Unit: 7 Genetics and Evolution

Chapter: 5 Principles of Inheritance and Variation

Module: 8 Mendelian Disorders in Human

Objectives: This module aims to give an idea about various human genetic disorders arise due point mutations.

Learning points: After going through this module the learner will understand:

- Mendelian disorders
- Types of Mendelian disorders
- Haemophilia
- Sickle cell anemia
- Phenylketonuria

Introduction

Genetic disorders: These are the diseases caused by abnormality in the genome. Many times these diseases are inherited from parents to progeny. Genetic disorders can be:

- **Mendelian disorders-** Arise due to gene mutation.
- **Chromosomal disorders-** Arise due to chromosomal mutation.

Mendelian disorders are mainly caused by mutation in the single gene. The mutant form of the gene is responsible for the disease phenotype. These disorders are transmitted from parent to progeny based on Mendelian principles of inheritance. The pattern of inheritance of such disorders can be traced in a family by the pedigree analysis. Haemophilia, cystic fibrosis, sickle-cell anaemia, colour blindness, phenylketonuria are some of the common mendelian disorders.

Classification of Mendelian Disorders

Autosomal dominant disorders:

- Autosomal dominant disorders appear in both sexes with equal frequency.
- An affected person must have at least one affected parent.

- The trait does not skip generations.
- Unaffected persons do not transmit the trait.

Examples: Familial hypercholesterolemia, Huntington disease

Autosomal recessive disorders:

- Autosomal recessive disorders appear with equal frequency in both the males and the females.
- Affected children are commonly born to unaffected parents who are carriers.
- The trait tends to skip generations.
- Recessive traits appear more frequently among the offspring of consanguine marriages.

Example: cystic fibrosis, phenylketonuria, sickle cell anemia

X- Linked dominant disorders:

- X-linked dominant traits are seen in both males and females, although they are more common in females than males.
- Daughter affected with an X-linked dominant trait must have an affected parent.
- Father does not inherit the disorder to the sons.

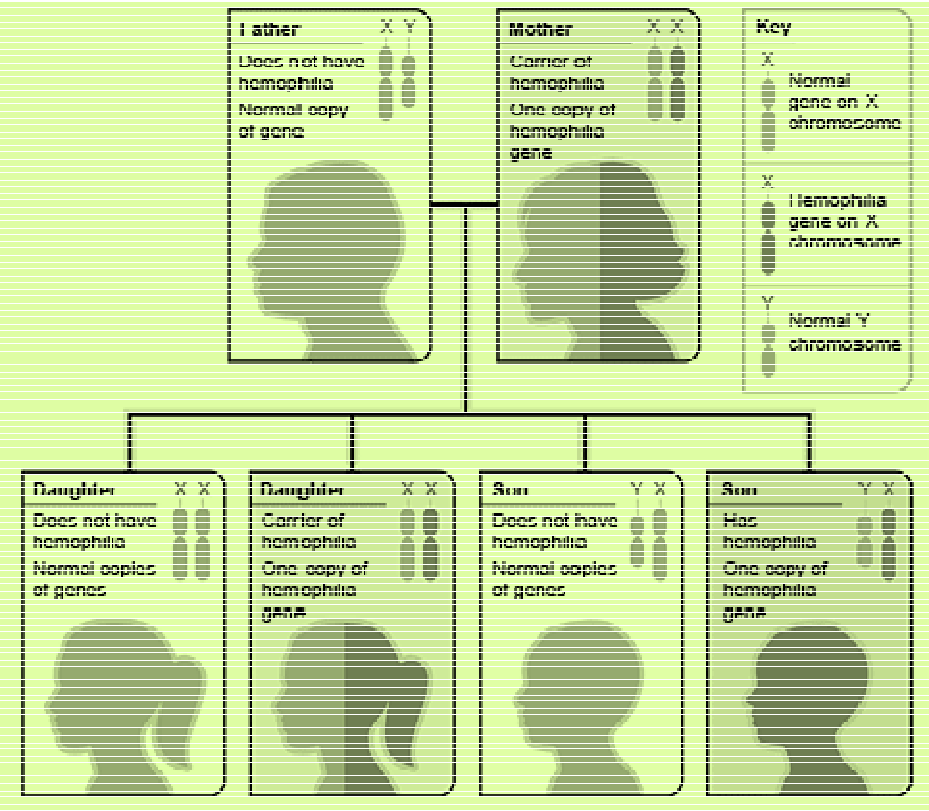
X- Linked recessive disorders:

- These traits appear more frequently in males than in females.
- These traits are not passed from father to son.
- Affected sons are usually born to unaffected mothers who are carriers.
- If daughters are affected the father would certainly be effected and mother would be at least a carrier.
- X-linked recessive traits tend to skip generations.
- Criss cross inheritance: The trait move from affected father to the daughters who are carrier and expresses in the grandson.

