Dr . Asseel M. Ghazi
Lec 10

Genetic disorders:

Introduction:

DNA Structure

DNA is found in the nucleus of every human cell. The information in DNA guides the cell (along with RNA) in making new proteins that determine all of our biological traits, and gets passed (copied) from one generation to the next

The key to all of these functions is found in the molecular structure of DNA, Although it may look complicated, the DNA in a cell is really just a pattern made up of four different parts called nucleotides.

Imagine a set of blocks that has only four shapes, or an alphabet that has only four letters.

DNA is a long string of these blocks or letters.

Each nucleotide consists of a sugar (deoxyribose) bound on one side to a phosphate group and bound on the other side to a nitrogenous base .

The nucleotide is the basic building block of nucleic acids.

There are two classes of nitrogen bases called purines (double-ringed structures) and pyrimidines (single-ringed structures).

The four bases in DNA's alphabet are :

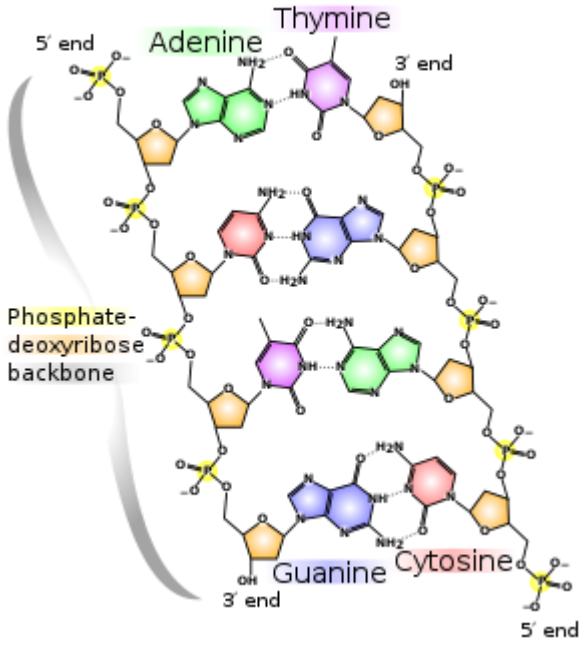
adenine (A) - a purine

cytosine(C) - a pyrimidine

guanine (G) - a purine

thymine (T) - a pyrimidine

Strands of DNA are made of the sugar and phosphate portions of the nucleotides, while the middle parts are made of the nitrogenous bases. The nitrogenous bases on the two strands of DNA pair up, purine with pyrimidine (A with T, G with C), and are held together by weak hydrogen bonds.



Watson and Crick discovered that DNA had two sides, or strands, and that these strands were twisted together like a twisted ladder -- the **double helix.**

The sides of the ladder comprise the sugar-phosphate portions of adjacent nucleotides bonded together.

The phosphate of one nucleotide is covalently bound to the sugar of the next nucleotide.

The hydrogen bonds between phosphates cause the DNA strand to twist.

Each base pair is formed from two complementary nucleotides (purine with pyrimidine) bound together by hydrogen bonds.

The base pairs in DNA are adenine with thymine and cytosine with guanine .

Normal karyotype

As is well known, human somatic cells contain 46 chromosomes; these comprise 22 homologous pairs of autosomes and two sex chromosomes, XX in the female and XY in the male. The study of chromosomes--karyotyping--is the basic tool of the cytogeneticist.

Fluorescence In Situ Hybridization.

Fluorescence in situ hybridization (FISH) has become an important adjunct to routine karyotyping and has greatly expanded the power of cytogenetic analysis.

A major limitation of karyotyping is that it is applicable only to cells that are dividing or can be induced to divide in vitro.

This problem can be overcome with DNA probes that recognize chromosome-specific sequences.
Such probes are labeled with fluorescent dyes and applied to nuclei.
The probe binds to its complementary sequence on the chromosome and thus labels the specific chromosome that can then be visualized under a fluorescent microscope.

Mutation:
Mutation is a permanent change in the DNA.
Mutations that affect germ cells are transmitted to the progenitor cells and give rise to inherited disorders (diseases), while the mutations that affect somatic cells do not cause hereditary diseases but are important in the genesis of cancers and congenital malformations.
Mutations can be divided into the following types:
1- **genome mutation (numerical mutation):** it represent loss or gain of whole chromosome and give rise to monosomy and trisomy.
The number of human chromosomes are 23 pairs (46 chromosomes), 22 pairs are somatic and the last pair represent the sex chromosomes.
2- structural mutations:
a- chromosomal mutations: result from rearrangements of genetic material and give rise to visible structural changes in the chromosomes, usually they result from chromosomal breakage followed by loss or rearrangement of genetic materials, many types of such mutations seen as followings:
Deletion: its refers to loss of a portion of chromosome.
A ring chromosome: is a special form of deletion. It is produced when a deletion occurs at both ends of a chromosome with fusion of the damaged ends .
Inversion: refers to a rearrangement that involves two breaks within a single chromosome with inverted reincorporation of the segment .
Isochromosome formation: results when one arm of a chromosome is lost and the remaining arm is duplicated, resulting in a chromosome consisting of two short arms only or of two long arms.
Translocation: a segment of one chromosome is transferred to another .

b- gene mutations : result from deletion of a gene or more, often affect a single base; as for example a single nucleotide base can be substituted by a different base result in 'point mutation'.

Trisomy 21: Down's syndrome:

Although Down's syndrome is very common, we don't understand the reason that the extra chromosome 21 causes so many problems.

It affects around 1 child in 700. Advanced maternal age is important risk factor. May be 1 in 25 live births to mothers over 45 have Down's syndrome. In only 20% of cases is the extra chromosome of paternal origin.
Pediatricians look for several signs. Don't expect to see them all:

1. flattened face
2. open mouth, big tongue.
3. slanting palpebral fissures and epicanthic folds ("mongolism")
4. mental retardation
5. lack of muscle tone at birth ("floppy baby")
6. low-set ears
7. single palmar crease ("simian crease")
8. heart defects (40%, notably endocardial cushion defects)
9. conductive hearing loss
10. bad respiratory infections
11. various leukemia's .

Turner's syndrome:

This is the result of monosomy for the short arm of the X chromosome. About 1 out of every 2000 women are affected.

The major problem is failure of feminization at adolescence.

Patients have "webbed neck", "shield-shaped chest", and "cubitus valgus" (elbows turned out). However, most patients are not diagnosed until the teens (if then). They fail to menstruate (i.e. "primary amenorrhea" -- Turner's is the most common identifiable cause) or develop secondary sex characteristics.

Rarely, lymph channels fail to form properly, and lymphedema of the hands and feet makes the diagnosis apparent at birth. Or an alert clinician notes the "webbed neck" or "shield-shaped chest" of the patient.