MEDICAL GENETICS

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LEARNING OBJECTIVES

1- How can we classify diseases?

2- What do we mean by Mendelian disorders?

3- What is a mutation?

4- What are multifactorial diseases?

Classification Of Human Diseases

1- Single gene diseases.

2- Multifactorial diseases.

3- Cytogenetic diseases.

4- Diseases with abnormal Mendelian inheritance.

Mutations

-Defined as permanent change in the DNA.

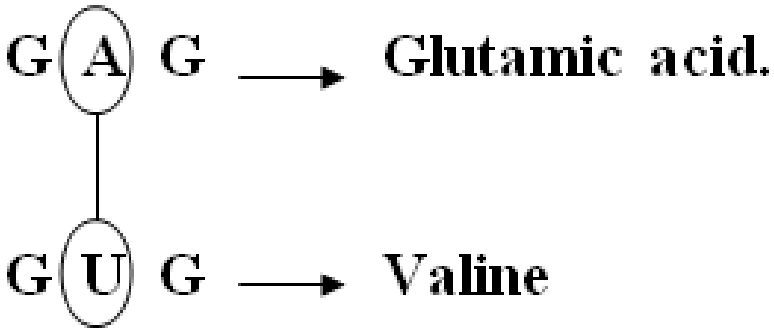
-Mutations that affect germ cells are transmitted to the progeny and may give rise to inherited diseases.

-Mutations that arise in somatic cells are important cause of cancer.

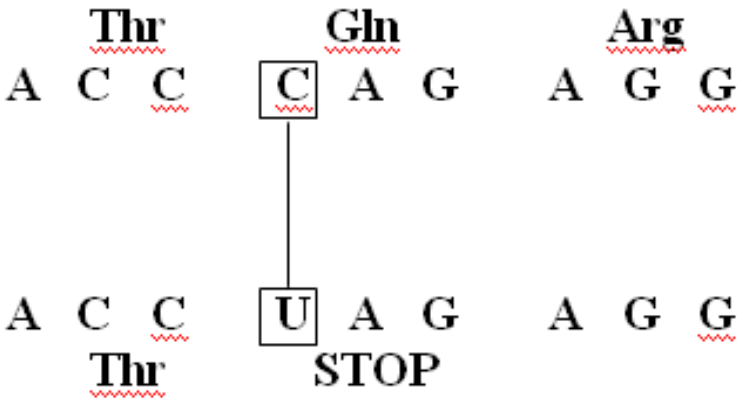
Types

1-Point mutations: **It is single base substitution.**

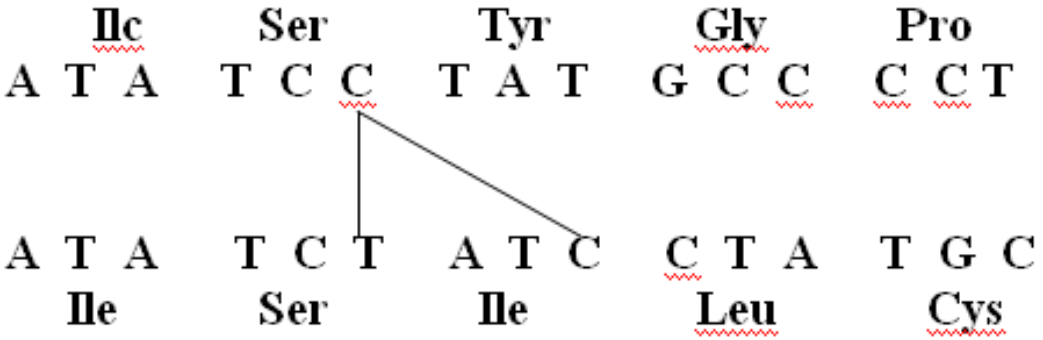
A-Missense mutation: **It is point mutation leading to the replacement of one amino acid by another in the gene product.**



B-Nonsense mutation: **It is point mutation that leads to a change in the amino acid codon into stop codon.**



2-Frameshift mutation: **It means small deletion or an insertion involving the coding sequence leads to alterations in the reading frame of DNA.**



