GENETIC BASIS OF DISEASE

This pdf was developed by
Stephan Grundy
for ReviewPathology.com

Reference notations: when references are listed, the following suffixes indicate:
pm = pubmed
i = Images (usally Google images)
w = Wikipedia
rg = ResearchGate
yt = YouTube
Selected text = various websites

What is the central dogma of genetics?

- The central dogma of genetics is a theory that genetic information is coded in self-replicating DNA and undergoes unidirectional transfer to messenger RNAs in transcription which act as templates for protein synthesis in translation.

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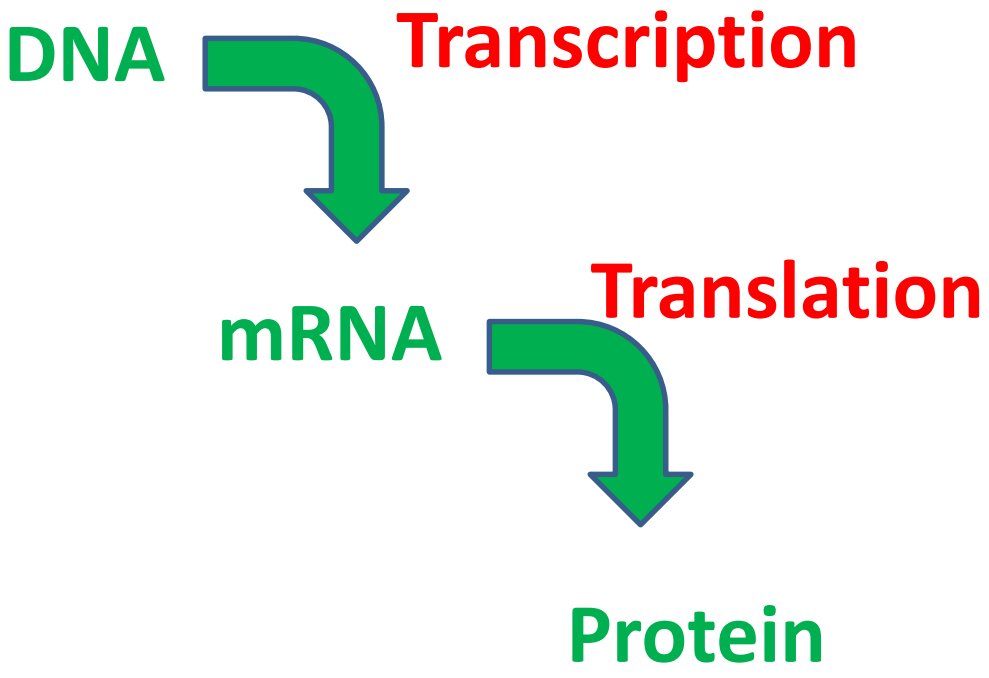

DNA

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What is DNA and what are its components?

- DNA, deoxyribonucleic acid, is a self-replicating molecule and is the carrier of genetic information.
- Most DNA molecules has two biopolymer strands coiled around to form a double helix.
- The two DNA strands, called polynucleotides, are composed of simpler monomers called nucleotides.
- Each nucleotide composed of one of four nitrogen-containing nucleobases (cytosine [C], guanine [G], adenine [A] or thymine [T]), a sugar called deoxyribose, and a phosphate group.

What is a nucleotide?

- Nucleotides consist of nucleobases, (A, G, C and T or U), a pentose sugar, and a phosphate group. The 3’ carbon of the pentose (ribose or deoxyribose) links to a phosphate group via a phosphodiester bond.
- A deoxyribose-phosphate polymer is the backbone in DNA.
- A nucleobase attaches to each pentose-phosphate segment.
- Nucleic acids (DNA and RNA) consist of millions of nucleotides strung together. This strand is called a polynucleotide

What is the DNA double helix?

- DNA double helix is two biopolymer strands coiled around each other forming a double helix.
- The two DNA strands run in opposite directions to each other, which is called antiparallel.

What are the grooves in the DNA molecule?

- The coiling of DNA creates two groves in the DNA molecule.
- The major groove is 22 Å wide, and the minor groove is 12 Å wide.
- DNA-binding proteins promoting transcription fit into these grooves.

What is meant by the directionality of DNA?

The directionality of the DNA molecule consists of the 5’ end having a terminal phosphate group and the 3’ end a terminal hydroxyl group

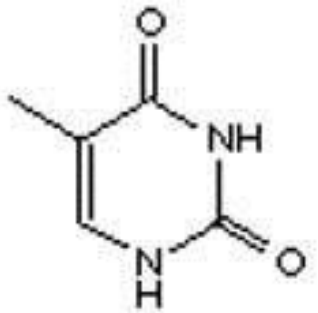
One strand of DNA is opposite in direction to the other strand, which is called anti-parallel.

How is the DNA molecule stabilized?

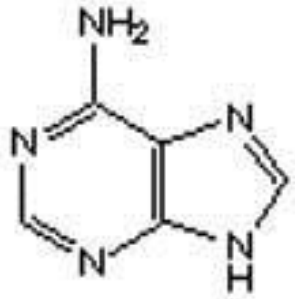
The DNA double helix is stabilized by hydrogen bonds between nucleotides and base-stacking interactions.

In DNA, adenine and thymine pair (A-T), as does guanine and cytosine (G-C).

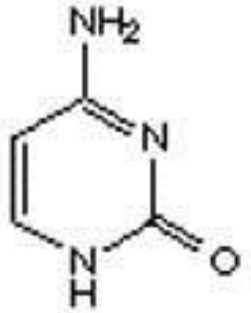
What are the nucleobases found in DNA?



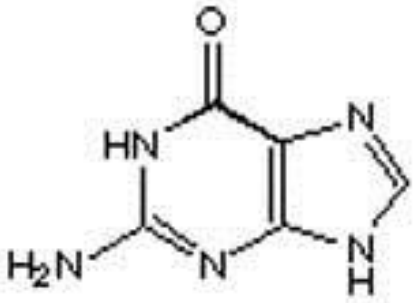
Thymine (T)



Adenine (A)



Cytosine (C)



Guanine (G)

What is non-canonical base pairing?

A non-canonical base pairing (1i) is a linkage between two bases of a nucleic acid other than the standard base pairings.

Their presence in DNA tends to disrupt the double helix.

What is complementary base pairing?

In complementary base pairing (1i) the rule is:

A with T: the purine adenine (A) always pairs with the pyrimidine thymine (T).

C with G: the pyrimidine cytosine (C) always pairs with the purine guanine (G).

What is nucleic acid thermodynamics?

- Nucleic acid thermodynamics (1i) describes how temperature affects the structure of double-stranded DNA (dsDNA).

- The melting temperature (T_m) of dsDNA is defined as the temperature at which half the DNA strands are pulled apart.

What is DNA sense?

The sequence of DNA that serves for coding of messenger RNA is called DNA sense (1i). The DNA sequence on the opposite strand is called anti-sense.

What is DNA supercoiling?

DNA supercoiling (1i) is the over- or under-winding of a DNA strand. It may affect access to the genetic code.

What are telomeres?

At the ends of chromosomes are segments of DNA called telomeres (1i). These protective "chromosome caps" (1i) “shield chromosomes from degradation, fusions, and checkpoint recognition” (1pm). Telomeres are segments of single-stranded DNA made up of thousands of repeats of TTAGGG sequence.

What are G-quadruplex structures?

G-quadruplex structures (1i) are helical sequences of DNA rich in guanine tetrads. They occur near in telomere regions and in regulatory regions of various genes. They associate through Hoogsteen hydrogen bonding (1i) and play a role in gene regulation.

What is chromatin?

- Chromatin (1i) is a complex of DNA, protein, and RNA. It packages DNA into a more compact, denser shape, prevents DNA damage, controls gene expression, and allows for DNA replication.
- Histones (1i) are proteins that compact DNA.
- Chromatin is constructed loose enough to allow access to RNA and DNA polymerases that transcribe and replicate the DNA.

What are mutagens?

- Mutagens (1i) are agents that damage DNA.
- Mutagens include reactive oxygen species (1i), alkylating agents (1i) and high-energy electromagnetic radiation.
- Types of damage include cross-links between pyrimidine bases, base modifications, and double strand breaks (1i).

What are intercalating mutagens?

Intercalating mutagens (1i), such as ethidium bromide and proflavine, insert themselves between DNA bases. These can cause frameshift mutations during DNA replication. Others, such as daunorubicin, interfere with transcription and replication.

What is the human genome?

- The human genome consists of about has approximately 3 billion base pairs of DNA that form 46 chromosomes.
- Most base pairs are part of junk DNA.
- The human genome contains about 22,000 genes.

What is non-coding DNA?

- Noncoding DNA (1i) consists of that part of DNA that does not encode protein sequences. Some of these may encode for non-coding RNA molecules that do not translate into proteins. Other proposed functions may be for transcriptional and translational regulation of protein-coding sequences, scaffolding of chromatin, regulation of DNA replication, centromeres and telomeres.

What are pseudogenes?

Pseudogenes (1i) are part of non-coding DNA that are related to real genes. They in part appear be result of accumulation of multiple mutations that are of no value to the cell.

What are transcription and translation?

Transcription (1i) occurs when the DNA sequence is copied into a complementary RNA sequence.

Translation (1i) occurs when RNA copy is used to create a matching protein sequence.

What is a nucleoid?

The nucleoid (1i) that part of a prokaryote cell containing most of the genetic material.

A prokaryote is a single-celled organism that has neither a distinct nucleus with a membrane nor other specialized organelles. Examples are bacteria and cyanobacteria.

