Chapter 56

Human Genetics and its Disorders

- **Human genetics** deal with the inheritance of characters in man.
- **Sir Francis Galton** recommended two methods to determine human genetics traits and their inheritance. These methods are - **pedigree analysis** & **studies of twins.**
- **Pedigree analysis** is a graphical method representing the generation of family with various symbols used for relationships or for particular chemical findings.
- **Genes,** the hereditary unit, contains the hereditary information encoded in their chemical structure for transmission from generation to generation.
- Any changes in the composition of one or more genes on a chromosomes may produce structural, physiological or biochemical abnormalities. Hence these are called **genetic disorders**.
- Genetic disorders are also called **congenital diseases** because these are present and existing from the time of birth.
- Genetic disorders may be **classified on the basis of** –
  - **Chromosomal abnormalities**
  - **Incompatibility of genes**
  - **Single gene disorders**.
- **Chromosomal abnormalities** may **arises due to** –
  - **Non disjunction :** When pair of chromosomes fail to separate.
  - **Translocation :** When a portion of chromosomes breaks & attached to another.
  - **Deletion :** When a piece of chromosomes may detatch & lost from karyotype (chromosomal complement of organisms).
  - **Duplication :** When some genes may appear twice in the same chromosomes.
  - **Inversion :** When chromosomal segment inverted & change or alter the order of sequence of genes.
  - Transverse division of chromosomes instead of longitudinal division (**iso chromosomes)**.
- Disorders arises due to chromosomal abnormalities may be **either due to autosomal chromosomal changes** or **sex chromosomal changes**.
- Disorders of incompatibility of genes are of two types – **Rh factor incompatibility** and **ABO incompatibillity**.
- Caused by gene mutation, **single gene disorders** (also called **unifactorial diseases**) **are of three types** –
  - **Recessive autosomal gene disorder** (eg. sickle cell anaemia, alkaptonuria, albinism, Tay sachs disease etc.)
  - **Defective dominant autosomal gene disorder** (eg. Huntington's chorea, achondroplasia etc.)
  - **Recessive sex linked gene disorder** (eg. haemophilia, colourblindness, muscular dystrophy etc.)

CHROMOSOMAL DISORDERS

Autosomal chromosomal changes

- Due to changes in number autosomal disorders are of two types – euploidy and aneuploidy.
- **Euploidy** is the numerical increase of chromosomes from normal 2*n* to multiples of complete haploid set *i.e.*, 3X (triploid), 4X (tetraploid), 5X (pentaploid), 6X (hexaploid). This is **more common in plants**, **rare in animals**, **and does not occur in humans**.

- **Aneuploidy** relates to variation in chromosome number with respect to one or only a few chromosomes. The entire set is not involved in aneuploidy. Thus, the person afflicted with this will have one or few chromosomes more or less than the diploid number.
- Aneuploids are of **three types** –
  - **Monosomic** ($2n - 1$)
  - **Nullisomic** ($2n - 2$) when entire pair of homologous chromosome from a diploid set is missing
  - **Polysomic** when one or more chromosome reduplicates.
- Polysomics can be of **4 types** –
  - **Trisomic** ($2n + 1$) : having 3 chromosomes (= copies) in one set instead of 2. This is due to non-disjunction of homologous pair.
  - **Double trisomic** ($2n + 1 + 1$) : 2 extra chromosomes
  - **Tetrasomics** ($2n + 2$) : one chromosome in quadriplicate.
  - **Pentasomics** ($2n + 3$) : one chromosome in pentaplicate.
- **Disorders of autosomal chromosomal abnormalities** are - Down's syndrome, Edward's syndrome, Patau's syndrome.

Down syndrome

- **Down's syndrome** occur due to **trisomy of 21st chromosomes** with rounded face, flaccid muscle, protruding tongue, folded eyelids short and broad neck, feeble minded, low 1Q (20 - 50), severe neurological disorders, prone to respiratory diseases etc.
- This syndrome is also known as **Mongoloid syndrome**.
- Survivers of Down's syndrome have higher chances of catching Leukemia and Alzheimer's disease.

Edward's syndrome

- Individual suffering from **Edwards' syndrome** due to **trisomy of 18th chromosomes** is characterized by mental retardation, micrognathia short sternum etc.

