Genetic Diseases
LEC. 1

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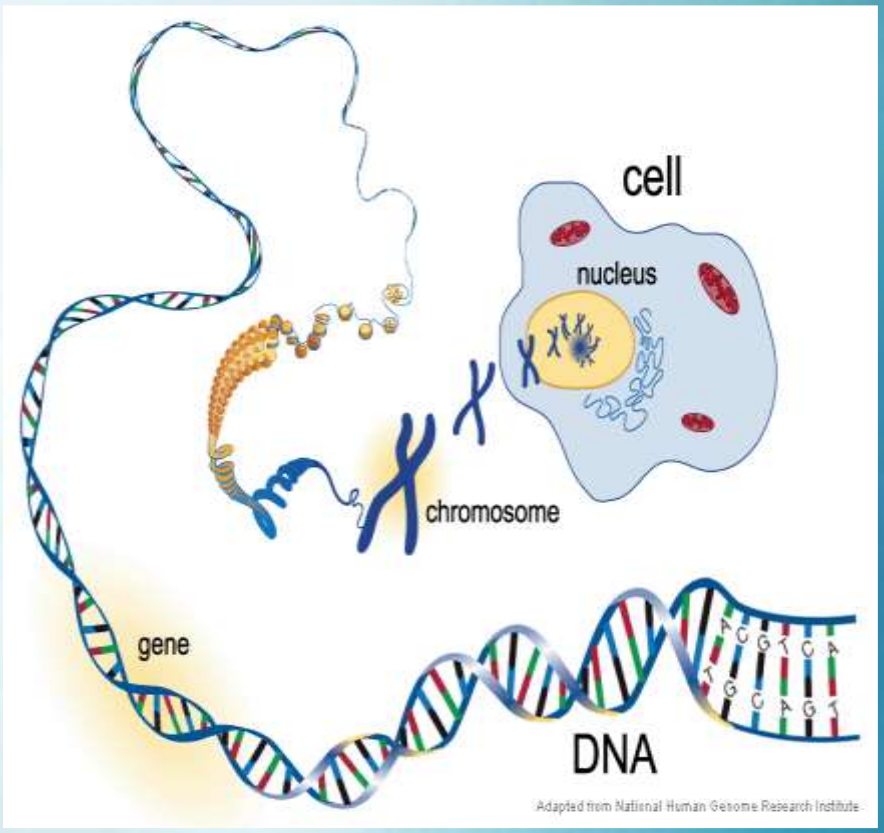
Review of what you've already known

- **Genes:**

Are the building blocks of heredity. They are passed from parent to child. Genes are coded instructions for making everything the body needs, especially proteins. An individual's genes are present in a large molecule called (DNA).

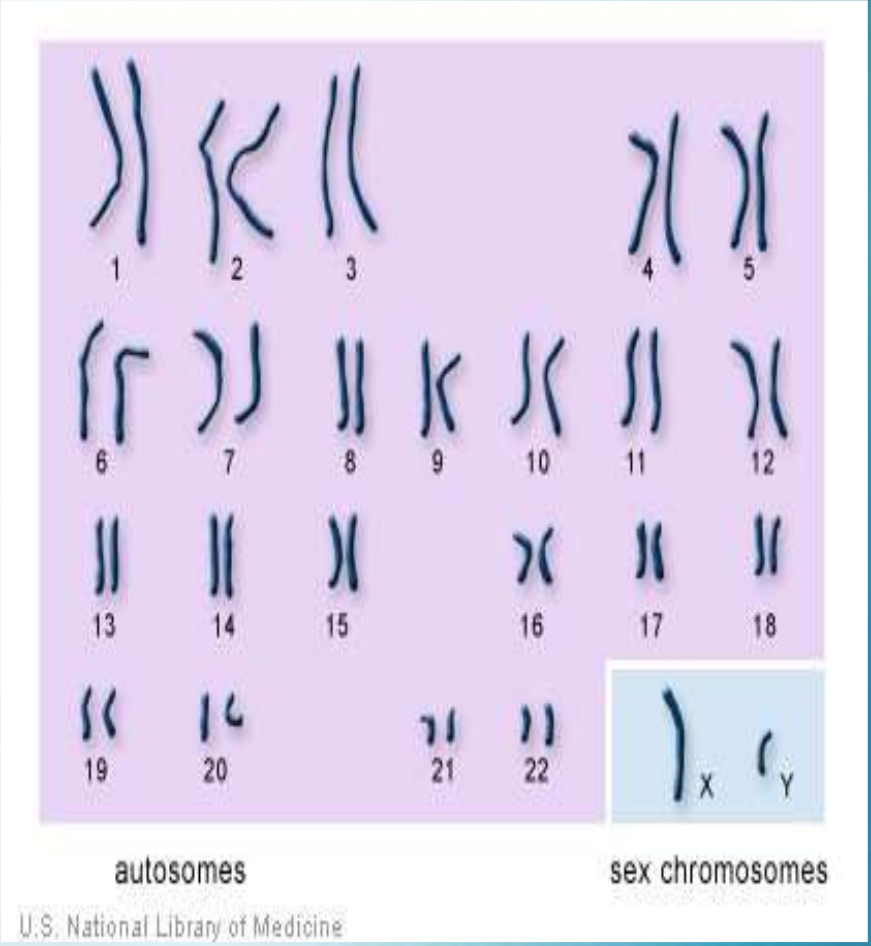
- **DNA** (deoxyribonucleic acid):

