PRINCIPLES OF INHERITANCE AND VARIATION

GENETIC DISORDERS

PEDIGREE ANALYSIS AND GENETICS DISORDER

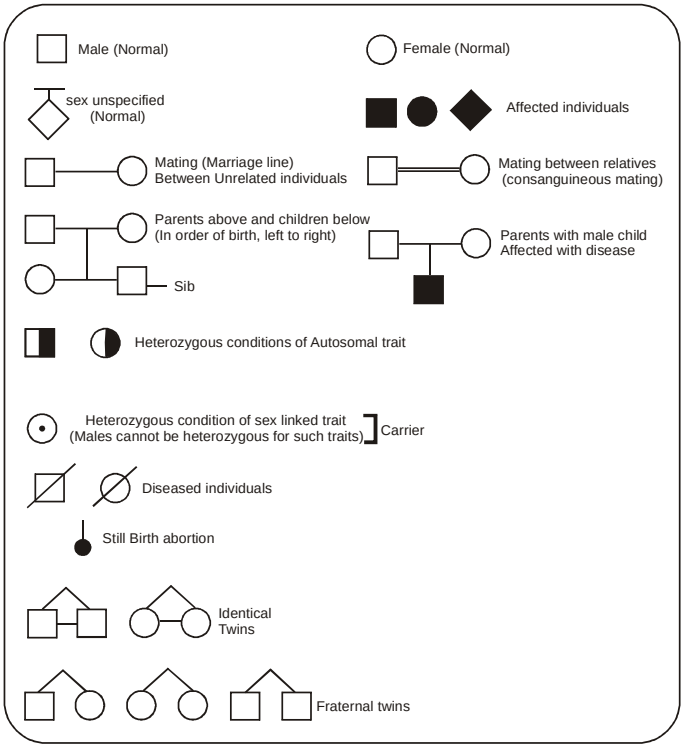
(MENDELIAN DISORDERS)

Devices Used In Human Genetical Studies :

The study and analysis of human genetics is performed by many methods like **pedigree analysis, statistical analysis** population genetics and **human karyotyping**. Of these the important ones, that is pedigree analysis and human karyotype is bing described here.

PEDIGREE ANALYSIS

Study of ancestoral history of man transmission of genetic characters from one generation to next, is pedigree analysis. Dwarfism, albinism, colour blindness, haemophilia etc. are genetically transmitted characters. To study and analyse them a pedigree of genetic facts/data and following symbols are used.



Usual practice is to place the males first, on the left if one parent is not shown in a pedigree, it indicates that this individual was phenotypically normal.

Pedigree analysis provides valuable information regarding genetical make up of human beings. If any genetic disease is occuring in a family, then pedigree analysis provides guidance to parents about their future progenies example polydactyly in humans.

HUMAN KARYOTYPE

Humans have 23 pairs (46) chromosomes. In this method, the chromosomes (autosomes and sex chromosomes) are arranged according to their size and structure. Based on the position of centromere and relative length of both arms of chromosome, three types of chromosomes are found in human – metacentric, submetacentric and acrocentric. Karyotype helps to know the relative structures (morphology) of chromosomes. Besides, it helps in chromosomal identificaiton. It is also used in studying chromosomal abnormalities (Down syndrome).

TYPES OF EUGENICS :

For improvement of hereditary characters in future generations there should be an increase in number of best individuals and reduction in number of defective individuals. Presently, eugenics is studied under following types :

POSITIVE EUGENCIS

Positive eugencis the main approach is to increase the number of progenies having best hereditary characters. This is achieved through genetic counselling, selective mating (planned marriages), arranging marriages at right age, freedom from social bonds etc.

Preservation of ovum of superior quality, artifical insemination and preserving the best quality sperms with aid of modern techniques are also included in positive eugencis.

Euphenics and gene engineering techniques are also being used to establish the best quality of hereditary traits in human society.