Example: Haemophilia, colour blindness

Haemophilia: It is X linked recessive disease, shows its transmission from unaffected carrier female to some of the male progeny. The possibility of a

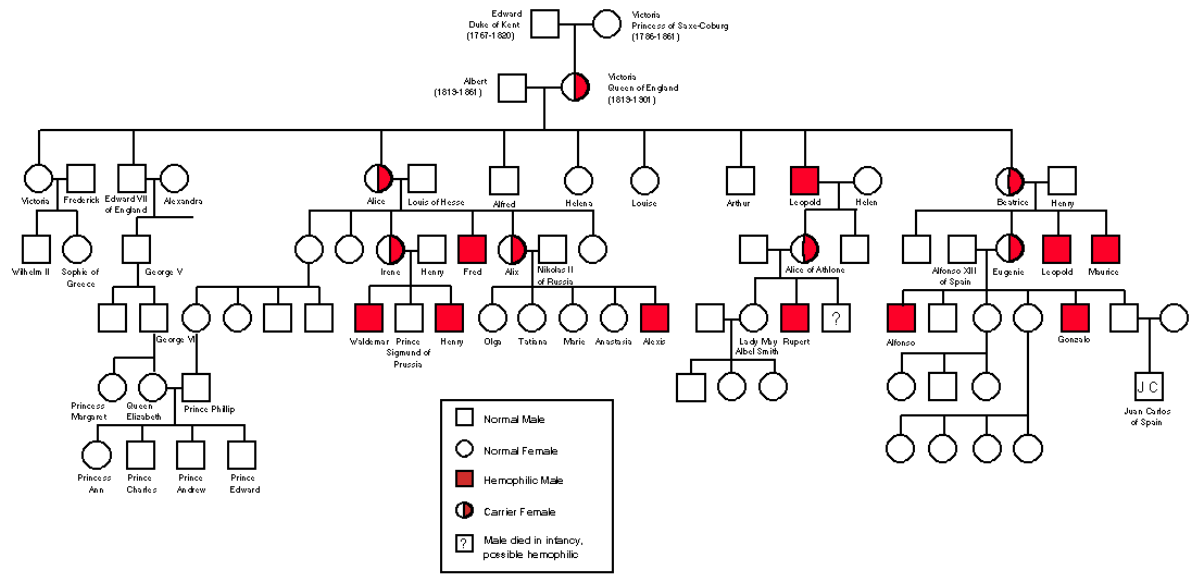
female becoming a haemophilic is extremely rare because mother of such a female has to be at least carrier and the father should be haemophilic.



In this disease, a single protein that is a part of the cascade of proteins involved in the clotting of blood is affected. Due to this, an affected individual shows profuse non stop bleeding even after a simple cut.

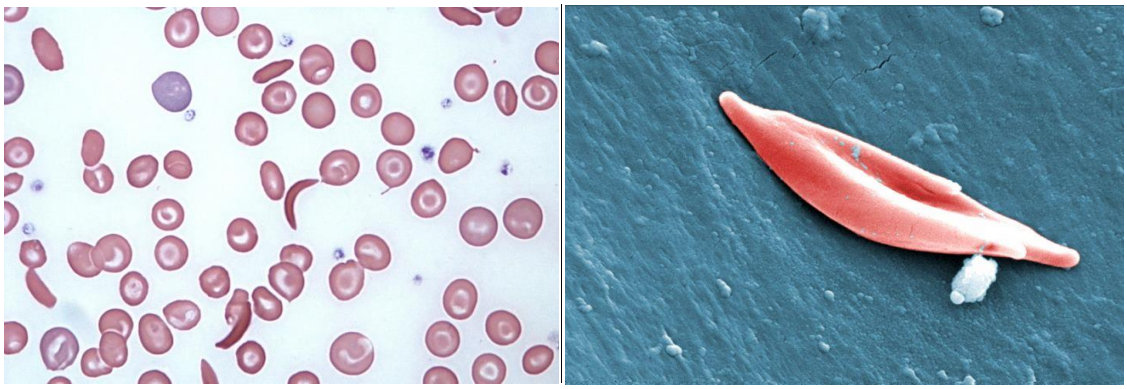
There are two main types of haemophilia - **Haemophilia A** is due to deficiency of clotting **factor VIII** (anti-hemophilic factor AHF) deficiency and **Haemophilia B** is due to deficiency of clotting **factor IX** (Christmas factor).