Carries the genetic information in the body's cells, made up of four similar chemicals called bases and abbreviated A, T, C, and G) that are repeated over and over in pairs.



- Genes are packaged in bundles called **chromosomes.**
- **Humans have 23 pairs of chromosomes (for a total of 46).**
  Arranged in 22 homologous pairs of autosomal chromosomes in addition to one pair of sex chromosomes (determines whether you are male or female).

- **Allele:** is a version of a gene that are located at the same position.
- Homozygous allele: the same versions of gene.
- Heterozygous allele: different versions of genes.



Hereditary disorders: Are derived from one parent, transmitted in the gametes through the generation &therefore are familial.

Congenital diseases: simply present at birth.

- *Note*: Not all congenital diseases are genetic (e.g., congenital syphilis). On the other hand, not all genetic diseases are congenital (e.g. the expression of Huntington disease, begins only after the third or fourth decade of life).

Mutations

- Permanent changes in the DNA, those that affect *germ cells* are transmitted to the progeny &give rise to *inherited disease,* while if in the *somatic cells* are not transmitted to the progeny but important in causation of *cancers &some congenital malformations*.

Types of mutations

1- Point mutation: result from the substitution of a single nucleotide base by a different base.

- If result in replacement of one amino acid by another in the protein product this type called **missense mutation, e.g. sickle cell anemia** (valine instead of glutamine)