Patau's syndrome

- **Trisomy of 13th chromosomes** results in **Patau's syndrome**.
- It is **characterised by hare lip** (a form of congenital defect, sometimes hereditary, marked abnormal clefts between the upper lip and the base of nose), **cleft palate** (results from the incomplete closure of palate or roof of the mouth during early embryonic life), **polydactyly** etc.
- Death usually occurs soon after birth or may survive upto 3 months.

Sex chromosomal changes

- The X and Y chromosome of humans differ in their shape, size and banding patterns. X contains more DNA than Y, also has more genes than Y. The genetic capabilities of X are relatively higher than Y.
- Y is very much condensed & contains few functional genes that determine male traits. They are called **holandric genes**.
- Recessive alleles present on X have no equivalent/ comparable gene on Y. It is because of this reason that **recessive allelic genes of X easily express themselves phenotypically**.
- In females of all placentals including humans one of the X chromosomes becomes inert by a process called *Lyonisation*. This inert chromosome was first discovered by Barr on the nuclear membrane as an intensely stained body and is appropriately designated as **barr body**.
- In genetically normal human female one barr body is present. The male do not have it.
- **Aneuploidy in sex chromosome** results in increase in the number of X (in some cases Y as well) called **trisomy**.
- Trisomy **arises by non-disjunction of homologous chromosomes** during egg cell formation.
- Non-disjunction is **more common in sex chromosomes** than the autosome.
- **Deletion** of large **part of the small arm of one of the 5th chromosomes** results in **Cat cry syndrome** (discovered by Lejeune in 1963). These syndrome is associated with malformation of the larynx.
- Child affected with cat cry syndrome during infancy has a characteristic high pitched cry of kitten.
- **Philadelphia chromosome** is one of 22 autosomes that has lost most of the distal part of its longer arm.
- This chromosome is present in those individual which are suffering from **chronic myeloid leukemia**.
- It is **characterised by** an excess of granular

leucocytes in the blood which in turn reduces the number of RBC resulting in severe anaemia.

- **Hypertrichosis** means excessive hair on ear pinna. Genes responsible for this are located on Y chromosomes only which are also known as **holandric genes**. This genes are not expressed in females. Y-linked holandric genes are transmitted directly from father to son.
- **Genetic disorder due to sex chromosomal numerical changes** are – Klinefelter's syndrome, Turner's syndrome, super males and super females.

Klinefelter's syndrome

- Klinefelter's syndrome is one of the **most common cause of hypogonadism in the male**.
- Klinefelter's' syndrome (XXY) is **caused by presence of extra X-chromosome due to union of nondisjunct XX egg** and **a normal X and abnormal XY sperms**.
- These are **genetically sterile male individual** with undeveloped testes, azospermia (less and deformed sperm), gynaecomastia (enlarged breast), mental retardation, occurrence of barr body etc.

Turner's syndrome

- Turners' syndrome (most common type of female genetic disease) **having XO genotype** is **caused by the absence of X chromosomes in female**.
- These are **sterile females with** poorly developed ovaries and underdeveloped breasts. They have webbed neck and broad chest.

Supermales

- Supermales (Y chromosome disorder) having XYY genotype shows over production of testosterone, unusual height, mental retardation, over aggressiveness and criminal bent of mind.

Superfemales

- Superfemales, having XXX genotype, **arises due to presence of extranumerary chromosomes.**
- These females are mentally retarded with congenital abnormalities like underdeveloped external genitalia, uterus and vagina.

INCOMPATIBILITY OF GENES

Rh factor incompatibility

- Rh factor was first of all reported in RBCs of *Macaca rhesus* **(rhesus monkey)** by **Landsteiner** and **Wiener** in 1940.
- Rh factor is **dominant character in heredity**.
- The disease **erythroblastosis foetalis** in human embryo is caused due to disadjustment of Rh factor.
- Erythroblastosis foetalis can **occur when father is Rh positive** and **mother is Rh negative**.
- An Rh negative woman can be sensitized when she bears an Rh^+ child, and future Rh^+ children may have erythroblastosis foetails (also called **haemolytic disease of the newborn**, **HDN)**.
- In developing foetus, erythroblastosis foetalis is caused by **haemolysis**.
- Injection of anti-Rh (**Rhogam)** into an Rh negative woman after the birth of each Rh positive baby can prevent sensitization of the woman by binding Rh positive blood cells from the baby.
- The **commonest cause of haemolytic disease of newborn** is **maternal alloimmunisation** (immunity arising from the mothers body itself).
- **No abnormality arises** when mother is Rh (+)ve and father is Rh(–)ve.
- Erythroblastosis foetalis occurs due to **transplanted transmission of maternally formed antibody against the foetus erythrocytes**, usually secondary to an incompatibility between the mothers Rh blood group and that of her offsprings.