NEGATIVE EUGENICS

negative eugencis the carriers of undesirable inferior traits (or characters or genes) are not allowed to produce their progenies by various checks such as marriage control, segregation, birth control, sterillzation and control of consanguineous marriages.

Example : Given pedigree shows inheritance of albinism which is an autosumal recessive disorder. If 4th individul is homozygous normal then find out the carrier individual.

FOR AIIMS & AIPMT :

1. **Pedigree Analysis :**

   A record of inheritance of certain genetic traits for two or more generations presented in the form a diagram or family tree is called pedigree. **Ex: Human, domesticated animals** Square represents the male . A circle represents the female .

   Solid symbol shows the trait under study and a cross or shade of any type or, or Words can also be used in place of symbols.

   Parents are shown by horizontal line while their offsprings are connected to it by a vertical line.

   Pedigree analysis is study of pedigree for the transmission of particular trait and finding the possibility of absence or presence of that trait in homozygous or heterozygous state in a particular individual.

   It is useful for the genetic counsellors to advice intending couples about the possibility of having children with genetic defects like haemophilia, colourblindness, alkaptonuria, phenylketonuria, thalassemia, sickle all anaemia, polydactyly & syndactyly.

   Pedigree analysis employs two tools.

(i) Realised ratio of probability and chances of difference in realised ratio due to smallness of the progeny

(ii) Elimination of alterantives.

2. **Pudy of Twins :**

   Birth of two babies simultaneously by woman. Twins are of following types.

(i) **Dizygotic twins or fraternal twins :** If twins develop from two separate fertilized eggs, they are called dizygotic or fraternal twins.

(ii) **Monzygotic twins :** Twins develop from the same fertilized egg (zygote) due to splitting of zygote in to two blastomeres. The former also called identical twins because they are genetically similar except occasional mutation.

(iii)**Siamese twins :** Sometime breaking of young embryo is incomplete so that monzygotic twins are joined in various regions.

3. **Population Genetics :**

The study of distribution of traits and frequency of gene distribution in the whole population is called population genetics. It is based on principles of probability and statistical tools.

Hardy-Weinberg law :

The frequency of different genotype produced due to random mating will depend upon the gene frequency and equillbirium is stablised after one single generation of random mating.

Gene A = p ;Gene a = q ; p + q = 1 or A + a = 1 ; and $(A + a)^2 = A^2 + 2Aa + a^2 = 1$.

The frequency of A p = the Frequency of homozygous dominant will be AA–p^2

The frequency of aq = Frequency of homozygous recessive will be q^2

The frequency of Aa = 2pq

Question : (1) Presence of recessive trait is 16% . The frequency of domimant allele in population will be

Solution

q = = 0.4. p = 1.0 – 0.4 = 0.6.

Question : (2) Frequency of an autosomal lethal gene is 0.4. The frequency of carrier in a popoulation of 200 individual will be

Solution

Given q = 0.4 p = 1 – 0.4 = 0.6

frequency of carrier 2 pq = 2 x 0.6 × 0.4 = 0.48 or 48%

hence 96 out of 200.

4. Karyotype **5. Cell Culture**

GENETIC DISORDERS

Genetic disorders are due to alterations or abnormalities in the genome of an organism. A genetic disorder may be caused by a mutation in a single gene or multiple genes. It can also be due to changes in the number or structure of chromosomes.

Genes are the basic unit of heredity. They hold the genetic information in the form of DNA which can be translated into useful proteins to carry out life processes. These genes undergo a mutation sometimes, which changes the instructions to formulate the protein, due to which the protein does not work properly. Such disorders are known as genetic disorders.

Some genetic disorders are innate, i.e., present by birth, while others are acquired due to mutations in a particular gene. The genetic disorders that are present by birth are inherited from parents, e.g. cystic fibrosis, haemophilia, sickle cell anaemia, etc. The genetic disorders that are acquired during the lifetime are not inherited from parents, these occur due to mutations that occur randomly or due to exposure to certain chemicals, environments or radiations such as cigarette smoke, UV radiations, etc. Cancer is one such disease.