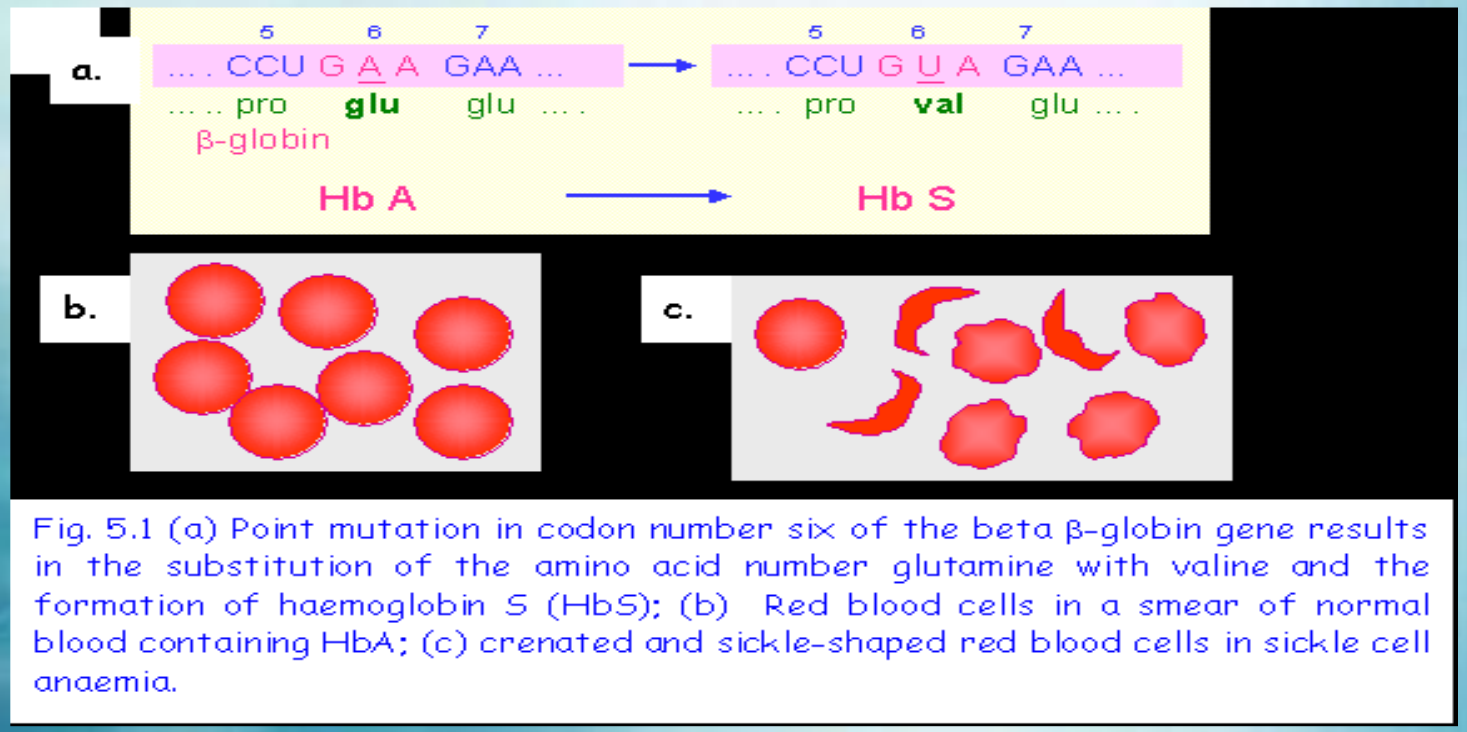
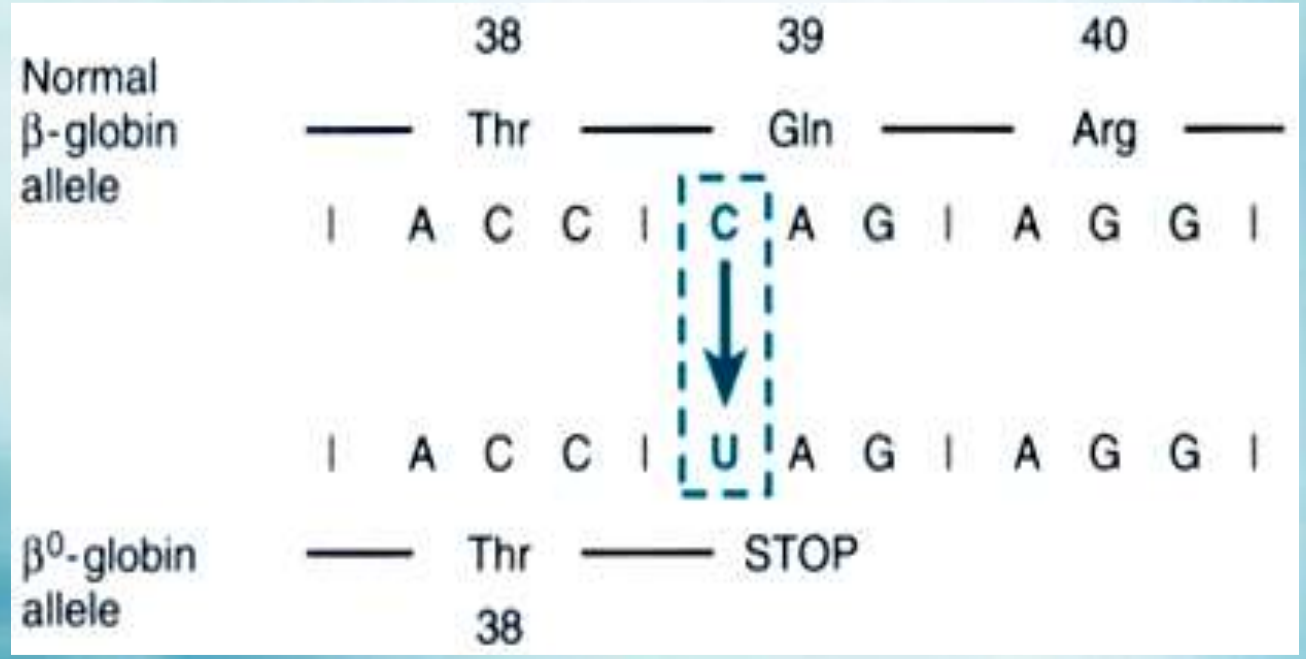


