# MANE-001
# Human Genetics

Indira Gandhi
National Open University
School of Social Sciences

Block

# 1

## INTRODUCTION TO HUMAN GENETICS

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# BLOCK 1 INTRODUCTION

The prevailing concept of heredity in Gregor Mendel's time was that the traits of the parents become blended in the progeny, as though the hereditary material consisted of fluids that become permanently mixed when combined. However, Mendel's observation that one of the parental characteristics was absent in $F_1$ generation and reappeared in unchanged form in the $F_2$ generation was inconsistent with the idea of blending. Mendel's experiments were simple and direct and revealed the most significant principles that determine how characteristics (traits) are passed from parents to offspring. Due to his careful analysis of inheritance of traits in garden peas carried out from 1856 to 1963 and published in 1866, heredity came to be recognized as a biological process separate from development. The Mendelian principles are the basis of 'transmission genetics' also referred to as 'formal genetics' because the subject can be understood and the rules clearly seen without any reference to the biochemical nature of genes or gene products. Mendel's story is one of the great legends in the history of science.

Although Mendel's work demonstrated that the units of heredity are stable and particulate but at that time the biological basis of the transmission of genes from parents to offspring was quite mysterious; neither the role of the nucleus in reproduction nor the details of cell division were known. The early geneticists began to wonder about the biochemical nature of the gene and raised questions like what kind of molecule is a gene. How can hereditary information be contained in a molecule? How can this information be transmitted from parents to offspring? In what way is the information different in a mutant? At that time, there was no logical starting point for such an investigation. In 1869, Friedrich Miescher discovered a new type of mild acid, abundant in the nuclei of white blood cells that turned out to be chemical substance of which genes are made and is called deoxyribonucleic acid (DNA). However, the connection between DNA and heredity was not demonstrated.

In the 1870s, the importance of the nucleus in inheritance was made clear by the observation that the nuclei of the male and female reproductive cells fuse in the process of fertilization. The next major advance was the discovery of the thread like structures, the chromosomes, inside the nucleus that become visible in the light microscope when stained with certain dyes. Chromosomes have a characteristic 'splitting' behaviour in cell division, in which each daughter cell formed by cell division receives an identical complement of chromosomes. Furthermore, the number of chromosomes differs among species but is constant within each species. These features of chromosomes, well understood by about 1900 made it likely that chromosomes were the carriers of the genes.

Beginning in the early 1920s, and especially in the 1940s, a few critical observations were made that implicated DNA in heredity. The three-dimensional structure of DNA proposed in 1953 by Watson and Crick gave many clues about the manner in which DNA functions as the genetic material. Within a decade, there came an understanding of the chemical nature of genes and how genetic information is stored, released to the cell, and transmitted from one generation to the next. By 1970s, the basic tools required for manipulation of DNA such as DNA ligases and restriction enzymes, respectively the molecular glues and scissors, were found. A novel technique of in vitro DNA amplification, polymerase chain reaction (PCR), was developed by Kary Banks Mullis in 1983 which found instant application in genomics and clinical genetics.

Though there was some awareness of the genetic basis of a number of diseases; it was not until 1956 that we finally knew how many chromosomes man had, thanks to the pioneer work of Tjio and Levan who using tissue culture and hypotonic shock discovered that our species has only 46 chromosomes. Among the great scientific movements initiating the study of human heredity, history will no doubt pick out after Mendelism and gene chemistry, chromosome analysis. Cytogenetic techniques permit detection of numerical anomalies and major structural anomalies.

Mendel worked with artificial populations of plants, but the principles of Mendelian genetics are equally applicable to natural populations. Population Genetics is the application of Mendel's laws and other principles of genetics to population of organisms. One of the goals of this branch of genetics is to determine the nature and extent of genetic variation in natural populations and in this analysis allele frequencies are often more useful than genotype frequencies because alleles, not genotypes, form the bridge between generations. Alleles rarely undergo mutation in a single generation and so they are relatively stable in their transmission from one generation to the next. On the other hand, genotypes are not permanent; they are totally broken up in the process of segregation and recombination that take place in each reproductive cycle.

While Mendelian genetics began with the rediscovery of Mendel's work at the beginning of the 20$^{th}$ century; modern human genetics as applied to anthropology only dates from the Second World War, though ABO blood groups were discovered in 1900 and some early beginnings were made by Hirszfelds pioneer studies on ABO blood groups of soldiers of different nationalities at the end of First World War. Certainly as late as the early 1940s we knew only four blood group systems, PTC tasting ability and red/green colourblindness as simply inherited normal genetic traits of anthropological interest.