The genetic disorders can be categorized into two types, namely Mendelian Disorders, i.e., a disorder in a single gene that follows Mendelian inheritance pattern, and Chromosomal Disorders, i.e., damage or alteration in the chromosomes structure or number, the chromosomes are either missing, duplicated or a part is translocated.

Let us explore genetic disorder notes to know about the different types of genetic disorders.

TYPES OF GENETIC DISORDERS

MENDELIAN DISORDER

- These disorders occur due to mutations in a single gene and can be easily detected by pedigree analysis.
- These disorders can be autosomal dominant, autosomal recessive, sex-linked dominant, sex-linked recessive, and mitochondrial.

The most common Mendelian disorders include:

- Cystic fibrosis (autosomal recessive)

- Haemophilia (sex-linked recessive)
- Albinism (autosomal recessive)
- Sickle cell anaemia (autosomal recessive)

CHROMOSOMAL DISORDER

- These disorders are caused by any alteration in the number or structure of the chromosomes.
- Sometimes the whole chromosome is gained or lost.
- This type of disorder is usually fatal and affects many genes.

Some of the major chromosomal abnormalities are:

- Down's syndrome- the addition of a chromosome 21 (trisomy)
- Turner's syndrome-absence of an X chromosome (XO)
- Kleinfelter's syndrome-addition of an X chromosome (XXY)

MULTIFACTORIAL GENETIC INHERITANCE

This is also known as polygenic inheritance. These are caused as a result of environmental factors and gene mutations. Some of the examples of this kind of disorder are:

- Heart disease
- High blood pressure
- Alzheimer's disease
- Obesity
- Diabetes
- Cancer
- Arthritis

MITOCHONDRIAL INHERITANCE

This type of genetic disorder is caused by mutations in the non-nuclear mitochondrial DNA. The mitochondrial DNA is inherited from the mother. Some of the diseases caused due to mitochondrial inheritance are:

- Leber's Hereditary Optic Atrophy (LHON)
- Myoclonic epilepsy with ragged red fibres
- Mitochondrial encephalopathy
- Lactic acidosis

GENETIC COUNSELLING

Genetic counselling is one of the remarkable ways of detecting whether a child to be born will be having a genetic disease, or if the person is going to have a genetic disorder. Genetic counsellors can help a person with the diagnosis and treatment of a particular disorder.

Some genetic disorders have been treated by gene therapy. Few of the techniques are under trial and will soon be implemented in medical science to cure genetic disorders.

There are many reasons one should go for genetic counselling:

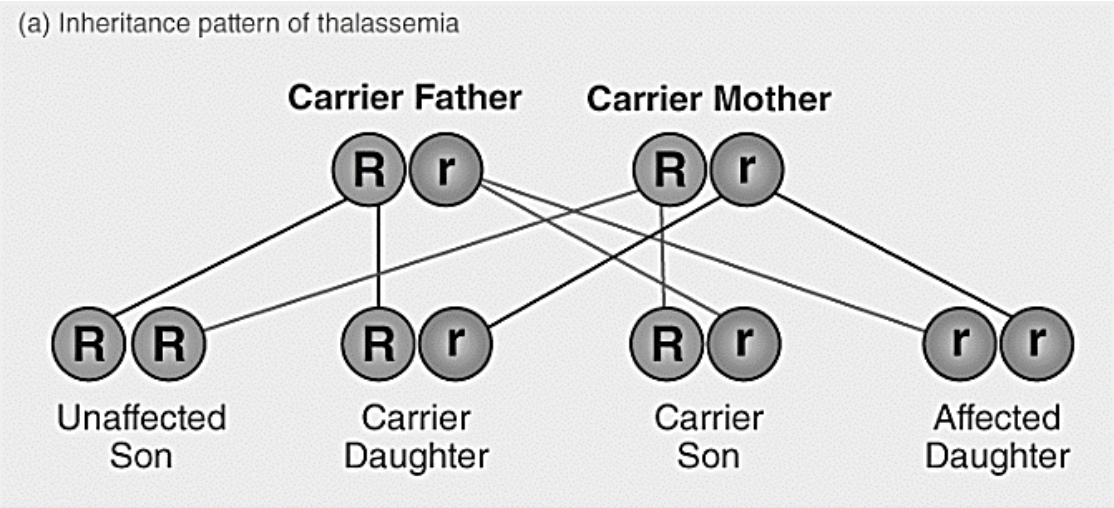
- Family history or a previous child with a genetic disease, heart defects, mental retardation, defect in the neural tube, short height, psychiatric disorders, cancer, etc.
- A parent with an autosomal dominant disease.
- If the pregnant lady is 35 years or older.
- Mother suffering from any disorder such as depression, alcoholism, diabetes, thyroid, schizophrenia, etc.