What is DNA replication?

DNA replication (1i) is required for cell division and proliferation. During replication, the two strands of the DNA molecule are separated , and each serves as a template for the production of new DNA molecules. This process is called semiconservative replication (1i). To ensure perfect fidelity during DNA replication, the cell carries out proofreading and error-checking (1i).

What are DNA polymerases?

DNA polymerases (1i) synthesize DNA from deoxyribonucleotides. They create two identical DNA strands from a single strand.

Before their action helicase (1i) enzymes unwind double-stranded DNA. This "unzips" the two strands. Then, DNA polymerases duplicate the DNA, so that a copy of the original DNA is transmitted to the each daughter cell.

What are nucleases, exonucleases, and endonucleases?

Nucleases (1i) cut DNA strands by catalyzing the hydrolysis of the phosphodiester bonds.

Nucleases that hydrolyse nucleotides from the ends of DNA strands are called exonucleases, whereas endonucleases cut within strands.

The most frequently used nucleases in molecular biology are the restriction endonucleases (1i), which cut DNA at specific sequences.

RNA

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What is RNA?

- Ribonucleic acid (RNA) (1i) is a large molecule used for coding, decoding, regulation, and expression of genes. One form of RNA, called messenger RNA (mRNA) (1i), transmits from the nucleus to the cytoplasm and directs synthesis of proteins.
- Another form of RNA, called transfer RNA (tRNA) (1i) carries amino acids to the ribosome, and ribosomal RNA (rRNA)(1i) connects the amino acids together to synthesize proteins.

What is the structure of RNA?

- The basic structure of RNA are the same for DNA except that the pyrimidine base uracil replaces thymine and ribose replaces deoxyribose.

How does RNA differ from DNA?

1. Generally, RNA is a single-stranded molecule. There are exceptions however.
2. The suger-phosphate backbone contains ribose instead of deoxyribose.
3. One nucleobase in RNA is uracil--not thymine.

How is RNA synthesized?

- RNA is synthesized by the enzyme enzyme—RNA polymerase (1i). This process uses DNA as a template (transcription). The DNA sequence determines the RNA sequence.
- There are also a number of RNA polymerases that use RNA as a template for new RNA synthesis (RNA-dependent RNA polymerase [1i]). Examples of the latter include RNA viruses.

What is messenger RNA (mRNA)?

- Messenger RNA (mRNA) (1i) is a large family of RNA molecules that convey genetic information from DNA to the ribosome.
- At the ribosome (1i), mRNAs define the amino acid sequence of the protein products of gene expression.

What is the structure of the ribosome?

- The ribosome (1i) is a molecular machine that joins amino acids as specified by messenger RNA.
- They consist of two major components: the small ribosomal subunits, which reads the RNA, and the large subunits, which joins amino acids to form a polypeptide chain.
- Each subunit contains one or more ribosomal RNA (rRNA) molecules several ribosomal proteins (r-protein).

What is transfer RNA?

- A transfer RNA (tRNA) (1i) is an adaptor molecule of 76 to 90 nucleotides that carries an amino acid to the ribosome for protein synthesis.

- One end of the tRNA matches the genetic code in a three-nucleotide sequence called the anticodon. Each type of tRNA molecule attaches to only one type of amino acid, However, several different tRNA molecules can carry the same amino acid.

What are other forms of RNA?

- MicroRNAs (miRNA) form a complex with enzymes to interfere with translation of mRNA or promote its degradation.
- Small interfering RNAs (siRNA), often formed during degradation of viral RNA, can act similarly to miRNAs.
- Antisense RNAs usually downregulate genes, but sometimes activate transcription.
- Riboswitches (1i, 2i, 3i) are regulatory sequences in mRNA that can regulate RNA or other genes.

GENES

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What categories of Mendelian Disorders can be caused by single gene defects?

- Mutations involving single genes follow one of three patterns of inheritance: autosomal dominant, autosomal recessive, or X-linked.
- Some mutations cause phenotypic effects (pleiotropy)—"the production by a single gene of two or more apparently unrelated effects"
- Some mutations occur in modifier genes -- altered expression of a gene at another locus causing another genetic disease. (e.g. modifier locus in cystic fibrosis)

What is a gene? an allele? a locus?

- A gene (1i, 2i) is a unit of heredity, generally carried in DNA.
- Scientifically, a gene is a sequence of DNA that determines distinct sequence of nucleotides that impart specific hereditary traits.
- An allele (1i, 2i, 3i, 4i) is one of two or more alternative forms of a gene.
- A gene locus is the fixed position of a gene (or gene maker) on a chromosome.

What is a phenotype? a genotype?

- The phenotype is a set of observable features representing the interaction of a genotype with the environment

- The genotype (1i, 2i, 3i, 4i) is that part of the genetic make-up that accounts for a particular phenotype

What is the difference between dominant and recessive alleles?

- Dominance is the relationship between alleles of one gene and the resulting phenotype. A dominant allele masks the influence of a second allele at the same locus.
- A recessive allele (1i, 2i, 3i) is expressed in the phenotype only when paired with an identical allele.

What are codominant and additive inheritance?

- In codominant inheritance (1i, 2i, 3i), two different alleles of a gene are expressed, and each encodes a similar protein. Hence, both alleles produce a similar phenotype (or mixed phenotype).
- Additive inheritance or polygenic inheritance (1i, 2i, 3i, 4i) require more than one gene to combine to produce a particular phenotype.

What are the major categories of genetic disorders?

- Mendelian disorders resulting from mutations in single genes
- Complex disorders involving multiple genes as well as environmental influences (multifactorial diseases)
- Diseases arising from chromosomal abnormalities
- Other genetic diseases

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What is the difference between a polymorphism and a mutation?

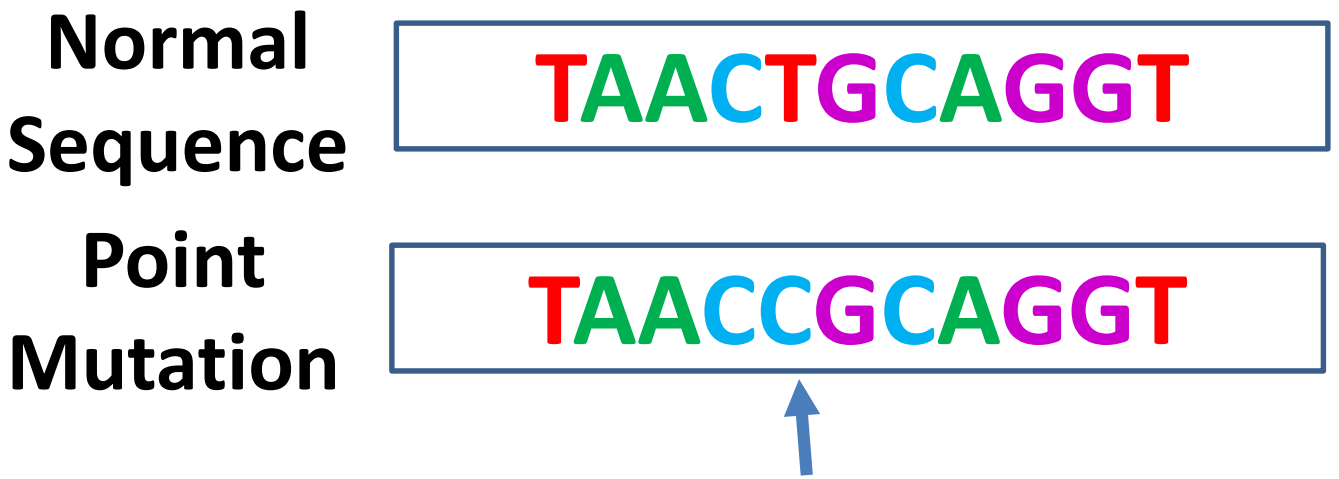
- A polymorphism (1i, 2i, 3i, 4i) is:
  - a. the presence of variation in alleles of genes in a population upon which natural selection can operate
  - b. the presence of more than one allele at a particular chromosomal locus within a population
  - c. As a general rule, to be counted as a polymorphism, allelic variation occurs at a rate greater then 1%
- A mutation (1i, 2i, 3i, 4i) is a change in the structure of a gene that lead to a disease phenotype.

What is the different types of mutation?

- Point mutations
  - Missense mutation
  - Nonsense mutation
  - Silent Mutation
- Insertion
- Deletion
- Duplication
- Frameshift mutation
- Trinucleotide repeat expansion

What is a point mutation?

- **Point mutations are mutations where a single nucleotide base is changed, inserted or deleted from a sequence of DNA or RNA.**



What are the different types of point mutation?

- Missense mutation: encodes a different amino acid (may produce a dysfunctional protein)
- Nonsense mutation: encodes for a truncated protein
- Silent Mutation: no change in amino-acid sequence or protein function

What is a silent mutation?

- With a silent mutation, a single nucleotide base is changed, inserted or deleted from a sequence of DNA or RNA without a change in the encoded protein.

Normal Sequence

TAT TGG CTA GTA CAT

Tyr Trp Leu Val His

Silent Mutation

TAC TGG CTA GTA CAT

Tyr Trp Leu Val His

What is a nonsence mutation?

- With a nonsense mutation, a single nucleotide base is changed, inserted or deleted from a sequence of DNA or RNA to produce a truncated protein

Normal Sequence	TAT TGG CTA GTA CAT
	Tyr Trp Leu Val His
Silent Mutation	TAT TGA CTA GTA CAT
	Tyr Stop

What is a missense (substitution) mutation?

- With a missense mutation , a single nucleotide base is changed, inserted or deleted from a sequence of DNA or RNA.