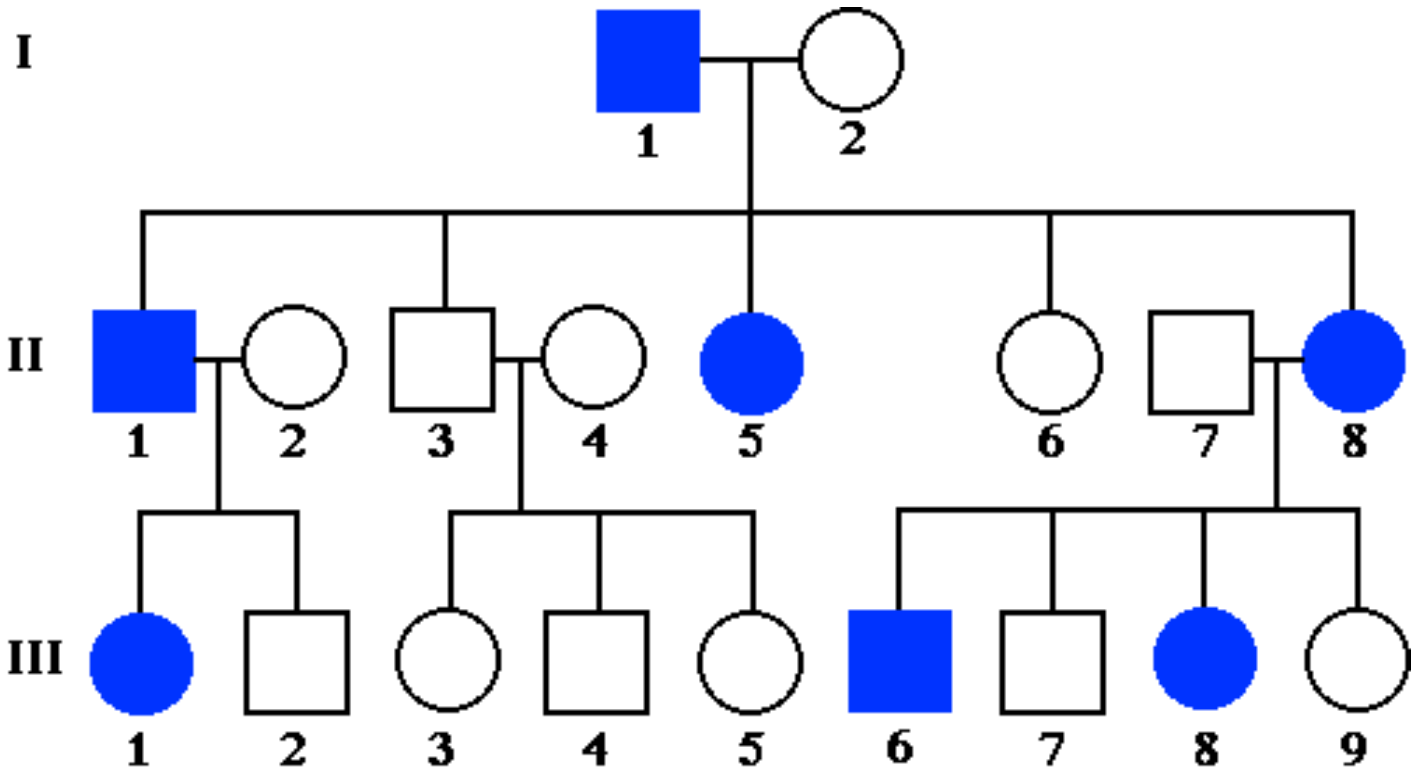
3-Trinuceotide repeats mutation: It is amplification of a sequence of 3 nucleotides (CGG).
Fragile X syndrome is the most common example.

Mendelian Disorders:

They are group of diseases that result from mutations in a single gene and follow Mendel's law.

Autosomal dominant disorders:

- Manifest in heterozygous.
- One parent of index case is affected.
- Both males and females are affected.
- Chance of transmission is 50%.
- Most common diseases are neurofibromatosis, Marfan syndrome, familial hypercholesterolemia.