LIST OF GENETIC DISORDERS

Following is the list of genetic disorders that occur in humans:

1. Cystic fibrosis
2. Thalassemia
3. Huntington's disease

4. Hemochromatosis
5. Turner's syndrome
6. Kleinfelter's syndrome



7. Leber's Hereditary Optic Atrophy
8. Cancer
9. High Blood Pressure
10. Obesit

MENDELIAN DISORDER DEFINITION

"Mendelian disorders are the genetic disorders caused at a single genetic locus."

In humans, Mendelian disorder is a type of genetic disorder primarily resulting due to alterations in one gene or as a result of abnormalities in the genome. Such a condition can be seen since birth and be deduced on the basis of family history using the family tree. The analysis hence carried out is known as pedigree analysis.

These genetic disorders are quite rare and may affect one person in every thousand or a million. Genetic disorders may or may not be inherited. Inheritable genetic disorders usually occur in the germline cells, whereas in non-inheritable genetic disorders the defects are generally caused by new mutations or due to some changes in the DNA. For instance, cancer may either be caused by an inherited genetic condition, or by a new mutation caused by the environmental causes or otherwise.

TYPES OF MENDELIAN GENETIC DISORDERS

According to Mendel's' laws of inheritance, the different types of Mendelian disorders include:

1. Autosomal dominant.
2. Autosomal recessive.
3. Sex-linked dominant.
4. Sex-linked recessive.
5. Mitochondrial.

The various types of Mendelian disorders can be identified easily from the pedigree analysis.

Examples of Mendelian Disorders

Few examples of the Mendelian disorder in humans are

- Sickle cell anaemia
- Muscular dystrophy
- Cystic fibrosis
- Thalassemia
- Phenylketonuria
- Colour blindness
- Skeletal dysplasia
- Haemophilia

HAEMOPHILIA

- This is a type of sex-linked recessive disorders. According to the genetic inheritance pattern, the unaffected carrier mother passes on the haemophilic genes to sons.
- It is a very rare type of disease among females because for a female to get the disease, the mother should either be hemophilic or a carrier but the father should be haemophilic.
- This is a disorder in which blood doesn't clot normally as the protein which helps in clotting of blood is affected. Therefore, a person suffering from this disease usually has symptoms of unexplained and excessive bleeding from cuts or injuries.

- This type of genetic disorder is caused when the affected gene is located on the X chromosomes. Therefore, males are more frequently affected.

SICKLE-CELL ANAEMIA

- This is a type of autosomal recessive genetic disorder.
- According to Mendelian genetics, its inheritance pattern follows inheritance from two carrying parents.
- It is caused when the glutamic acid in the sixth position of the beta-globin chain of haemoglobin molecule is replaced by valine. The mutant haemoglobin molecule undergoes a physical change which changes the biconcave shape into the sickle shape.
- This reduces the oxygen-binding capacity of the haemoglobin molecule.

PHENYLKETONURIA

- This genetic disorder is autosomal recessive in nature.
- It is an inborn error caused due to the decreased metabolism level of the amino acid phenylalanine.
- In this disorder, the affected person does not have the enzyme that converts phenylalanine to tyrosine. As a result, phenylalanine accumulation takes place in the body and is converted into many derivatives which result in mental retardation.