Normal Sequence	TAT TGG CTA GTA CAT
	Tyr Trp Leu Val His
Silent Mutation	TAT TGT CTA GTA CAT
	Tyr Cys Leu Val His

What are examples of diseases caused by point mutations?

- Cystic fibrosis
- Sickle cell anemia
- Tay-Sachs disease
- Phenylketonuria
- Color-blindness
- Familial hypercholesterolemia

What is a frameshift mutation?

- A frameshift mutation (1i, 2i, 3i, 4i) occurs when the addition or loss of DNA bases change a gene's reading frame.
- A reading frame consists of 3 bases that encode one amino acid. The frameshift mutation shifts the sequence of bases, which change the code for amino acids.
- Frameshift mutations can be caused by insertions, deletions, or gene duplications.

What is a frameshift mutation?

- **A frameshift mutation** causes the reading of the codons after the mutation to code for different amino acids

Normal Sequence	**TAT TGG CTA GTA CAT** **Tyr Trp Leu Val His**
Frameshift Mutation	**TAT TCG CTA GTA CAT** **Tyr Ser Ala Ser Thr**

In what diseases have frameshift mutations been observed?

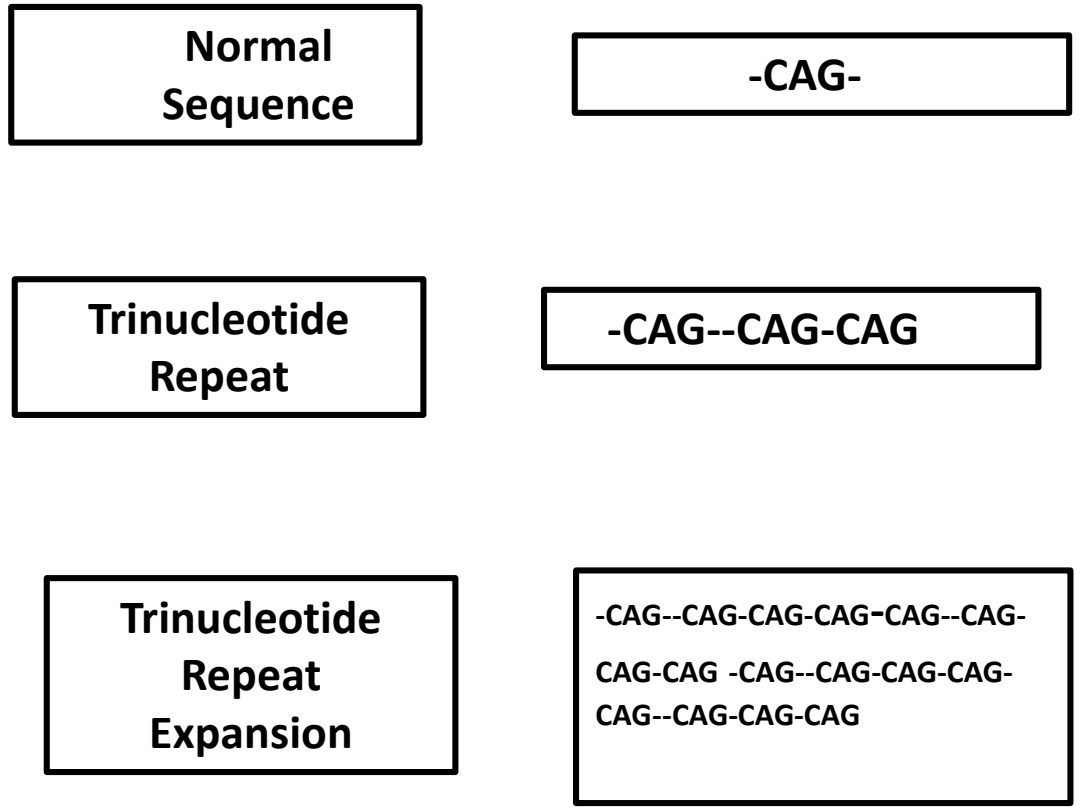
- Colorectal cancer (several frameshift mutations found)
- Breast cancer (BRAC 1 gene) (1pm, 2pm)
- Ovarian cancer (BRAC 1 gene)
- Crohn's disease (NOD2 gene)
- Cystic fibrosis (CFTR gene)
- Tay-Sachs disease (8 of 78 mutations are frameshift)
- Hypertrophic cardiomyopathy (troponin C gene)

What is a repeat expansion mutation?

- A repeat expansion mutation (1i, 2i, 3i, 4i) increases the number of times a DNA sequence is repeated.
- A trinucleotide repeat is made up of repeats of 3 base-pair sequences. Example trinucleotide.
- A tetranucleotide repeat is made up of repeats of 4 base-pair sequences.
- Trinucleotide repeat disorders are a set of genetic disorders caused by trinucleotide repeat expansion, a kind of mutation where trinucleotide repeats in certain genes or introns exceed the normal, stable threshold (Wikipedia)

What are trinucleotide repeat mutations?

- Trinucleotide repeat disorders are a set of genetic disorders caused by trinucleotide repeat expansion, a kind of mutation where trinucleotide repeats in certain genes causing the synthesis of abnormal proteins



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What was the first triple-repeat disease discovered?

- Fragile X syndrome
- In this syndrome (mapped to the long arm of the X chromosome) there are from 230 to 4000 CGG repeats, compared with 60 to 230 repeats in carriers and 5 to 54 repeats in unaffected individuals.

What tri- nucleotide repeat disorders are caused by loss of protein function?

- Fragile X syndrome*
- Fragile XE syndrome
- Friedreich ataxia

*Defects in learning skills, language, impulse control, and behavior

Orr and Zoghbi Ann Rev Neuroscience 2007. 30: 575-621

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What tri-nucleotide repeat disorders are caused by RNA mediated gain of function mechanism?

- Myotonic dystrophy protein (50 to >1000 CTG repeats)
  - Normal protein (<35 CTG repeats)
- Fragile X-associated tremor ataxia syndrome

Orr and Zoghbi Ann Rev Neuroscience 2007. 30: 575-621

What is a polyglutamine (“poly Q”) disorder?

- A polyglutamine (“poly Q”) disorder (1i) consists of:
- Several neurologic disorders are caused by an increased number of CAG repeats.
- During protein synthesis, the expanded CAG repeats translated into a series of glutamine residues (polyglutamine or "polyQ“ tract).

How many trinucleotide repeats are required to produce the polyQ Huntington disease?

- 10-26 CAG repeats: encoded protein remains healthy
- 37-80 CAG repeats: encodes protein* for Huntington disease

* Altered protein (huntingtin [1w]) disrupts nerve cells

What are some neurological diseases caused by polyglutamine (PolyQ) repeats?

Disease (Gene)

Normal PolyQ [Pathogenic PolyQ]

DRPLA (Dentatorubropallidoluysian atrophy)

(atrophin-1 protein) 6 – 35 [49 – 88]

HD (Huntington's disease) (HTT)

6 – 35 (36 – 250)

SBMA (Spinal and bulbar muscular atrophy) (AR)

9 - 36 [38 - 62]

SCA1 (Spinocerebellar ataxia Type 1) (ATXN1)

6 - 35 [49 - 88]

SCA2 (Spinocerebellar ataxia Type 2) (ATXN2)

14 - 32 [33 - 77]

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What are some neurological diseases caused by polyglutamine (PolyQ) repeats? (con't)

Disease (Gene)

Normal PolyQ [Pathogenic PolyQ]

SCA3 (Spinocerebellar ataxia Type 3 or Machado-Joseph disease) (ATXN3)
12 - 40 [55 - 86]

SCA6 (Spinocerebellar ataxia Type 6) (CACNA1A)
4 - 18 [21 - 30]

SCA7 (Spinocerebellar ataxia Type 7) (ATXN7)
7 - 17 [38 - 120]

SCA17 (Spinocerebellar ataxia Type 17) (TBP)
25 - 42 [47 - 63]

What are examples non-polyglutamine triple-repeat diseases?

Disease (Gene) {Codon}

Normal/wild type [pathogenic]

FRAXA (Fragile X syndrome) (FMR1 on X Ch) {CGG}

6 - 53 [230+]

FXTAS (Fragile X-associated tremor/ataxia syndrome) (FMR1, on X-ch) {CGG}

6 - 53 [55-200]

FRAXE (Fragile XE mental retardation)

(AFF2 or FMR2 on X-ch) {CCG}

6 - 35 [200+]

What are examples non-polyglutamine triple-repeat diseases? (con't)

Disease (Gene) {Codon}

Normal/wild type [pathogenic]

FRDA (Friedreich's ataxia) (FXN or X25) {GAA}

7 - 34 [100+]

DM1 (Myotonic dystrophy Type 1) (DMPK) {CTG}

5 - 34 [50+]

SCA8 (Spinocerebellar ataxia Type 8) (OSCA or SCA8) {CTG} 16 - 37 [110 - 250

SCA12 Spinocerebellar (ataxia Type 12)

(PPP2R2B or SCA12) {nnn n 5' end}

7 - 28 [66 - 78]

What is an insertion mutation?

- An insertion (insertion mutation) (1i, 2i, 3i, 4i) adds one or more nucleotide base pairs into a DNA sequence

What is a deletion mutation?

- A deletion (1i, 2i, 3i, 4i, 5i) reduces the number of DNA bases by cutting out a segment of removing of DNA. Deletions can be small or large.

What is a duplication mutation?

- A duplication mutation (1i, 2i, 3i, 4i) is when a segment of DNA is copied one or more times.

What is gene amplification?