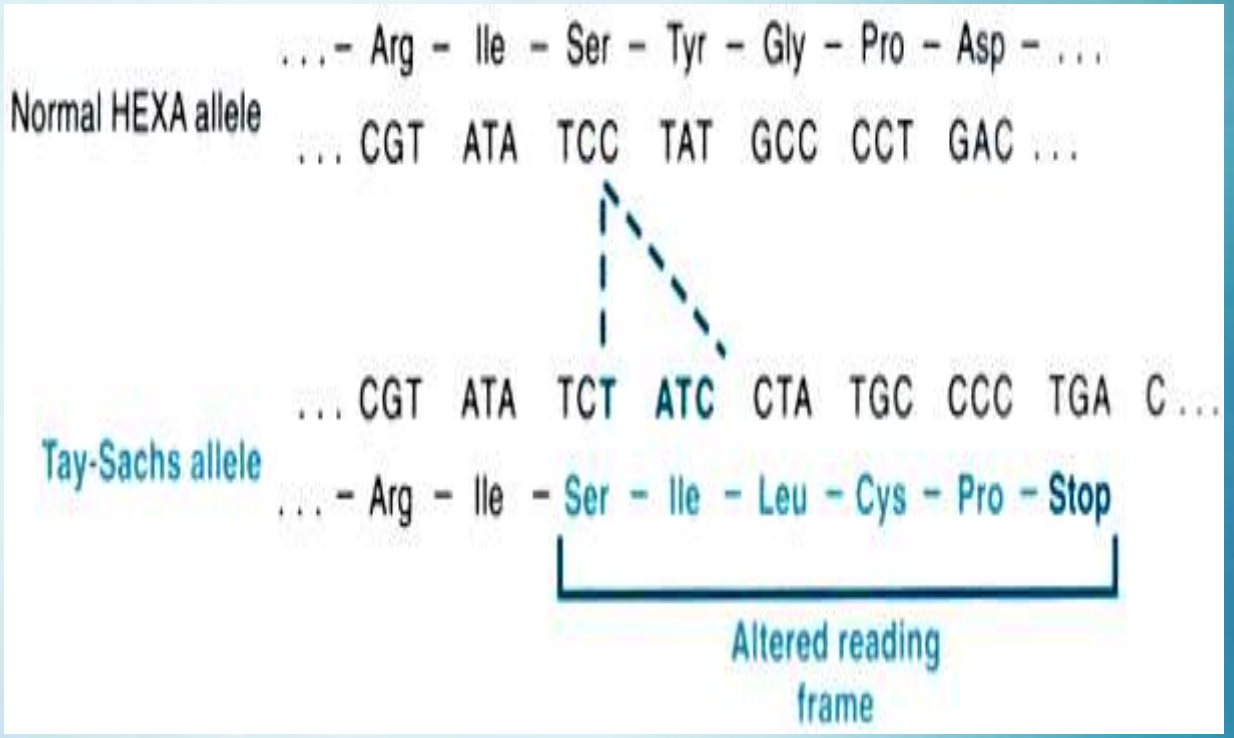
Fig. 5.1 (a) Point mutation in codon number six of the beta β-globin gene results in the substitution of the amino acid number glutamine with valine and the formation of haemoglobin S (HbS); (b) Red blood cells in a smear of normal blood containing HbA; (c) crenated and sickle-shaped red blood cells in sickle cell anaemia.

While if the point mutation change an amino acid codon to one of the **termination codon or *stop codon*** (UAG, UAA and UGA) interrupt translation &the resultant protein are rapidly degraded **(nonsense mutation).**



2- Frameshift mutation:

occur when the insertion or deletion of one or two base pair alter the reading frame of the DNA strand (if three or more this is not frame shift).



3- Trinucleotide repeat mutations: characterized by the amplification of a sequence of three nucleotide e.g. in ***fragile X syndrome***, there are 250-4000 repeats of the sequence CGG within the gene called FMR-1.

- In the normal population, the number of repeats is small 29, so amplification of FMR-1 giving rise to *mental retardation*.