THALASSEMIA

- This is a type of disorder in which the body makes an abnormal amount of haemoglobin. As a result, a large number of red blood cells are destroyed that leads to anaemia.
- It is an autosomal recessive disease.
- Facial bone deformities, abdominal swelling, dark urine are some of the symptoms of thalassemia.

CYSTIC FIBROSIS

- This is an autosomal recessive disorder.

- This disease affects the lungs and the digestive system and the body produces thick and sticky mucus that blocks the lungs and pancreas.
- People suffering from this disorder have a very short life-span.

CHROMOSMAL DISORDERS :

(i) Sex Chromosomal Disorders : These are as follows.

(1) Klinefelter's Syndrome :

It is found in man. Its patient contains 47 chromosomes and Its genotype is **44 + XXY**. These persons are sterile males having undeveloped testes. sparse body hair, mental retardation, and some female characters like **development of breasts (gynaecomastia).** It is due to the presence of additional X-chromosome. It has one barr body. One in every 500 male births is victim of this syndrome.

(2) Turner's Syndrome :

It is found in woman. The patient has 45 chromosomes instead of 46. and its genotype is **44 + X 0**. These are sterile females having rudimentary ovaries, small uterus undeveloped breasts, short stature,abnormal intelligence, webbed neck. menstrual cycle is abnormal or absent. One in every 3000 children is a victim of this syndrome.

FOR AIIMS

XO- Chromosomal abnormality in human beings causes turner's syndrome. While in some insects like grasshopper, XO type of sex chromosome determines male sex.

(3) Supermales (Jacob's syndrome or criminal syndrome) :

The genotype of supermale is **44 + XYY** & total number of chromosomes are 47 instead of 46. These males are characterised by abnormal height, mental retardation and criminal bent of mind **(Jacob's syndromes)** supermales are more aggressive than normal males due to over secretion of male sex hormones.

(4) Superfemale :

The genotype of superfemale is either **44 + XXX (47 chromosomes) or 44 + XXXX (48 chromosomes) or 44 + XXXXX (49 chromosomes).** They have abnormal sexual development and mental retardation.

(ii) Autosomal Disorders : These are as follows.

(1) Down's Syndrome (Mongolian Idiocy) :

It was discovered by **Langdon Down**. In this Syndrome **21-pair of chromosomes** show **trisomy** (presence of an extra chromosome number 21.

It is caused by nondisjunction of 21^{st} chromosome pair during anaphase. Thus the total number of chromosomes are 47 instead of 46 & genotype is 45 + XY in male & 45 + XX in female.

Symptoms of this syndrome are broad fore-head, rounded face, permanently open mouth with protruding tongue, projecting lower lip, Mongolian type eye lid fold,verticalfold epicanthus on either side of nose, stubby fingers,broad palm with characteristic palmer crease, Short neck , little intelligence, undeveloped Gonads and genitalia.

(2) Edward's Syndrome :

It is due to **trisomy** in **18^{th} pair of chromosomes**.The affected person keeps the fingers tightly clenched against the palm of the hand. Other symptoms are small jaws, deformed ears, small mouth, nose and fingers, small sternum and pelvis. The patient is mentally retarted and dies within 6 months after birth.

(3) Patau's Syndrome :

It occurs due to **trisomy** in **13th pair of chromosomes**. It is characterised by small head, abnormalities of the face, eyes and forebrain, cleft lip and palate, deformed ears, small chin and the hands are often clenched as edward's syndrome. The average life span of the affected person is about 4 months.

(4) Cri du chat Syndrome or Cat Cry Syndrome :

It is due to **deletion** of half part in the **short arm of the chromosome number 5.** It was reported by **Lejeune (1963)**.The affected newborn cries like mewing of a cat hence it named Cri du chat (Cat Cry). Its other symptoms are moon like face, Widely spaced eyes, small head, receding chin, congenital heart disease.