- The multiple replication of a section of the genome, which occurs during a single cell cycle and results in the production of many copies of a specific sequence of the DNA molecule.
- Gene amplification can occur either in vivo (e.g., in cancer cells or drug induced) or by PCR

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What are examples of alterations in protein-coding genes other than mutations?

- Amplifications or deletions —or translocations
- Pathogenic germline alterations (1i)
- Somatically acquired structural alterations (1i)

  (e.g., Philadelphia chromosome)

Complex Genetic Traits

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What are complex traits?

- A complex trait (quantitative trait) (1i, 2i, 3i, 4i), a trait that does not follow Mendelian Inheritance patterns, is usually the result of actions of multiple genes, and is manifest by a variety of phenotypes.
- Examples of complex traits are coronary heart disease, type 2 diabetes, cancer, and Alzheimer disease.
- Environmental factors as well as genetic factors contribute to complex traits (multifactorial trait).

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What is polygenic inheritance?

- Polygenic inheritance (1i, 2i, 3i, 4i) is one in which a single characteristic is determined by two or more genes.
- Examples of polygenic inheritance include height, skin color, eye color and weight.

What is a monogenic trait?

- A monogenic trait (1i, 2i, 3i, 4i) is a characteristic that is dependent only on a single gene or a single allele.

What is epistasis?

Epistasis (1i, 2i, 3i, 4i, 5i, 6i, 7i) exists when the expression of one gene depends on one or more 'modifier genes'. Epistasis has a profound effect on the evolution of phenotypic traits.

What is pleiotropy?

Pleiotropy (1i, 2i, 3i, 4i, 5i) exists when one gene affects multiple traits.

What is a haplotype?

- A haplotype (1i, 2i, 3i, 4i, 5i) is a group of alleles inherited together from a single parent.
- Another definition refers to a collection of specific alleles in a cluster of tightly linked genes on a chromosome that are likely to be inherited together.

What is a haplotype phase?

- Haplotype phase (1w) signifies which allele belongs to which copy of the chromosome. It also refers to which alleles appear together on the same chromosome.
- Determination of haplotype phase is important defining for large-scale sequencing imputing low frequency variants and defining the relationship between genetic variation and disease susceptibility.

What is a multilocus genotype?

- A multilocus genotype (1i, 2w) is the combination of alleles found at two or more loci in a single individual.
- For example, temperature sensitivity of a yeast colony trait is determined by five multi-locus genotypes involving seven environmentally responsive loci.

What is allelic association?

- Allelic association (1w) is statistical association of a genetic marker allele with a phenotypic trait. A positive association suggests but does not prove a causative relationship between and allele and trait.

What is linkage disequilibrium?

- Linkage disequilibrium (1w) is the non-random association of alleles at different loci (1i, 2i, 3yt, 4yt)
- Loci are in linkage disequilibrium when association frequency of their different alleles is different from expected if the loci were independent and associated randomly.
- Linkage disequilibrium is key in population genomics.

What is genetic identity?

- **Genetic identity is the relatedness of two populations as determined by the percentage of the genes they share.**

What are quantitative traits?

- Quantitative traits (complex traits) (1i, 2w) are traits that do not behave according to simple Mendelian inheritance laws.
- Inheritance cannot be explained by the genetic segregation of a single gene.
- Quantitative traits demonstrate a continuous range of variation; they are usually determined by both environmental and genetic factors.

What is a phenocopy?

- A phenocopy (1w) is a variation in phenotype caused by environmental conditions.
- Has a nongenetic effect .
- For example, a high blood cholesterol caused by the diet can resemble high blood cholesterol caused by genetics.

What are major categories of genetic disorders?

- Mendelian disorders resulting from mutations in single genes
- Complex disorders involving multiple genes as well as environmental influences (multifactorial diseases)
- Diseases arising from chromosomal abnormalities

Chromosomes

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What are chromosomes?

- Chromosomes are packages of DNA. Humans have 23 pairs of chromosomes (46 in total). One of each chromosome pair is inherited from each parent. Each chromosome has a centromere that divides the chromosome into two uneven sections. The shorter section is the p arm, and the longer section is the q arm.
- Each chromosome consists of a single DNA molecule.

What is chromatin?

- Chromatin (1i, 2i, 3i, 4i) is a complex of DNA, RNA, and protein in the cell nucleus. It packages very long DNA molecules into compact shape, and protects DNA strands from entanglement.
- Chromatin protects DNA from damage during cell division

What is a nucleosome?

- A nucleosome is a unit of DNA packaging.
- In a nucleosome, a sequence of DNA is wound around eight histone protein cores.
- Nucleosomes are progressively folded to form a chromosome.

What are histones?

- Histones are proteins that package DNA into nucleosomes.
- They are "spools" around which DNA is wound.
- They protect DNA against damage.
- They are the major proteins of chromatin.

What is a chromatid?

- A chromatid (1i, 2i, 3i) is one copy of a newly copied chromosome.
- It is joined to the other copy by a centromere.
- Before replication, each chromosome consists of one DNA molecule.
- After replication, each chromosome has two DNA molecules .
- Later in cell division each chromatid becomes a a chromosome.

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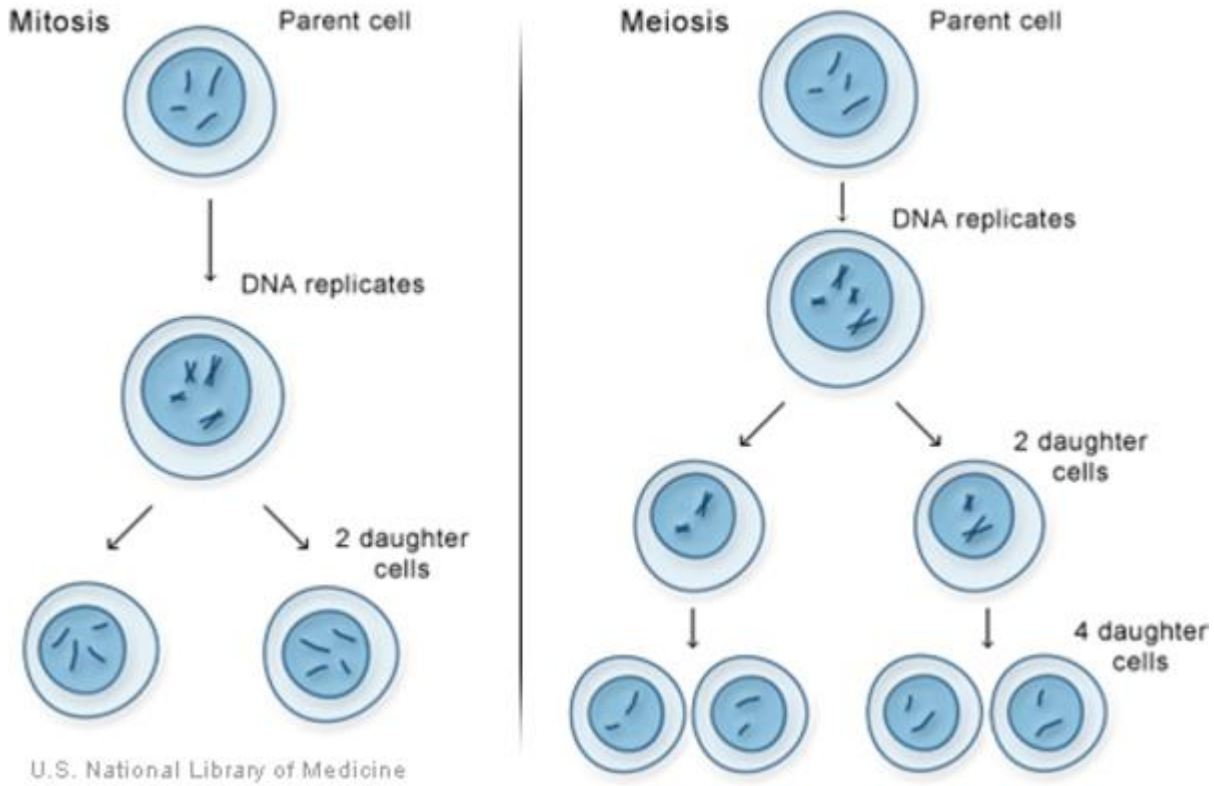
What are mitosis and meiosis?

- **Mitosis: Division of a parent cell, producing 2 daughter cells.**
  Meiosis: 2 divisions of a germ cell, producing 4 gametes.



What is a centromere?

The centromere (1yt) is a specialized DNA sequence of a chromosome that links a pair of sister chromatids.

What are the different types of chromosomes?

- There are two different types of chromosomes; sex chromosomes and autosomal chromosomes.
- The sex chromosomes are called X and Y chromosomes. Females have two X chromosomes, XX, one X from each parent. Males have one X chromosome from their mother and one Y chromosome from their father. Males thus are XY.
- The remaining chromosomes (pairs 1 through 22) are called autosomal chromosomes.

What is sex-linked inheritance?

- Sex linked inheritance depends on the gender of the individual and is directly tied to the sex chromosomes.

- In mammals the homogametic sex is female (XX) and the heterogametic sex is male (XY), thus the sex linked genes are carried on the X chromosome.

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What is the X chromosome?

- The X chromosome is one of the two sex chromosomes (the other being the Y chromosome). The X chromosome carries about 155 million DNA base pairs. It constitutes about 5 percent of the total DNA in cells.
- Approximately 800-900 genes encode for proteins on the X chromosome.

Why are males more likely to have an X-chromosome relay disorder than are females?