The family pedigree of Queen Victoria shows a number of hemophilic descendents as she was a carrier of the disease.



Sickle-cell anaemia :

It is an autosomal recessive disorder. The disease is caused due to mutation in haemoglobin. The mutant haemoglobin molecule undergoes polymerization under low oxygen tension. This causes the change in the shape of the RBC from biconcave disc to elongated sickle like, which results in anemia and other pleiotrophic effects.



In human haemoglobin is made up of 2 α and 2 β- globin chains. In sickle cell anemia Glutamic acid (Glu) at the sixth position of the β- globin chain of the haemoglobin molecule is substituted by Valine (Val).

Normal β Globin Chain of Haemoglobin

NH2 – VALINE – HISTIDINE – LEUCINE – THREONINE – PROLINE – GLUTAMIC ACID – GLUTAMIC ACID…

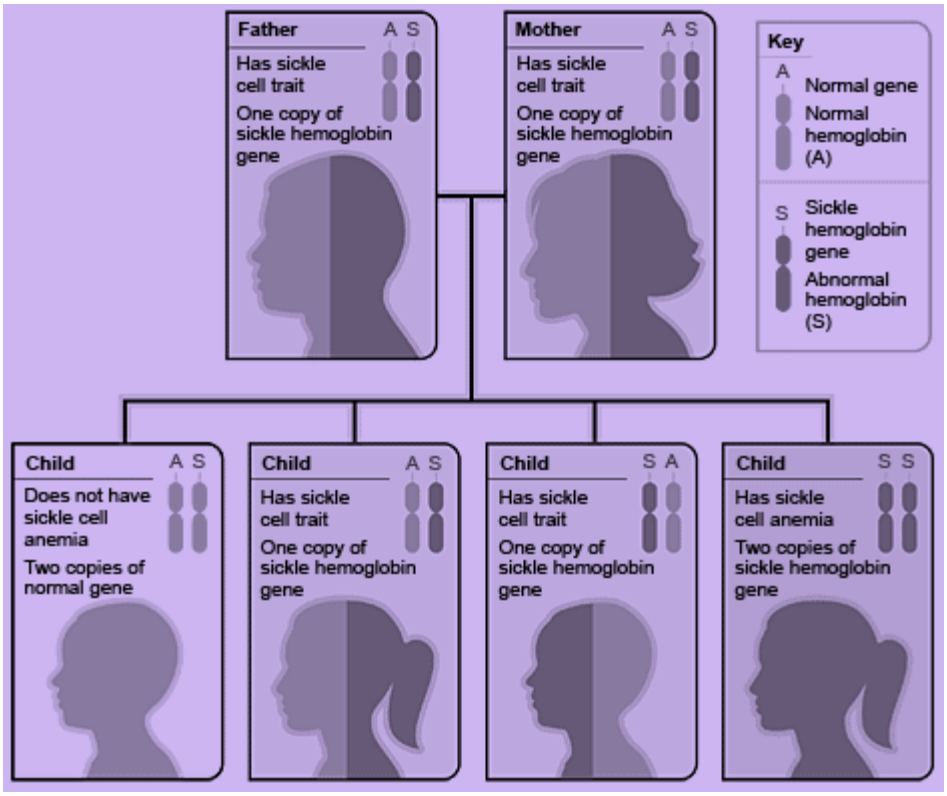
Sickle cell anemia:

NH2 – VALINE – HISTIDINE – LEUCINE – THREONINE – PROLINE – VALINE – GLUTAMIC ACID…

The normal allele for beta globin gene is HbA. The mutant allele responsible for sickle cell anemia is HbS. The allele HbS arises as a result of single base substitution at the sixth codon of the normal β- globin gene from GAG to GUG.