The great advance in human genetics since the Second World War has been truly impressive. There was the great blossoming of serology, giving the discovery of dozen odd more public blood group systems. Of technical advances, in the biochemical sphere the coming of electrophoresis and isoelectric focusing techniques brought to light the enormous variation in serum proteins and red cell enzymes and undreamed-of richness of genetic variability in DNA was revealed by the molecular techniques of southern blotting and PCR; improved microscopy allowed us to visualize the chromosomes, and indeed their ultra-structure, as also differential staining of the human chromosomes showing characteristic banding patterns; development of tissue culture methods brought the possibility of establishing gene location by somatic cell hybridization, and by combining the cytogenetic process of producing metaphase on slides and recombinant DNA technology, the resultant technique of molecular cytogenetic or in situ hybridization (ISH) with increased resolution enabled detection of chromosomal aberrations not detected by the light microscope. The general theory of population genetics was steadily advancing, and the computer revolution provided power to apply this theory to man, applying models of genetic structure and evolution to populations of great complexity. The development of clinical genetics provided further proof of enormous genetic heterogeneity, filling in the gaps that the study of normal genetic variants had left.

With the above background, the present Block on Human Genetics comprising three Units viz., Definition and Scope, Biological Basis of Human Heredity and Formal Genetics provides a comprehensive account of the subject in a lucid manner.

# UNIT 1 DEFINITION AND SCOPE

**Contents**



**Learning Objectives**

After reading this unit, you will be able to:

- understand about the subject of human genetics, its origin, growth and emergence of its branches;
- expalin how the characters/traits are inherited from parents to offspring;
- discuss about the normal and abnormal composition of the chromosomes leading to syndromes/ disorders;
- elucidate the concept of "one-gene-one-enzyme hypothesis" which explains development of genetic diseases/disorders caused by defective genes controlling the functions of enzymes in metabolic pathways;
- discuss about ABO and RHD blood groups, blood group incompatibility and the development of the branch of immunogenetics;
- know about the genetic defects caused by nucleotide variations in the DNA sequence of a gene, providing understanding of molecular basis of genetic diseases;
- explain the importance of somatic cell genetics, pharmacogenetics and population genetics; and
- discuss the importance of clinical diagnosis, genetic counselling and management of genetic diseases in maintaining human health.

## 1.1 INTRODUCTION AND BACKGROUND

Man's insatiable thirst to know more and more about himself and his surroundings has led to the discovery of many secrets of life. Bestowed with the power of thinking, imagination and judgment, man has been applying the knowledge he acquired to his day to day needs and his own betterment. In this attempt he pursued the search for explanations and scientific proofs for the origin and existence of other forms of life including plants and animals, their organization, life processes and their use to the mankind.

Initially it was a puzzle how the individual species maintain their identity with characteristic features and reproduce individuals similar to them. It was observed that a mouse reproduces mouse, an elephant another elephant and tamarind seeds grow only as tamarind trees. In other words, it was understood that "like begets like". Still differences or variations were found to occur between the members of the same species i.e. no two individuals appear to resemble exactly. What contributes to these differences between the individuals is studied at various levels using advanced technologies. Such studies provided explanation for understanding the mechanisms related to the following.

a) The inheritance of characters from parents to offspring that may be simple or complex.

b) The resemblance between the members of the same species or members of the same family.

c) The reasons for individual differences.

d) Process of reproduction.

e) Maintenance of species identity and many more.

Such knowledge led to the development of several branches of science and of them the "science of inheritance" attracted the attention of several scientists over centuries which could explain the facts of life.

Inheritance of characters (traits) through generations in man was noticed from time immemorial and in 1644 Sur Kenelm Digby cited a five generation family with inheritance of polydactyly (extra fingers/toes) (Fig. 1.1).