- Males have only one X-chromosome. Since females have two X-chromosomes, a defect in one chromosome can be off set by normality in the X-chromosome partner.
- Example : "Haemophilia A is inherited as an X-linked recessive trait" (e.g. Alexei Nikolaevich, Tsarevich of Russia).

What are most common forms of X-linked recessive disorders?

- Red-green color blindness
- Hemophilia A (deficiency of Factor VIII)
- Hemophilia B (deficiency of Factor IX)
- Duchenne muscular dystrophy (mutation in dystrophin gene)
- X-linked ichthyosis (mutation in steroid sulfatase gene)
- Glucose-6-phosphate dehydrogenase

What are examples of X-linked dominant diseases?

- Vitamin D resistant rickets: X-linked hypophosphatemia
- Rett syndrome: Developmental defects; scoliosis
- Most cases of Alport syndrome: Glomerulonephritis (type 4 collagen defect)
- Incontinentia pigmenti: Disorder of skin, hair, teeth, nails and CNS
- Giuffrè–Tsukahara syndrome: radial ulnar synostosis and microcephaly
- Goltz syndrome: Focal dermal hypoplasia
- X-linked dominant porphyria: defect in porphyrin metabolism
- Fragile X syndrome

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What is the Y chromosome?

- The male has two sex chromosomes--X and Y
- Sex is determined by the SRY gene on the Y chromosome
- SRY is responsible for the development of a male.
- Other Y chromosome genes contribute to male fertility.
- The Y-chromosome has about 59 million base pairs, which encodes for over 200 genes.

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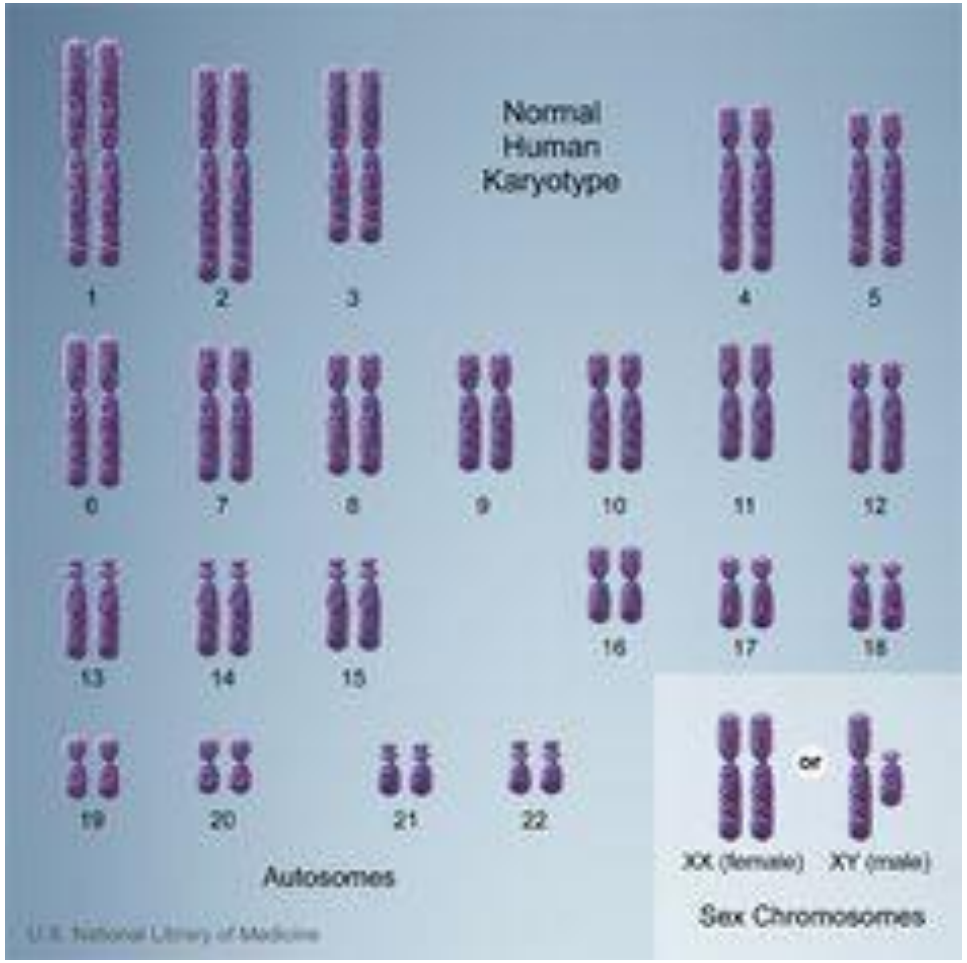
What is a normal human karyote?

- A karyotype is the number and appearance of chromosomes and its study is part of cytogenetics.
- The basic number of chromosomes in somatic cells is called 2n. In humans 2n is 46.



What are types of chromosomal abnormality?

- **Numerical chromosomal disorders (change in the number of chromosomes (more or fewer than 46).**
  - **Trisomy**
  - **Monosomy**
  - **Triploidy**
- **Structural chromosome disorders (breakages within a chromosome).**
  - **Chromosomal deletions**
  - **Chromosomal duplications**
  - **Balanced translocations**
  - **Unbalanced translocations**
  - **Inversions**
  - **Isochromosomes**
  - **Dicentric chromosomes**
  - **Ring chromosomes**

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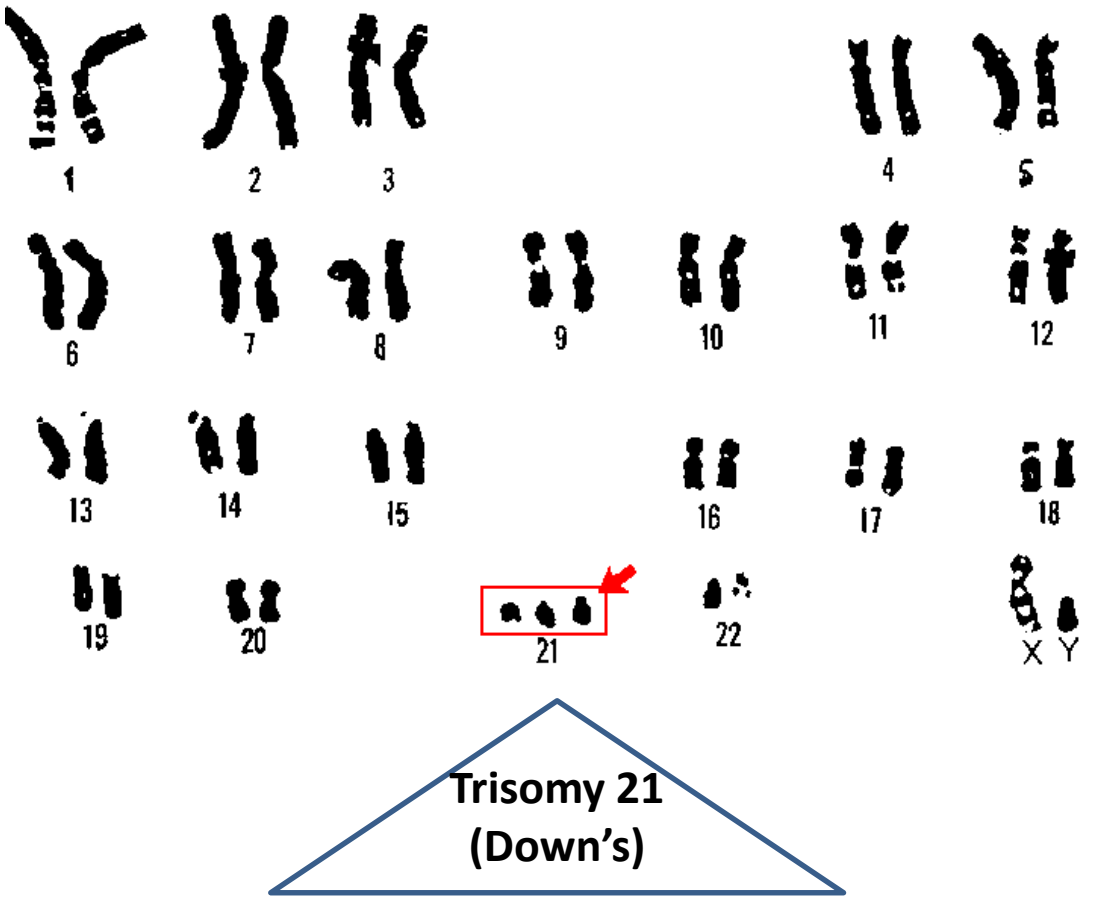
What is aneuploidy?

- Aneuploidy is the presence of an abnormal number of chromosomes in a cell
- Aneuploidy often results in miscarrige
- In live births, aneuploidy as often occurs in chromosomes 21, 18 and 13

What is trisomy?

- Three instances of a particular chromosome, instead of the normal two. It is a type of aneuploidy (an abnormal number of chromosomes).
- Trisomy is not the same as triploidy (having an entire extra set of chromosomes, making 69. People with trisomy have a single extra chromosome, making a total of 47. Down syndrome patients have extra chromosome 21 (trisomy 21); this, is the best known example of trisomy.



What are examples of aneuploidy on the Y chromosome?