- **We will discuss four major categories of genetic disorders:**

1. Mendelian disorders resulting from mutations in single genes.

2.Complex disorders involving multiple genes as well as environmental influences. These are sometimes called **multifactorial** diseases.

3.Diseases arising from chromosomal abnormalities, including changes in the number or structure of chromosomes.

4. Other genetic diseases, which involve single gene mutations but do not follow Mendelian rules of inheritance.

1- Mendelian disorders resulting from mutations in single genes.

- Approximately 1% of all adult admission to the hospital & 6-8% of all pediatric hospital.
- Mutation involving single gene follow one of **three patterns of inheritance:**

* Autosomal **dominant**
* Autosomal **recessive**
* **X-linked** diseases.

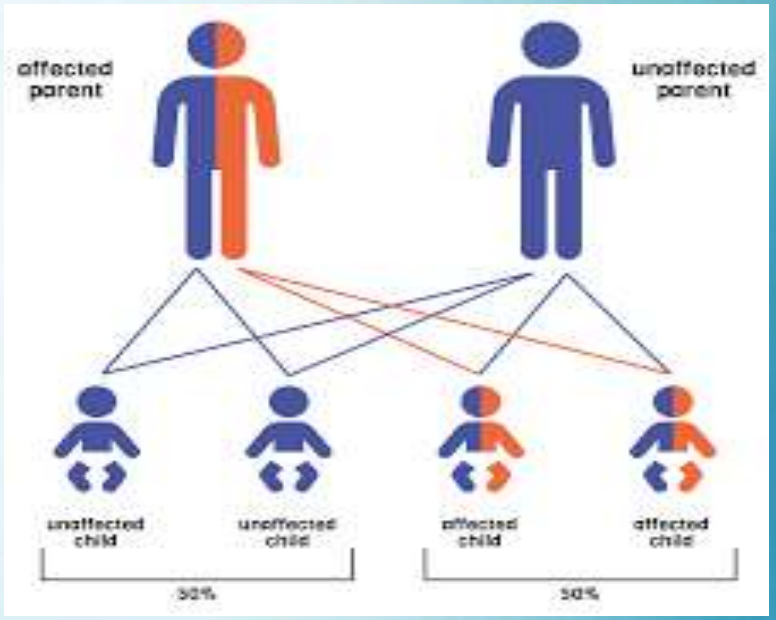
- A single gene mutation may lead to many phenotypic effects **(pliotropy)** e.g **Marfan"s syndrome,** the defect in the base of connective tissue (defect in skeleton, eyes, cardiovascular) all of them from mutation in fibrillin.
- Conversely several different mutations may produce the same trait **(genetic heterogeneity) e.g. retinitis pigmentosa** can be caused by several different types of mutation.

A. Autosomal dominant disorders

1- Manifested in the heterozygous state, so at least one parent in an index case usually is affected.

2- Both males and females can be affected, and both sexes can transmit the condition.

3- When an affected person marries an unaffected one, every child has 50% chance of having the disease.



4- With every autosomal dominant disease, some patients do not have affected parents, so there is new mutation involving either the egg or the sperm from which they derived.

5- Clinical features can be modified by ***reduced penterance &variable expressivity.***

- *Reduced penterance*: Some patients inherit the mutant gene but are phenotypically normal.
- *Variable expressivity*: If the trait is seen in all individuals carrying the mutant gene but is expressed differently among individuals.

6- In many conditions, signs & symptoms do not appear until adulthood.

7- **50% reduction** in normal gene products is **associated with clinical symptoms.**

8- Two main types of ***non-enzyme*** proteins are affected:

a- Those involved in **regulation of complex metabolic pathways** e.g. familial hypercholesterolemia.

b- **Key structural proteins** e.g. collagen &cytoskeletal components of red cell membrane e.g. spectrin in hereditary spherocytosis.