Pedigree 1. An idealized pedigree of a family with hypercholesterolemia, an autosomal dominant disease where the heterozygote has a reduced number of functional low density lipoprotein receptors.

Achondroplasia

2-Autosomal recessive disorders:

-Manifest in homozygous.
-Do not usually affect parents.
-Both male and females are affected.
-Chance of transmission is 25%.
-Examples of such disorders are lysosomal storage diseases, glycogen storage diseases, and alkaptonuria.

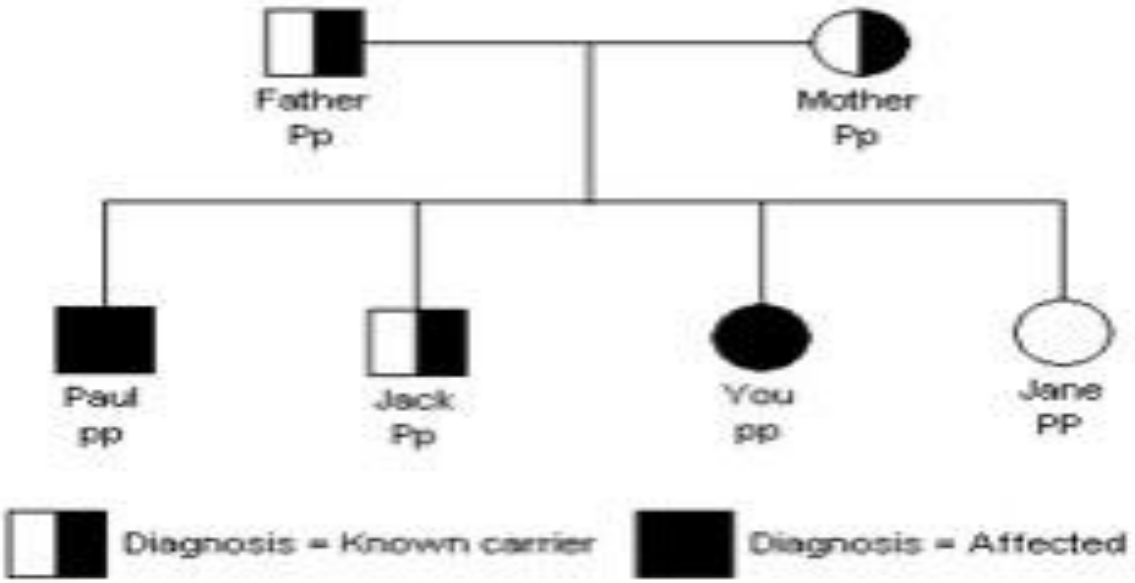
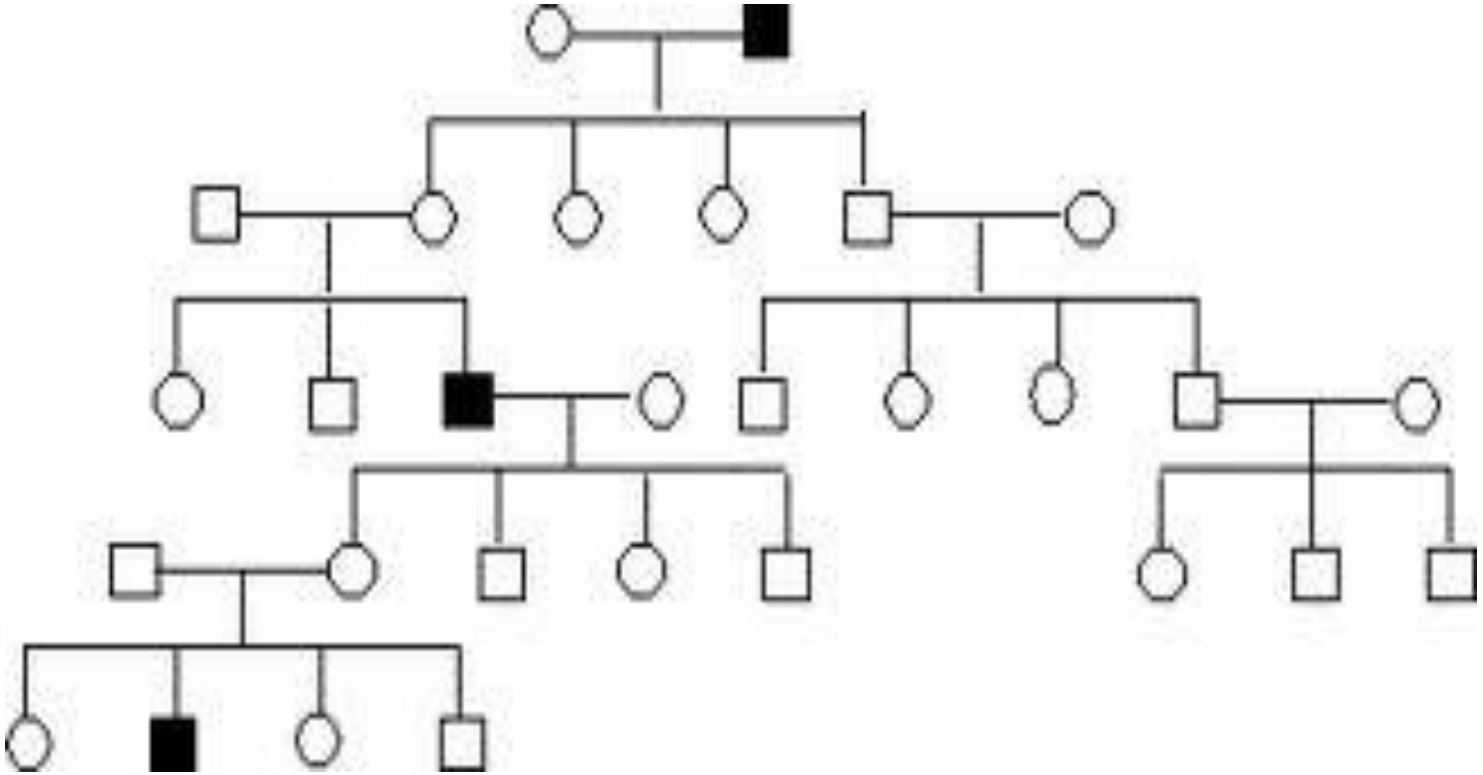
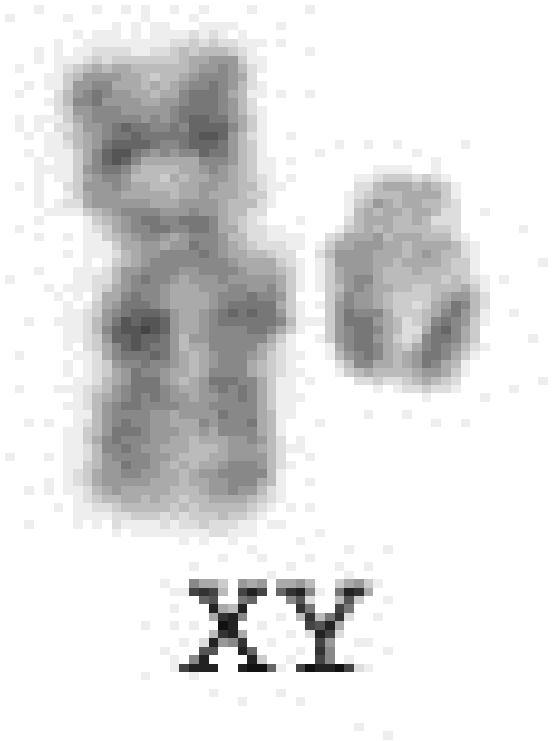

Father
Pp
Mother
Pp
Paul
pp
Jack
Pp
You
pp
Jane
PP
Diagnosis = Known carrier
Diagnosis = Affected