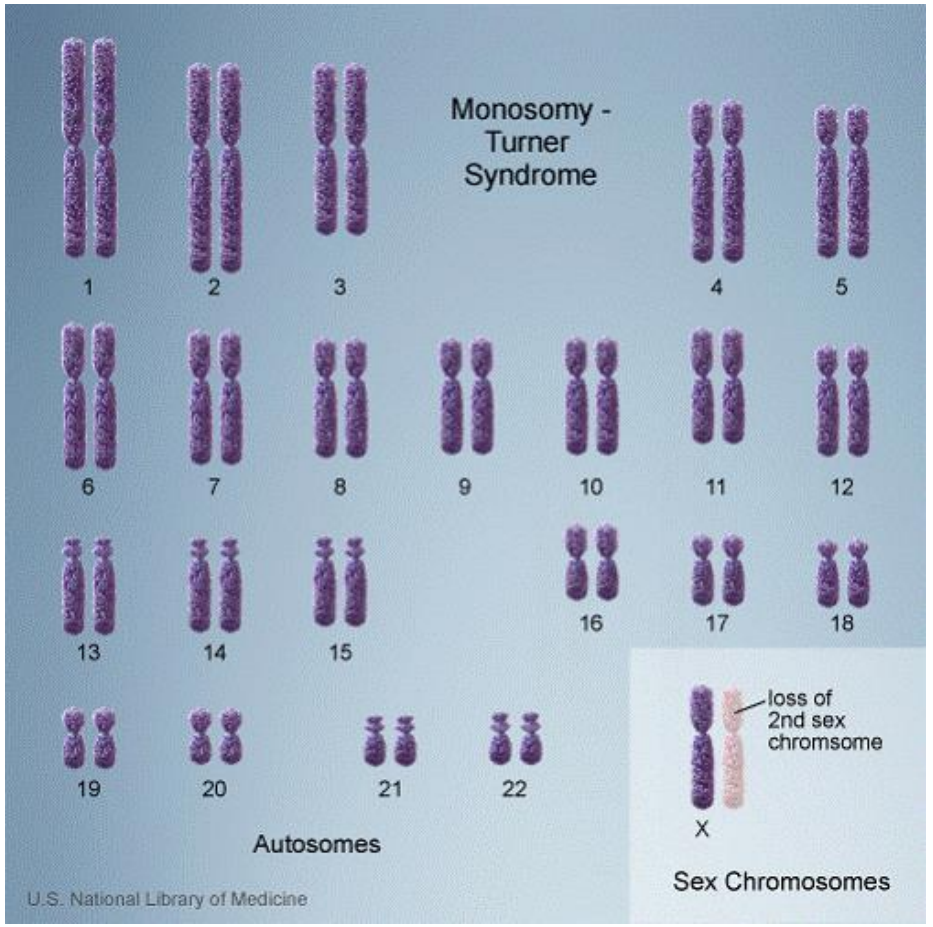
- XYY syndrome: This condition and associated with relatively few symptoms
- XXYY syndrome: this condition is characterized by developmental delay, speech impairment, behavior outburst and mood swings, learning disabilities, intellectual impairment, attention-deficit hyperactivity disorder (ADHD), autism spectrum disorders, tall stature, scoliosis, low muscle tone, sterility, delayed sexual development, and undescended testicles
-

What is monosomy?

- In monosomy, a diploid chromosome, one (usually the X) chromosome lacks a homologous partner
- In monosomic cell one chromosome is missing
- For example, Turner syndrome exhibits monosomy XO

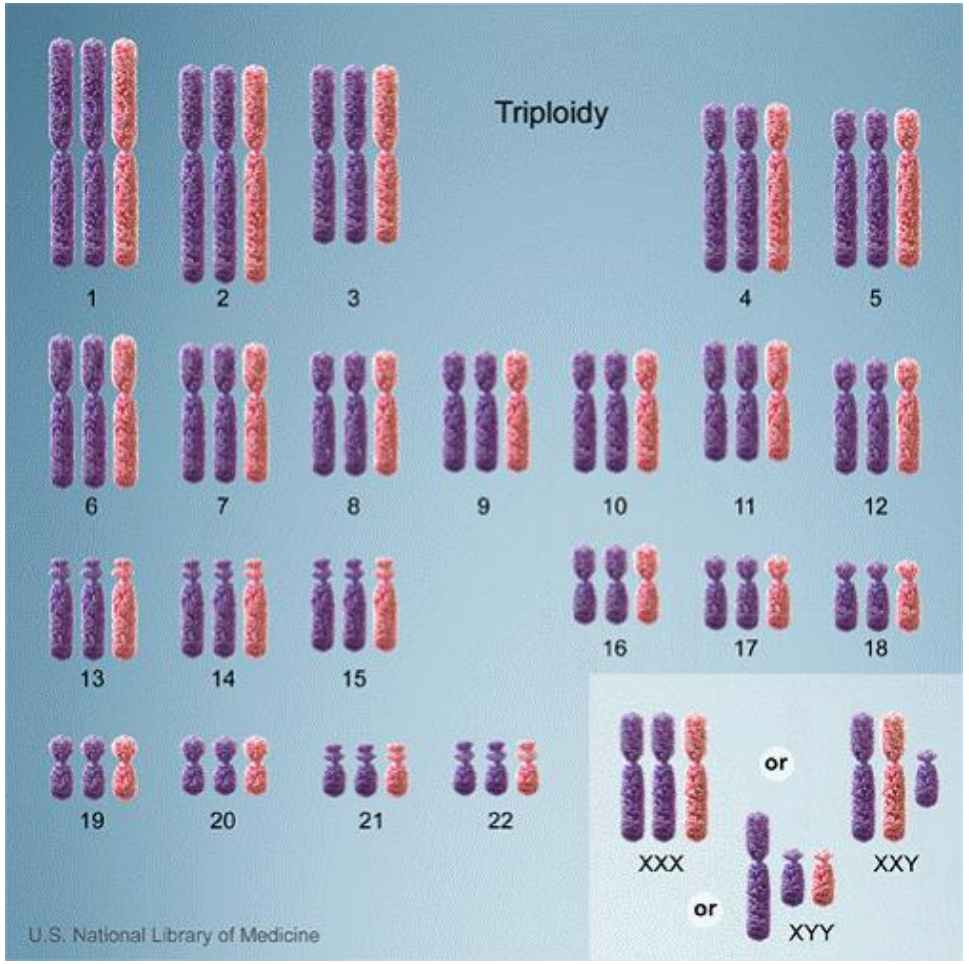
What is Turner syndrome?

- **XO monosomy: absence of Y chromosome**



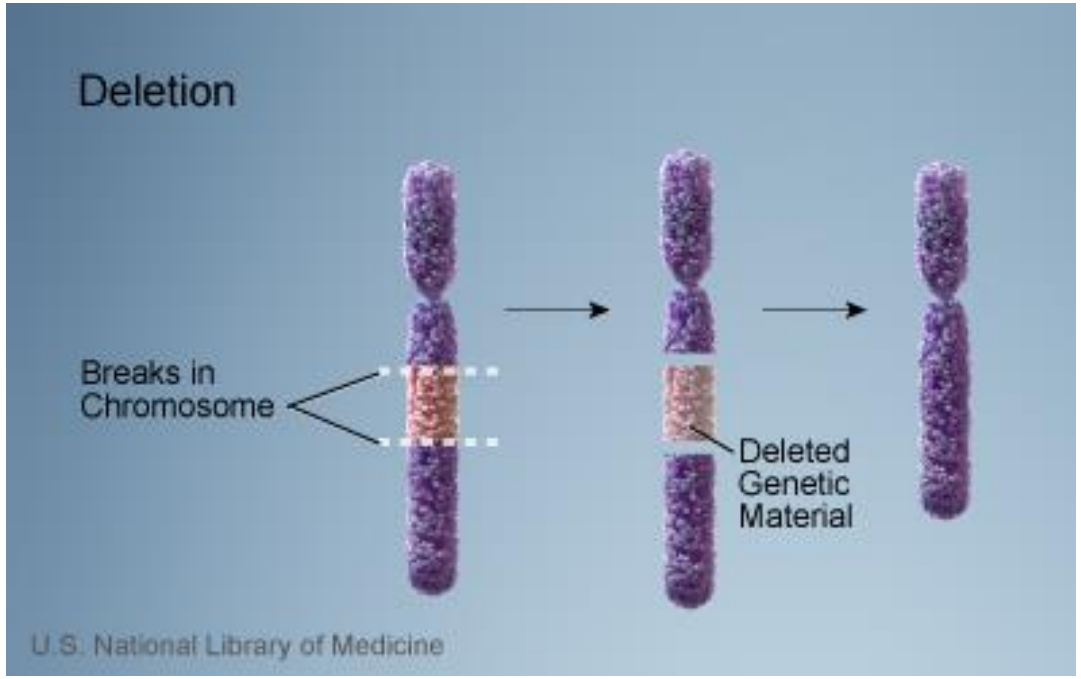
What is triplody?