ABO incompatibility

- ABO incompatibility may lead to haemolytic disease of new born, characterised with **anaemia and jaundice**.
- ABO incompatibility is **less severe** as compared to Rh-incompatibility disorder. It **occurs even in the first baby**.

SINGLE GENE DISORDERS

Recessive autosomal gene disorder

- **Type of recessive autosomal gene disorders** are – phenylketonuria, albinism, alkaptonuria etc.
- Phenylketonuria, albinism and alkaptonuria etc are **caused by the absence of specific enzymes**.

Phenylketonuria

- Phenylketonuria **occurs due to absence of** *phenylalanie hydroxylase* enzyme in liver which is essential for the conversion of phenylalanine to tyrosine.
- It is **characterised by** severe mental retardation, hypopigmentation of skin and hair, eczema (itchy

skin), mousy odour of skin, hair and urine due to **increased phenylalanine in blood and urine**.

Alkaptonuria

- Alkaptonuria is also called **black urine disease**.
- Alkaptonuria occurs **due to absence of liver enzyme**, *homogensate/alkapton oxidase* which is essential for the metabolism of homogentisic acid (formed from phenylalanine and tyrosine).
- It is **characterised by** the **increased excretion of alkapton** and its accumulation in body produces arthritis and other **damages**.

Albinism

- Albinism **arises due to** absence of enzyme **tyrosinase** which catalyses the formation of dihydroxy-phenylalanine (DOPA) which form dark brown pigment.
- During this eye disorders may occur due to **damage from bright light**.

Tay Sach's disease

- Tay Sach's disease appears after birth **due to deficiency of enzyme β-D-N-acetyl hexosaminidase**.
- It is **characterised with abnormal fat metabolism** leading to damage to brain and spinal cord resulting in mental retardation and paralysis.

Thalassemia

- Thalassemia is a group of genetic disorders which **results from defective synthesis of subunits of haemoglobin** (α and β-globin chains of haemoglobin).
- In **α-thalassemia**, out of four genes on **11th chromosomes,** absence of 2 genes leads to microcytic and hypochromic erythrocytes without significant anaemia. Death occurs in case of deficiency of all the genes.
- **β-thalassemia** is **characterised by** presence of two defective β-gene on **16th chromosomes**.

Sickle cell anaemia

- Sickle cell anaemia is **due to inheritance of a defective allele coding for β-globin**. It results in the transformation of Hb-A into Hb-S in which **glutamic acid is replaced by valine at sixth position in each of two β-chains of haemoglobin**.
- Sickle cell anaemia is a **blood disease** (affective black Africans) where the red blood cells become **sickle shaped** as compared to normal one.
- The sickle cells are **rigid** and **exhibit a higher viscosity to flow** causing them to lodge in capillaries.
- The major characteristics of this disease are **anaemia and a tendency of the red blood cells to change shape** at low oxygen concentration.
- Due to insoluble in deoxygenated state sickle cell haemoglobin precipitate in the **red blood cells** and giving their characteristic **bizzare shape**.
- These cells are **useless**, so they have to broken down and tend to jam in capillaries and small blood vessels and prevent normal blood flow.
- The absent or reduced blood flow results in **ischemic damage** to many different organs in affected individuals.
- Sickle cell anaemia is an **excellent example of single mutation**.

Galactosemia

- Galactosemia in man is inherited as an autosomal recessive, and the **affected person is unable to convert galactose to glucose**.
- The disease is **due to the deficiency** of the enzyme *galactose phosphate uridyl transferase* (GPT).
- Untreated infants develop hepatomegaly, jaundice and hypotonia and the symptoms can be relieved if galactose is removed from the diet.
- **The gene involved in the galactosemia is located on the short arm of chromosome 9**. Affected individuals, who are homozygous for the allele, exhibit enlargement of liver and spleen and some mental retardation.