Examples of autosomal dominant disorders

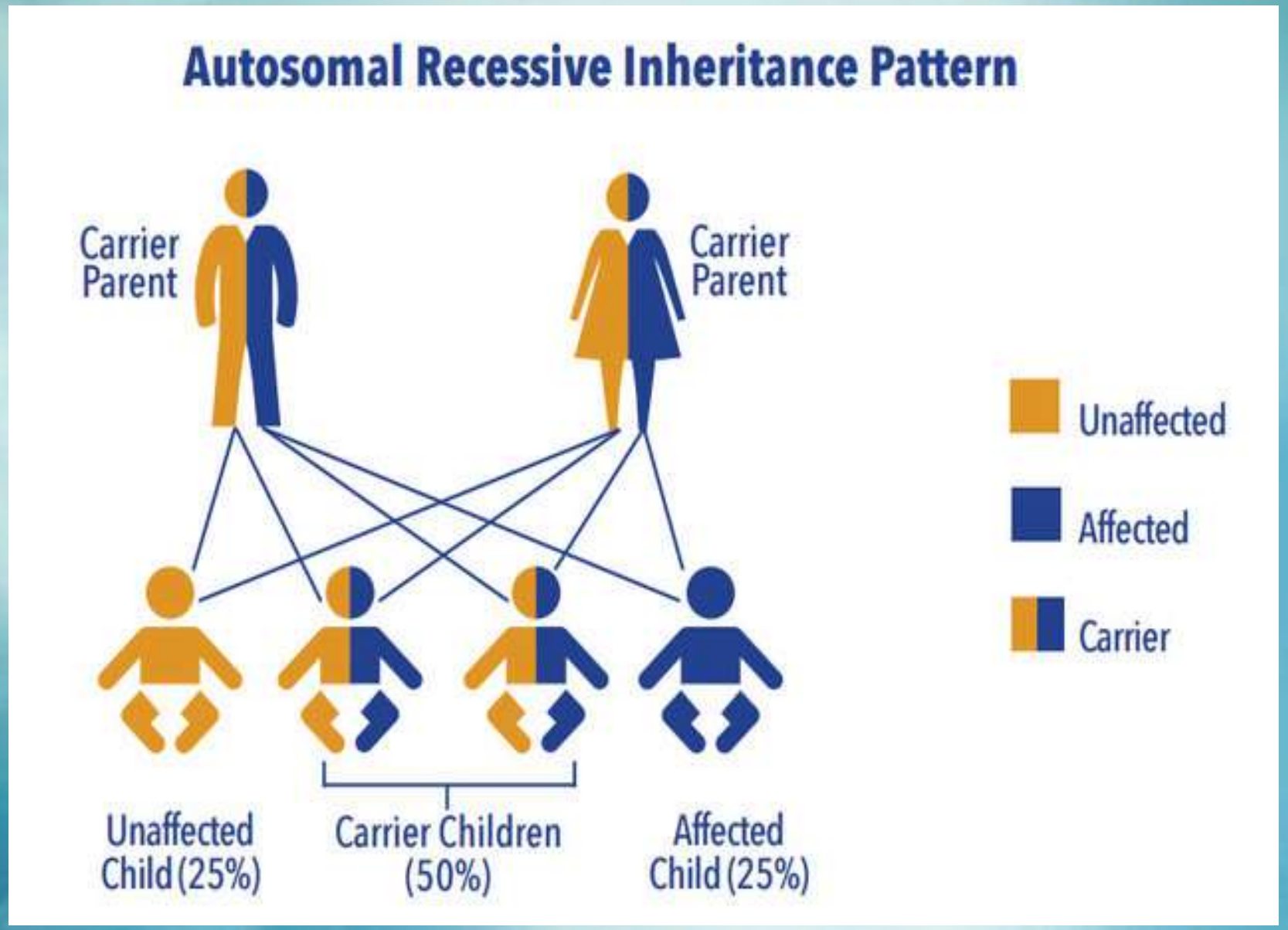
- Marfan syndrome
- Hypercholesterolemia
- Polycystic kidney disease
- Hereditary spherocytosis
- Familial polyposis coli