- **“Triploidy is a rare chromosomal abnormality in which fetuses are born with an extra set of chromosomes in their cells. One set of chromosomes has 23 chromosomes. This is called a haploid set. Two sets, or 46 chromosomes, are called a diploid set. Three sets, or 69 chromosomes, are called a triploid set. et of chromosomes in their cells. One set of chromosomes has 23 chromosomes. This is called a haploid set. Two sets, or 46 chromosomes, are called a diploid set. Three sets, or 69 chromosomes, are called a triploid set”. (Google note)**



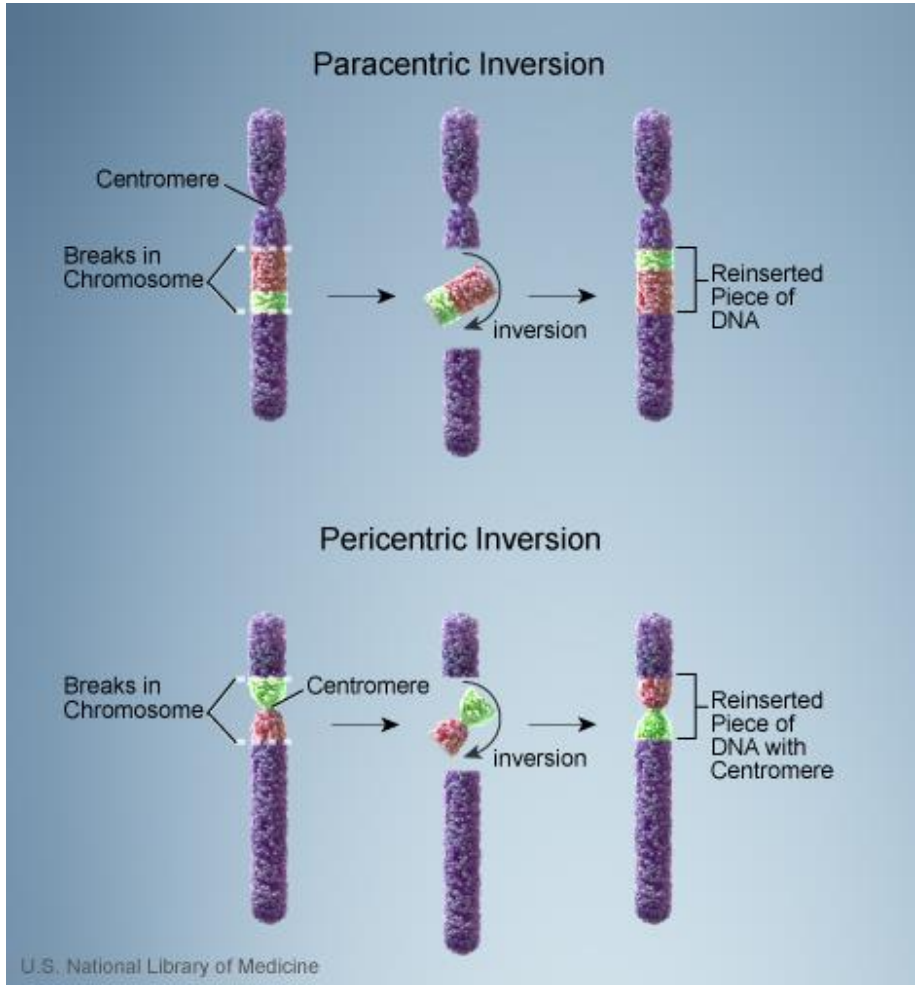
What are chromosomal deletions?

- **A chromosomal deletion is a mutation (a genetic aberration) in which a part of a chromosome or a sequence of DNA is lost during DNA replication.**



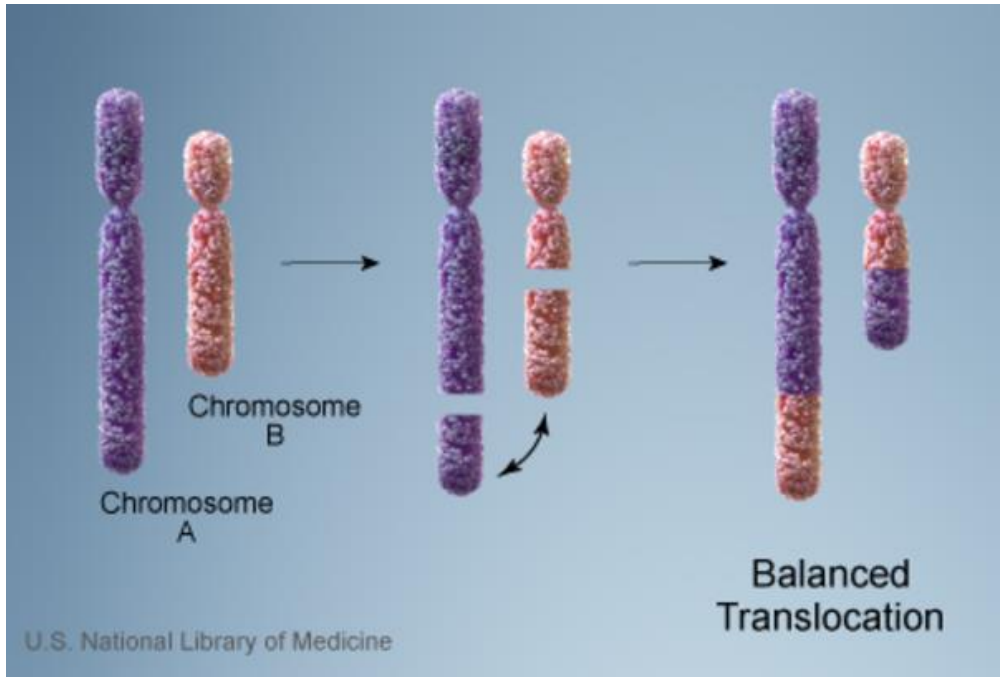
What is a paracentric inversion and a pericentric inversion?

A chromosome inversion is a rearrangement in which a segment of a chromosome is reversed end to end. Here a chromosome undergoes breakage and rearrangement within itself. Inversions are either paracentric or pericentric (see picture).



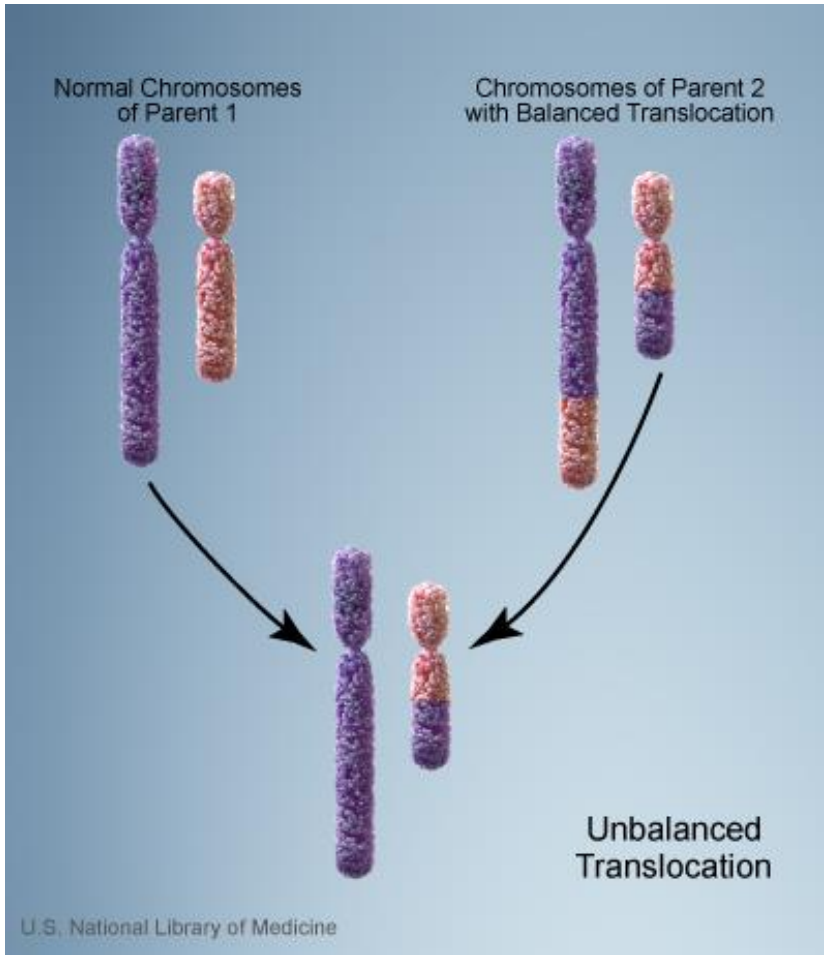
What is a balanced translocation?

- Translocations can be balanced (in an even exchange of material with no genetic information extra or missing, in contrast to unbalanced (causing extra or missing genes) .