(5) Myelogenous Leukemia :

It was firstly reported in Philadelphia in 1959 hence it is also called Philadelphia syndrome. It is due to deletion of small part of **long arm of chromosome 22** and its addition to **chromosome 9 (reciprocal translocation).**

(b) Gene Related Disorders : They occur due to alternation or mutation in the single gene. These are as follows.

(i) Gene Mutations in Autosomes : Two types involve in them.

(A) Recessive Traits. **(B) Dominant Traits.**

(A) Recessive Traits : Recessive autosomal genes in homologous condition are responsible for them.

(1) Phenylketonuria (PKU) :

It described by Folling (1934). It is an **autosomal recessive metabolic disorder. Enzyme phenylalanine hydroxylase** is absent due to abnormal autosomal recessive gene on **chromosome 12** as a result phenylalanine (amino acid) is not converted into tyrosine (amino acid) in liver. It is called **hyperphenylalaninemia.** The latter is characterised by accumulation and excretion of phenylalanine, phenylpyruvic acid and related compounds. Symptoms are mental retardation (**IQ less than 20),** decreased pigmentation of hair and skin and eczema.

(2) Alkaptonuria :

It was **first inborn metabolic disease** explained by **Garrod**. It is an autosomal recessive, metabolic disorder. **Deficiency** of an **alkapton oxidase/homogentisate oxidase enzyme** of liver is responsible for it. as a result **homogentisic acid/Alkapton** accumulates in the tissues and is also excreted in the urine. The latter turns black in the air due to oxidation of homogentisic acid & other symptoms are arthritis, bronz pigmentation .

(3) Albinism :

Albinos lack dark pigment **melanin** in the **skin, hair** and **iris**. It is an autosomal, recessive genetic disorder. Synthesis of melanin pigment from dihydroxyphenyalanine is absent due to lack of **enzyme tyrosinase**. Only homozygous individual (aa) is affected by this. It is due to recessive

allele of **long arm of chromosome 11** but may also be caused by another recessive allele of **P-gene** on long arm of **chromosome 15**.

(4) Cystic Fibrosis :

The disease is common in caucasian population. It occurs due to recessive allele of **chromosome number 7**. Symptoms of this disease are the **failure of chloride ion transport mechanism** followed by elevated levels of sodium and chloride in the sweat. Thick mucus accumulates in lungs and respiratory path, It causes blockage and secondary infection. This disorder was formerly called **mucoviscoides**. There is impairment of pancreatic and liver functions in most of the cases of cystic fibrosis. Cardiac failure may occur.

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(5) Tay-Sach's Disease (TSD)/ Infantile Amourotic Idiocy :

It is recessive autosomal disorder that occurs due to **deficiency** of **enzyme -D-N- acetyl hexosaminidase** after birth. Symptoms of this disease involve damaging brain and spinal cord. Mental retardation and paralysis due to **accumulation of lipid GM_2 or Tay-Sach's ganglioside**. The child is dead at the age of 3–4 yrs.

(6) Sickle Cell Anaemia :

It occurs due to autosomal codominant (formerly considered recessive) allele Hb^S present on **chromosome 11**.

It is caused by the formation of an abnormal **haemoglobin-S**. In which **Glutamic acid**, of **6^{th} position** in **-chain** is replaced by **Valine** amino acid due to substitution of T by A in the second position of the triplet **codon (CTC)** on chromosome 11.The codon **CTC** usually transcribed into **GAG (coding for Glutamic acid).** but due to substitutions of T by A The new codon **CAC** is transcribed into **GUG** that codes **Valine**. It is the **major effect** of allele.

Other secondary effects involve formation of **sickle-shaped erythrocytes** during oxygen deficiency. The cells cannot pass through narrow capillaries resulting the latter become clogged. Spleen and brain get damaged. The homozygotes having only haemoglobin-S (Hb^SHb^S) usually die before reaching maturity due to erythrocyte distortion but Hb^AHb^S individuals survive.