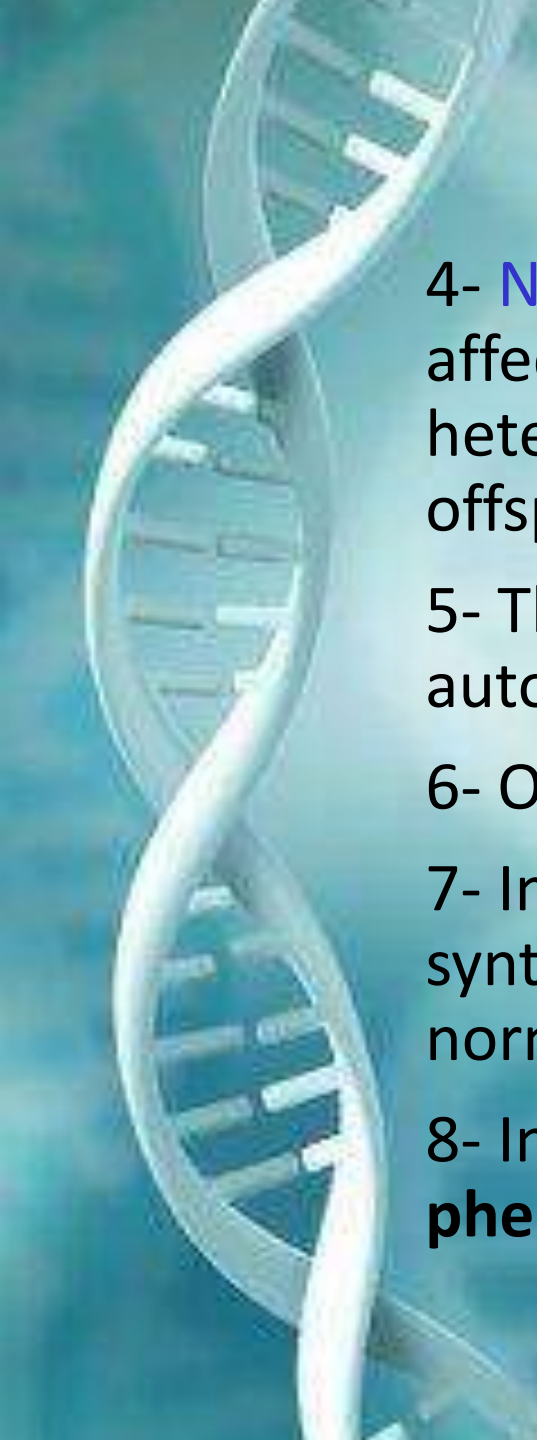
B. Autosomal recessive disorders

1- Manifested in the homozygous state (occur when both of the alleles at a given locus are mutants), so the trait does not usually affect the parents who are carriers of one diseased allele, but siblings may show the disease.

2- If the mutant gene occurs with a low frequency in the population, there is a strong likelihood that the proband is the product of a consanguineous marriage.

3- Siblings have 25% risk for each birth (one chance in four).


Autosomal Recessive Inheritance Pattern
Carrier Parent
Carrier Parent
Unaffected
Affected
Carrier
Unaffected Child (25%)
Carrier Children (50%)
Affected Child (25%)



4- New mutation occur but rarely detected clinically because the affected person is a symptomatic heterozygote, unless this heterozygous marry other heterozygous &produce affected offspring.

5- The expression of the defect tends to be more uniform than autosomal dominant and Complete penetrance is common.

6- Onset of signs &symptoms early in life.

7- In heterozygotes equal amount of normal &defective enzymes are synthesized, cells with half of their complement of enzyme function normally & **50% reduction not associated with clinical symptoms.**

8- In many cases, enzyme proteins are affected by the mutation e.g. **phenylketonuria, thalassemia, sickle cell anemia.**

Examples of autosomal recessive disorders:

- Sickle cell anemia
- Thalassemias
- Cystic fibrosis
- Phenylketonuria
- Wilson disease
- Glycogen storage diseases