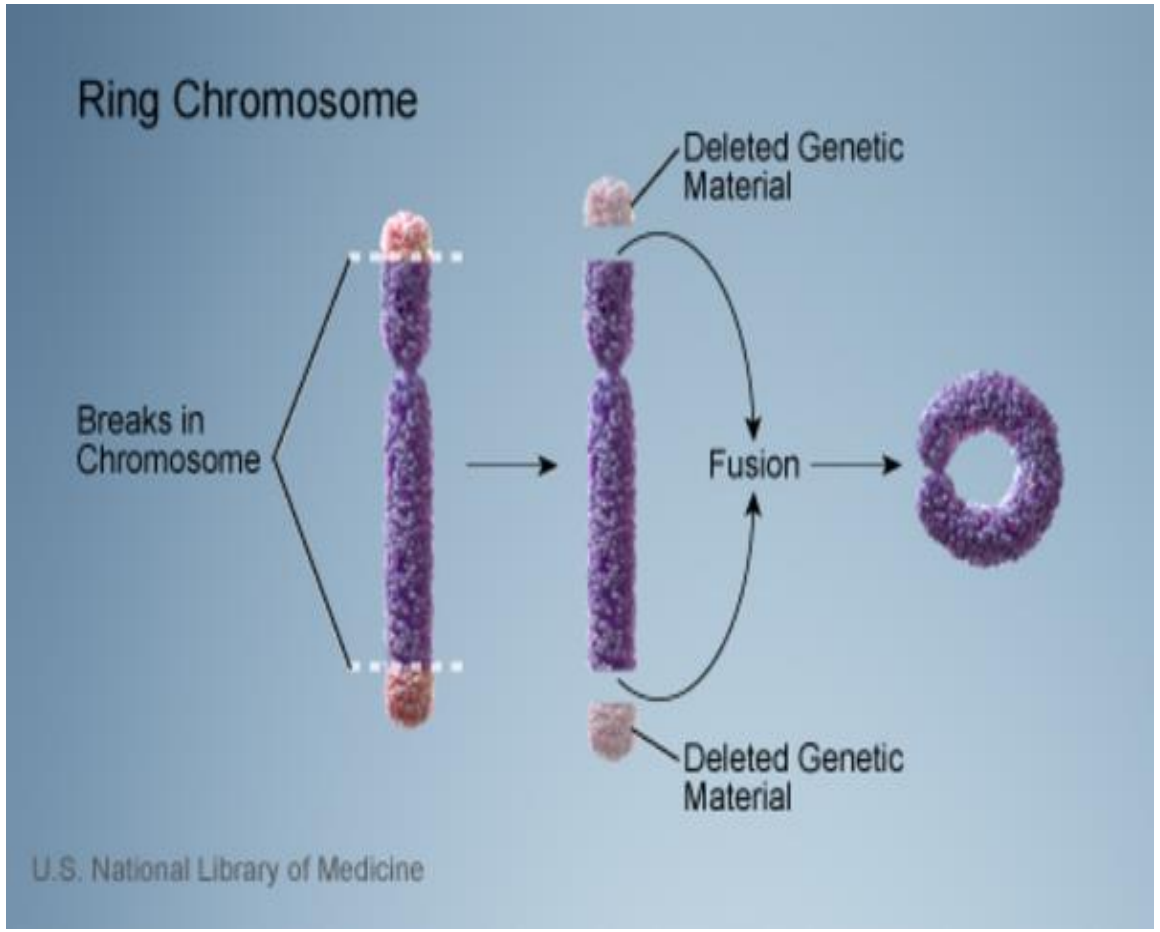
What is an unbalanced translocation?

- **In unbalanced translocations, the exchange of chromosome material is unequal resulting in extra or missing genes**



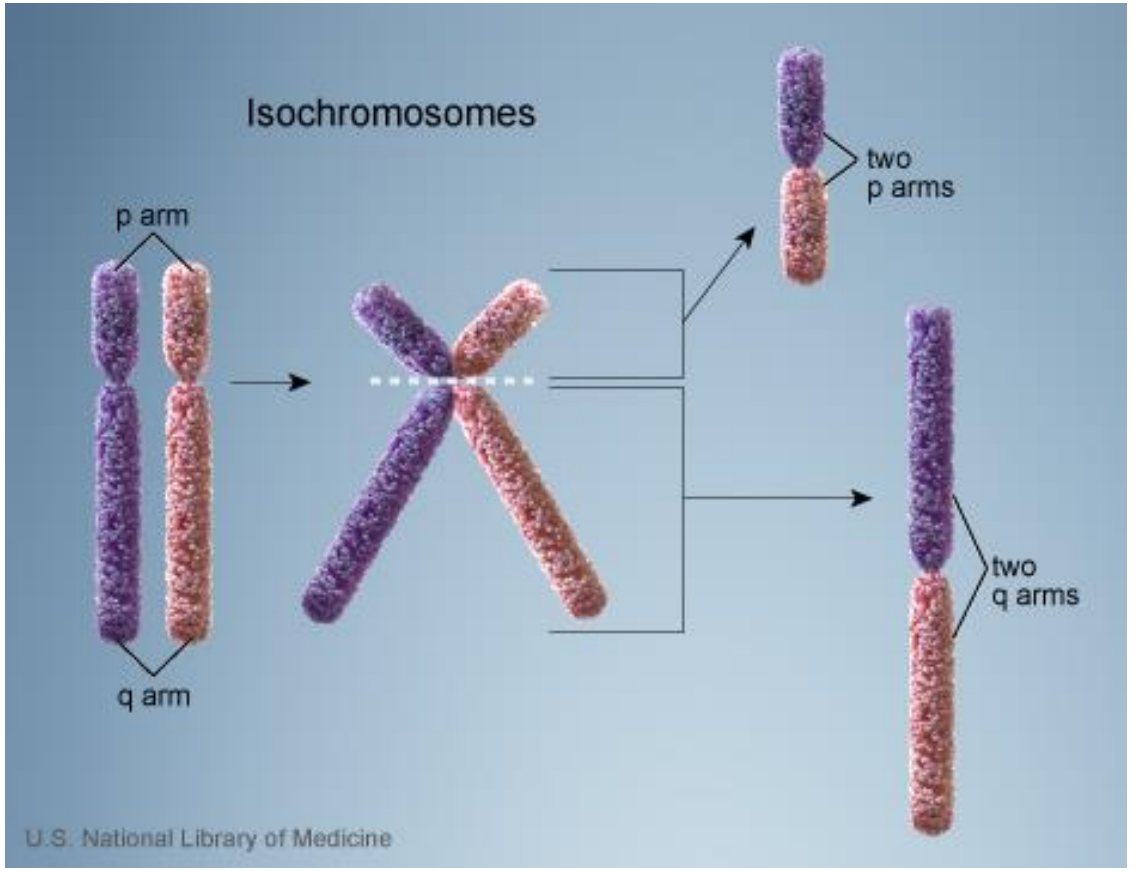
What is a ring chromosome?

- A ring chromosome has two ends fused together to form a ring. A ring chromosomes can be caused by chromosomal damage from mutagens or radiation.



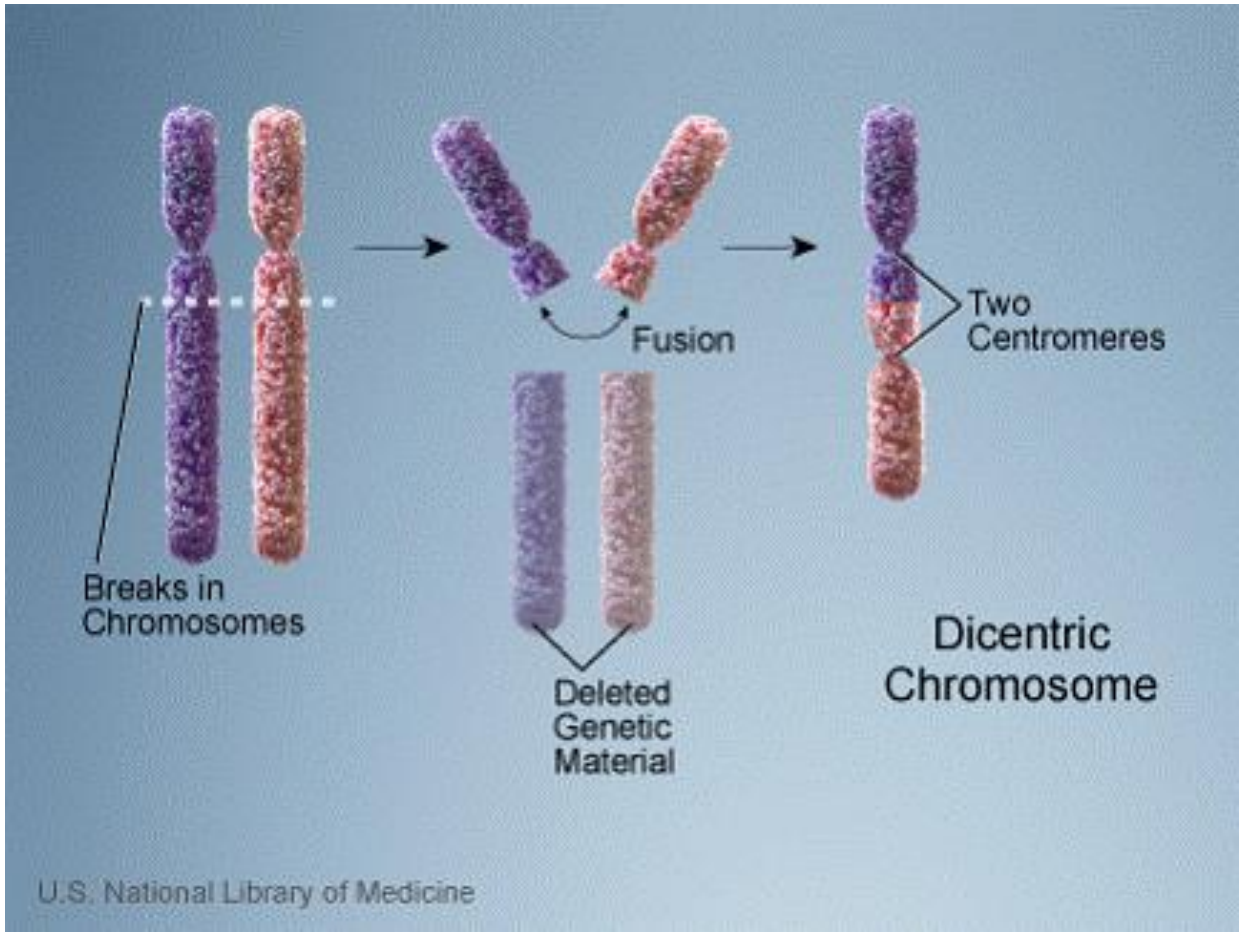
What are isochromosomes?

- An isochromosome is one in which the arms of the chromosome are mirror images of each other.



What is a dicentric chromosome?

- A dicentric chromosome has two centromeres. It results from fusion of two chromosome segments, each having a centromere, resulting in the loss of acentric fragments (lacking a centromere).



Summary: What are major categories of genetic disorders?

- Mendelian disorders resulting from mutations in single genes
- Complex disorders involving multiple genes as well as environmental influences (multifactorial diseases)
- Diseases arising from chromosomal abnormalities