Figure 1

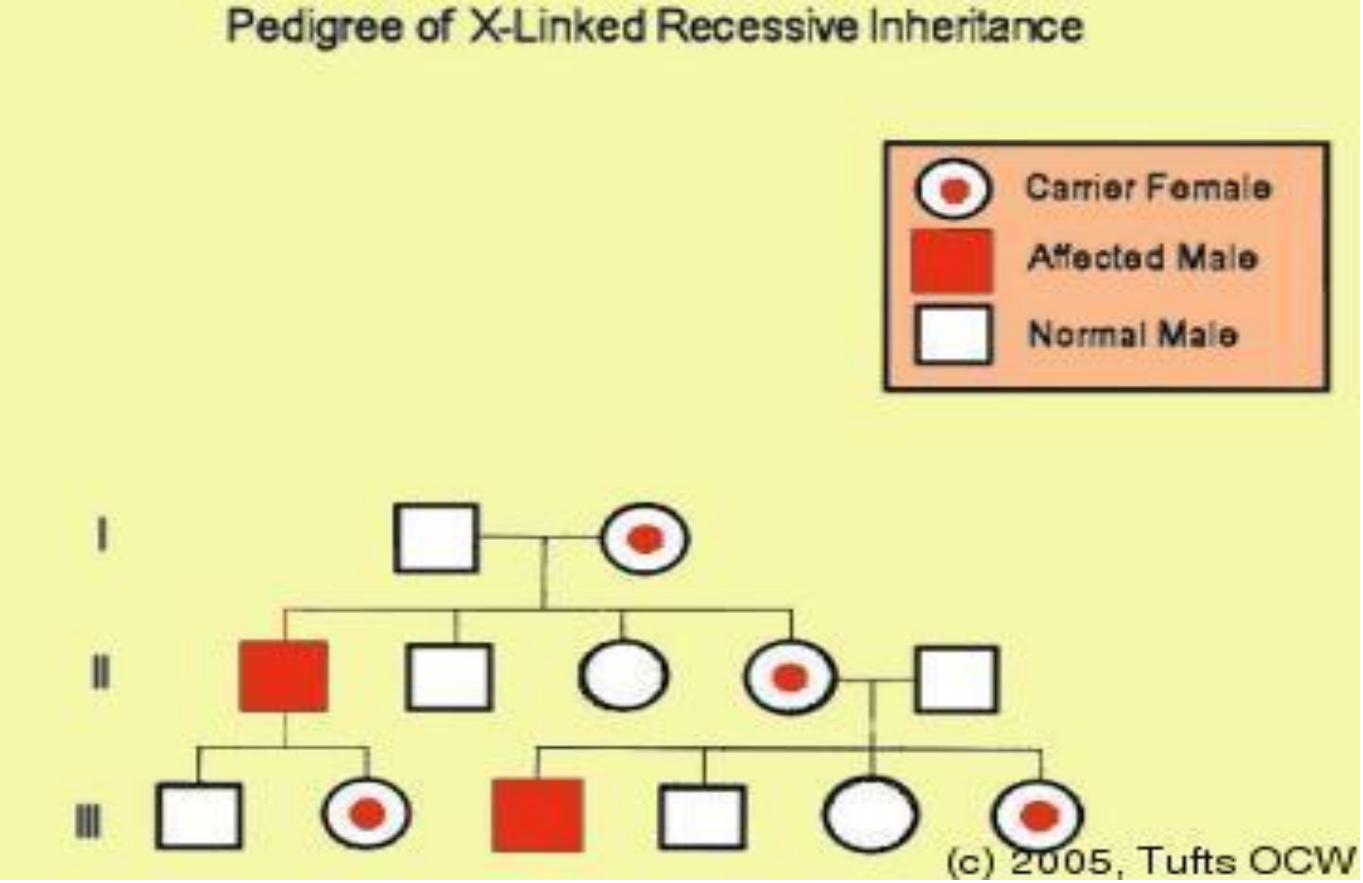


SEX LINKED DISEASES



3-X- linked recessive disorders:

- Manifest in males.
-Affected male does not transmit the disease to his sons, but all his daughters will be carriers.
•Carrier women can transmit the disease to 50% of her sons.
•Best known examples are hemophilia A, G6PD deficiency, and diabetes insipidus.