X-linked disorders

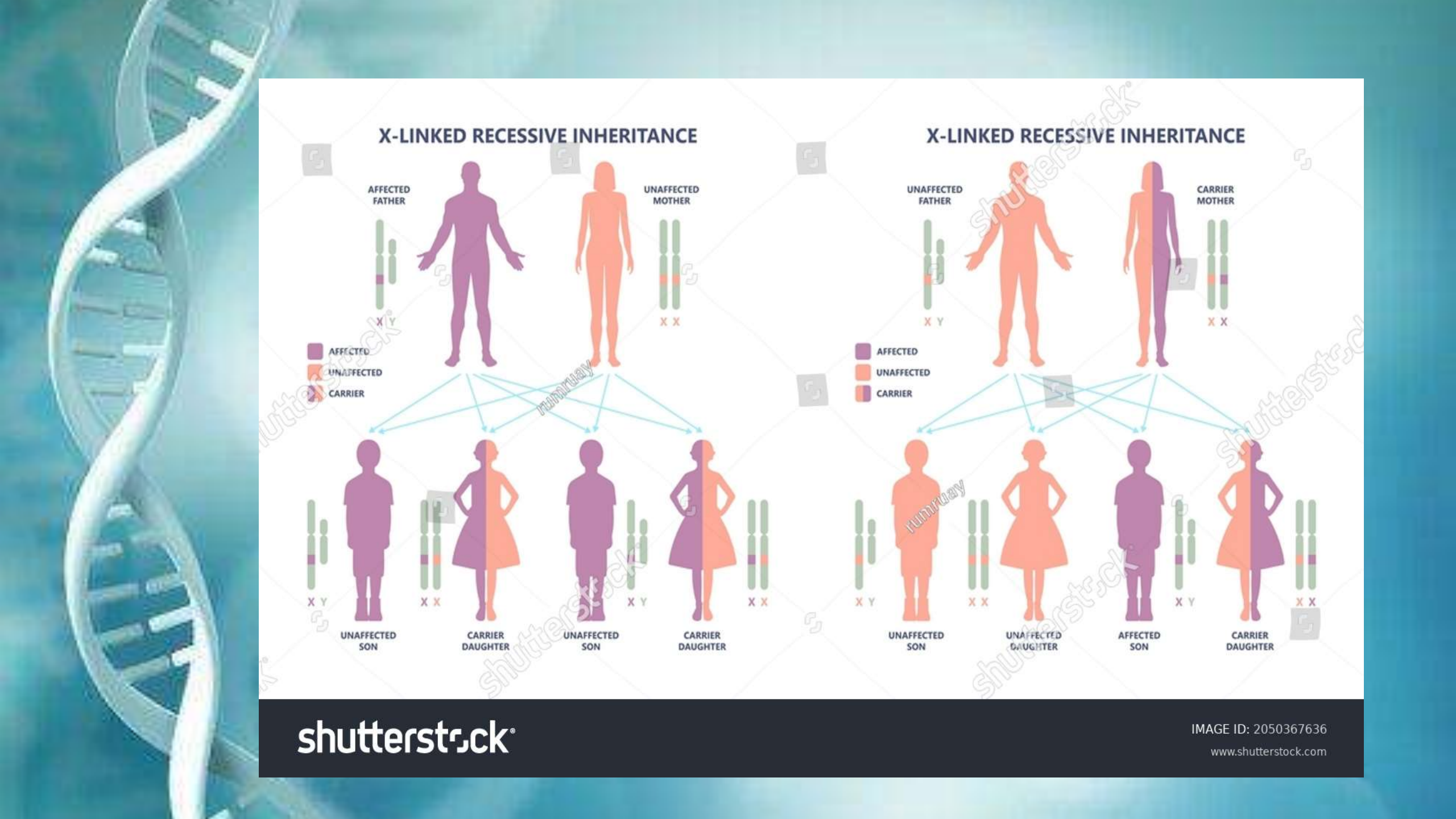
- Because most of the genes are carried on the “X” chromosome and very few are present on the “Y” chromosome, **Thus; for the most part, sex-linked disorders are X linked.**
- Most X-linked disorders are **X-linked recessive.**

➢ The usual pattern, in clinical practice, is that **only males** who carry the mutated gene on their “X” chromosomes are clinically affected while **females** are usually **silent carriers** as males have only one X-chromosome while **females have two.**

➢ **Heterozygous female (carrier)** rarely express the full phenotypic change: if there is **inactivation of one of the X chromosome (*Lyon’s hypothesis*) which is the normal X** , **So** full expression of the disease in heterozygous female.

- **Sons** of heterozygous mothers are **50%** chance of affection.
- **Daughters** of heterozygous mothers are **50%** carriers.

➢ An affected male does not transmit the disease to sons, but **all daughters are carriers.**


X-LINKED RECESSIVE INHERITANCE
AFFECTED FATHER
UNAFFECTED MOTHER
X Y
X X
AFFECTED
UNAFFECTED
CARRIER
UNAFFECTED SON
CARRIER DAUGHTER
UNAFFECTED SON
CARRIER DAUGHTER
X-LINKED RECESSIVE INHERITANCE
UNAFFECTED FATHER
CARRIER MOTHER
AFFECTED
UNAFFECTED
CARRIER
UNAFFECTED SON
AFFECTED SON
CARRIER DAUGHTER
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Examples of X-linked recessive disorders

- Hemophilias A and B
- Glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency)
- Duchenne muscular dystrophy


Thanks