Defective dominant autosomal gene disorders

- **Disorders due to dominant defective autosomal genes** are – Huntington's chorea, achondroplasia, polydactyly, bradydactyly, dwarfism.
- **Huntington's chorea** (late acting dominant disorder) is caused by a dominant gene mutation on **short arm of 4th chromosome**.
- It is **characterised by** abnormal speech and respiration, irregular arrhythmic movements of limbs etc. **due to atropy of brain parts**.
- This disease **does not appear** till the age of 25 to 35.
- **Achondroplasia** is a **hereditary disorder of cartilage formation leading to dwarfism**.
- **Polydactyly** and **bradydactyly** is a disease of more **than five digits in fingers and toes** and a **small sized fingers respectively**.
- **Marfan syndrome** is due to dominant mutation

resulting in the production of abnormal form of connective tissues and characteristic extreme looseness of joints. The long bones of body grow longer, fingers are very long called '**spider fingers**' or **arachnodactyly**; weakness develops in the connective tissue and lenses in eyes become displaced. The diagnosis is made on clinical grounds, with involvement in at least two body systems.

- The **molecular basis of Marfan syndrome** is **mutation of a structural gene** (related to fibrillin protein) **on chromosome 15**.
- **Cystic fibrosis** is most common diseases in North America, rare in Asia including India. The body **produces abnormal glycoprotein which interferes with salt metabolism**. The sweat in body becomes rich in sodium chloride; the mucous secreted by body becomes abnormally viscid which blocks passages in the lungs, liver and pancreas. Due to defective liver functioning the fat digestion will not be normal. One of the **principal organ affected by cystic fibrosis is pancreas** which develops fibrous growth.
- The **gene**, responsible for this defect (cystic fibrosis), has been **localized to chromosome 7** and it codes for a chloride transport factor (CFTR) and multiple alleles.
- **Gaucher's disease** is a genetic disease associated with **abnormal fat metabolism**. It is **caused by** the **absence of the enzyme** *glucocerebrosidase* required for proper processing of lipids.

Recessive sex linked gene disorders

- **Disorders occurs due to recessive sex linked genes** are – haemophilia, red-green colourblindness, muscular dystrophy etc.

Haemophilia

- Haemophilia is **also known as bleeder disease** (John Otto, 1803).
- It is an **popular example of sex linked inheritence in human beings**.
- It **occurs due to deficiency of plasma thromoboplastin** (haemophilia, Christmas disease) or **antihaemophilia globulin** (haemophilia A) during which the exposed blood does not clot.
- Haemophilia **appears only in human male** which can be transferred to their grandson through his carrier daughter **(criss-cross inheritance)**. Homozygous condition is **lethal**.

Red green colourblindness

- Red green colourblindness is **more common in male** than females (20 : 1) due to presence of only one X chromosome.
- The sufferer are **not able to distinguish between red and green colour.**
- Red green colour blindness is also called **Daltonism** or **proton defect**.
- Colourblindness is of **three types : protanopia** (red colour blindness), **deuteranopia** (green colour blindness) & **tritanopia** (blue colour blindness.)
- Colourblindness show **criss-cross inheritance** as in haemophila.

Muscular dystrophy

- Muscular dystrophy **occurs due to non-synthesis of protein, dystrophin** which is required for transfer of nerve impulse to calcium storing regions of the muscle.
- Muscular dystrophy is of **two types – Duchenne's pseudohypertrophy** and **Becker's/benign pseudohypertrophic dystrophy** (less severe).
- It is **characterised by deterioration of muscles at an early age** with progressive weakness of girdle muscles, inability to walk after age of 12, cardiomyopathy and mental impairment.

G-6-PD deficiency syndrome

- G-6-PD deficiency syndrome **occurs due to deficiency** of *glucose 6-phosphate dehydrogenase* (essential for carrying out hexose monophosphate shunt).
- In the absence of G-6PD, **haemoglobin crystallizes** and **erythrocyte membrane ruptures** during oxidant stress.

Congenital night blindness

- **Congenital night blindness** causes reduced development of visual pigment (rhodopsin) that interferes with the function of retinal rods and hence night blindness. (Also **occurs due to vitamin A deficiency**).
- It is **caused by** a recessive gene carried by X-chromosomes.