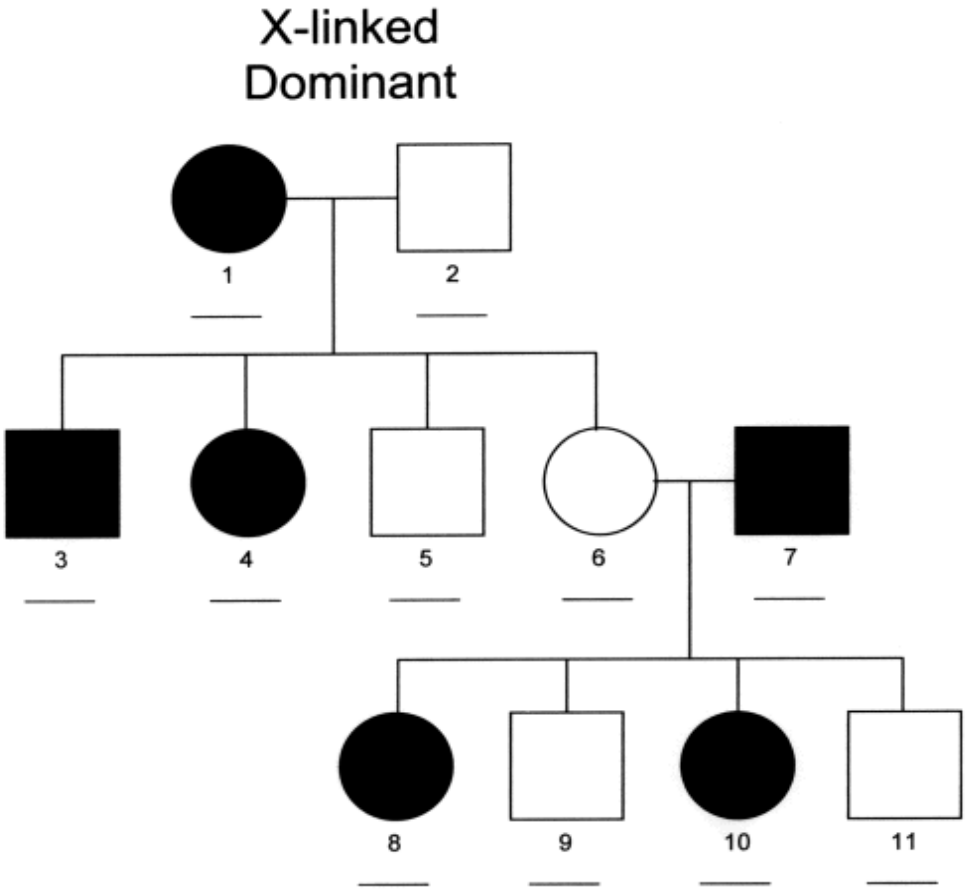

Pedigree of X-Linked Recessive Inheritance
Carrier Female
Affected Male
Normal Male
I
II
III
(c) 2005, Tufts OCW

A FEMALE IS PRESENTED WITH AN X-LINKED RECESSIVE DISORDER

EXPLAIN HOW?

4- X- linked dominant disorders:

- Affected heterozygous women transmit disease to 50% of her sons and daughters.
- Affected men can transmit the disease to all of his daughters but none of his sons will be affected.
- Vitamin D resistant rickets is a good example.


X-linked
Dominant
1
2
3
4
5
6
7
8
9
10
11

Multifactorial disorders:

It results from the combined actions of environmental influences and 2 or more genes.

- The rate of recurrence of the disorder for the first degree relatives (parents, offspring, and siblings) is between 2-7%.
- The risk for identical twins to have a disease is 20-40%.
- The risk is increased in siblings of index case that has severe phenotypic expression of the disease. For example, siblings are at risk of 2.5%to have cleft lip if the index case has a unilateral cleft lip, but are at 6% if the index case has bilateral cleft lip.
- The greater the number of relatives to have a disease, the higher the risk for relatives to have a disease in future.
- The risk of recurrence in subsequent pregnancies depends on the outcome of previous pregnancies.