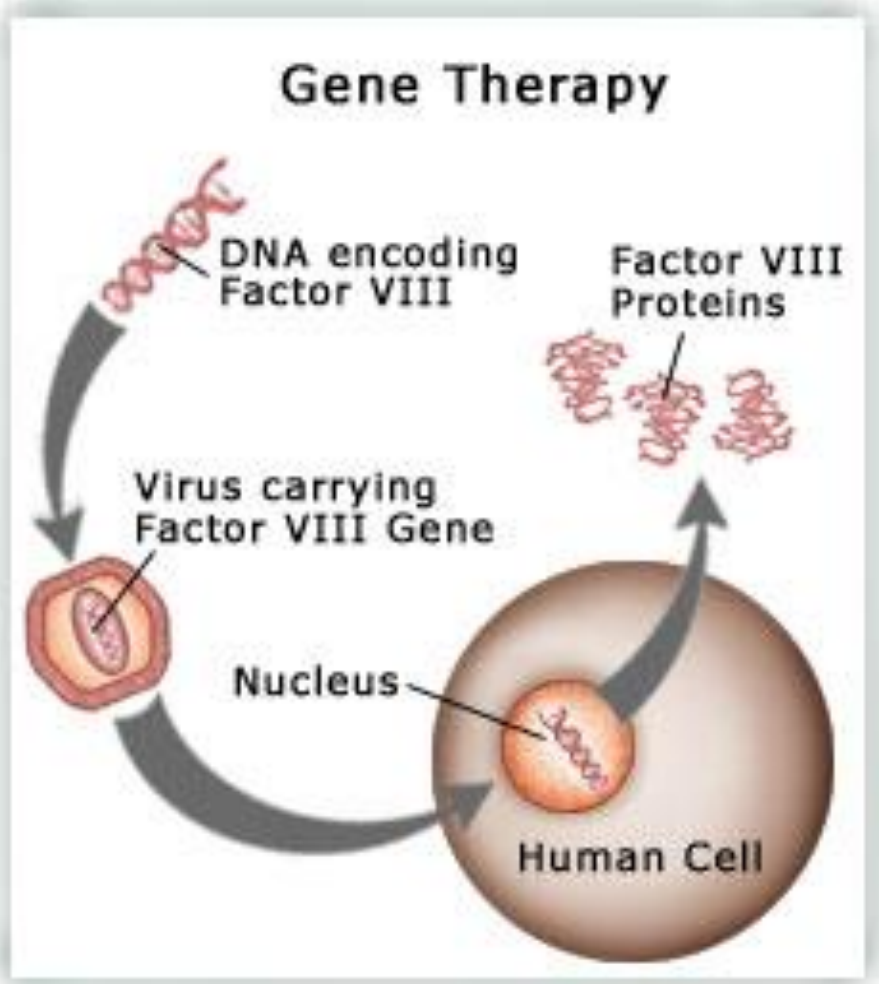
Gene Therapy 1

Gene Therapy

- In 2000, the first gene therapy "success"
  - A viral vector was used to carry a normal gene into SCID patients.
  - SCID patients had immune system function restored.
  - BUT three of eleven patients in one trial developed leukemia.
  - The gene-carrying retrovirus had inserted itself near a proto-oncogene (a gene that causes cancer when mutated).
  - New trials focused on correcting the genetic defect without triggering an oncogene.
- Today gene therapy has been used to successfully treat a number of disorders mostly in small clinical trials. (SCID, hemophilia A, beta thalassemia, leukemia, etc.)
- Improved techniques are developed through very careful research.

Gene Therapy 2

Theoretical Gene Therapy for Hemophilia



QUIZ 4AB

- COMPLETE QUIZ 4AB.
- THEN GO ON TO MODULE 4CD PPT.