Normal β-globin DNA:	**TGA GGA CTC CTC.**
mRNA :	**ACU CCU GAG GAG..**
Amino acid	**Glu**
Mutant β-globin DNA. .	**TGA GGA CAC CTC…**
mRNA	**ACU CCU GUG GAG…**
Amino acid	**Val**

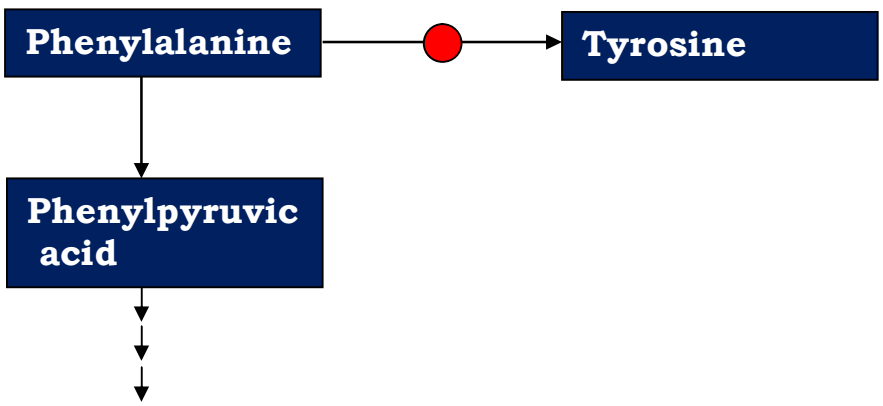
The three possible genotypes can be HbA HbA, HbA HbS, and HbS HbS. Out of these only homozygous individuals for HbS (HbS HbS) show sickle cell anemia. Heterozygous (HbA HbS) individuals appear unaffected but they are carrier of the disease.



Phenylketonuria :

Phenylketonuria is an inborn error of metabolism. It is inherited as the autosomal recessive trait.

The affected individual lacks enzyme phenylalanine hydroxylase that converts the amino acid phenylalanine into tyrosine. As a result of this phenylalanine is accumulated and converted into phenylpyruvic acid and other derivatives. Accumulation of these in brain results in mental retardation.



'Inborn errors of metabolism' are the genetic diseases involving congenital disorders of metabolism. The majority are due to defects in a single gene that codes for enzyme that facilitates conversion of substrates into products in a metabolic pathway. Some of the common examples of 'inborn errors of metabolism' are phenylketonuria, alkaptonuria, albinism.

In most of the disorders, problems arise due to accumulation of substances which are toxic or interfere with normal functions. In the absence of enzyme synthesis of essential molecules may also get hampered.

Sir Archibald Edward Garrod was the first to propose that the diseases like Alkaptonuria are due to inborn error of metabolism.

Check Yourself

1. Which of the following is not a Mendelian disorder of human beings
    a) Haemophilia
    b) Sickle cell anemia
    c) Down syndrome
    d) Phenylketonuria

2. Which of the following pair of genetic disease and its nature is **wrongly** matched
    a) Sickle cell anemia - Autosomal recessive disease
    b) Haemophilia A - X-linked recessive disease
    c) Alkaptonuria – Inborn error of metabolism
    d) Cystic fibrosis – Autosomal dominant disease

3. Which of the following statements about sickle cell anemia is not true?
    a) It arise due to non sense mutation in β globin gene
    b) It is an autosomal recessive disorder
    c) It involves change in RBC shape under low oxygen tension

d) It confers resistance to acquiring malaria

4. If a female affected with autosomal recessive disease married to a normal male, whose father was affected by the disease. Among the progeny the probability is that
    a) 50% sons would be affected and no daughter would be affected.
    b) 50% sons and 50% daughters would be affected.
    c) All the sons would be affected and no daughter would be affected.
    d) All the sons as well as daughters would be affected.

5. Red green colour blindness is a sex-linked recessive disease in humans. In a family son as well daughter was found diseased. This indicates:
    a) Both mother and father can be normal
    b) Mother is affected and father is normal
    c) Father is affected and mother can be normal phenotypically
    d) Both mother and father has to be effected

Q. No.	1	2	3	4	5
Ans:	c	d	a	b	c