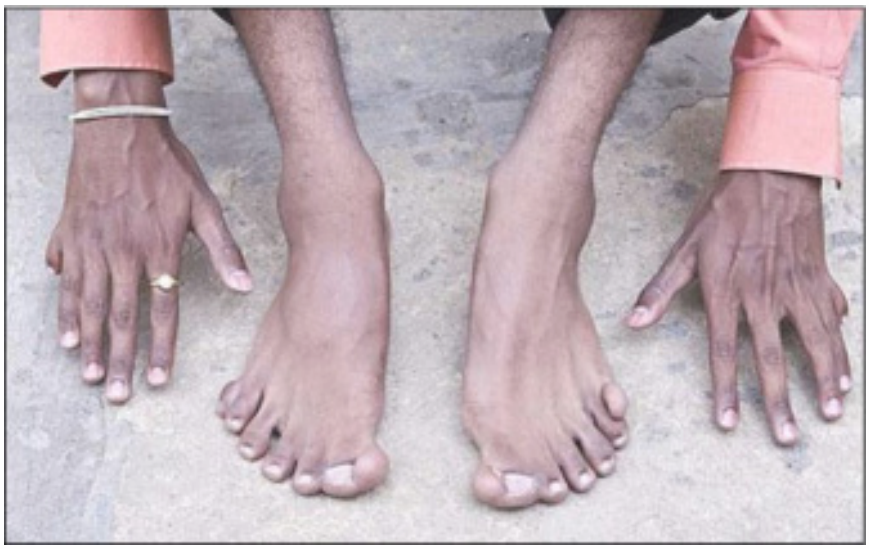


**Fig. 1.1: Polydactly showing extra fingers on hands and extra toes on the feet (source: handfacts.wordpress.com**

After a century, the French scientist Maupertuis through family studies described segregation of polydactyly and albinism (lack of pigmentation) in family members and suggested that these two characters are inherited following different patterns of inheritance. Further, based on animal breeding experiments he stated that both the parents contribute equally to the inheritance of traits to their offspring.

Later in 18th and early 19th centuries the inheritance of haemophilia, a bleeding disorder in which the affected individuals have continuous bleeding as their blood fails to clot when there is cut or injury and colour blindness, in which the affected individuals can not differentiate either red or green colours, was discovered. These two conditions showed high frequency of occurrence in males compared to females, a typical feature of X-linked inheritance. These initial observations of inherited characters in man prompted the concept of structural basis of heredity which was similar to the ideas suggested later by George Mendel through his laws of inheritance (Box 1.1).

**Box 1.1**

**Mendel's laws**

The two laws of heredity formulated by Gregor Mendel, based on his experiments with the garden pea plants are as follows:

1) Law of segregation (The "First Law"): It states that the members of a pair of homologous chromosomes segregate during meiosis and are distributed to different gametes.

2) Law of independent assortment (The "Second Law"): It states that each member of a pair of homologous chromosomes segregates during meiosis, independently of the members of other pairs, so that alleles carried on different chromosomes are distributed randomly to the gamets.

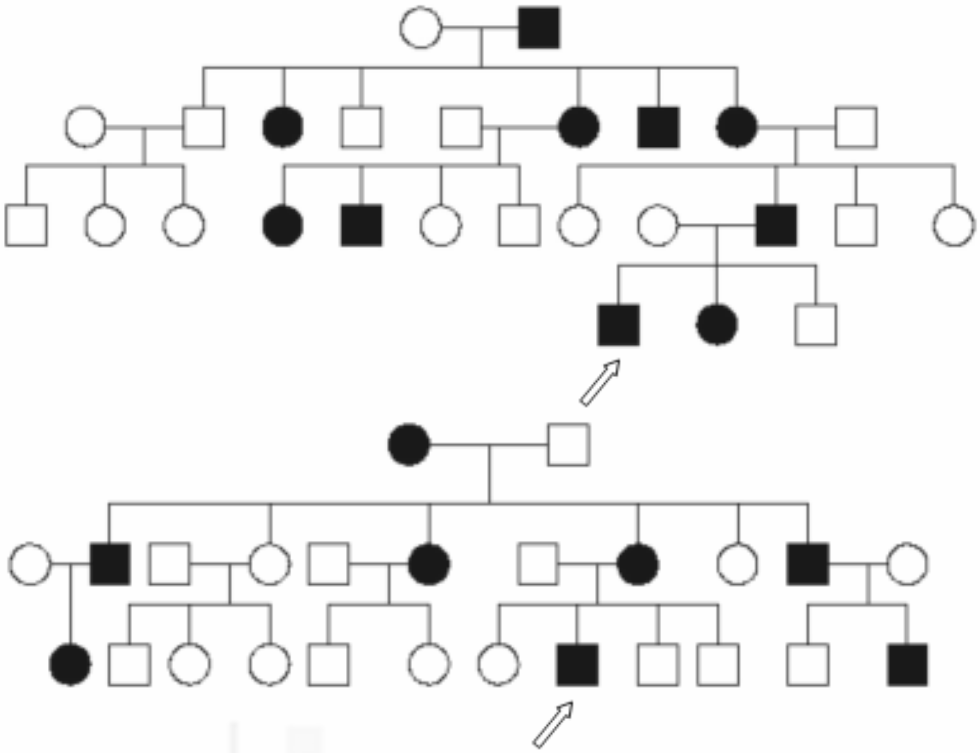
Understanding the principles of biology was possible in the later part of 19th century when the nature and functions of the building blocks of life "the cells" and the stages of cell division and formation of daughter cells were discovered. Sutton and Boveri in 1903 proposed independently the "chromosomal theory of inheritance". They drew one to one correlation between various stages of cell division leading to the formation of daughter cells and the segregation of characters from the parents to their offspring. They suggested that the hereditary factors (genes) are located on the chromosomes and are transmitted along with the chromosomes to the daughter cells.

## 1.1.1 Modes of Inheritance

### Autosomal dominant inheritance

### Characteristic features

Every affected individual has an affected parent; trait does not skips generation (vertical inheritance), both males and females are equally affected.

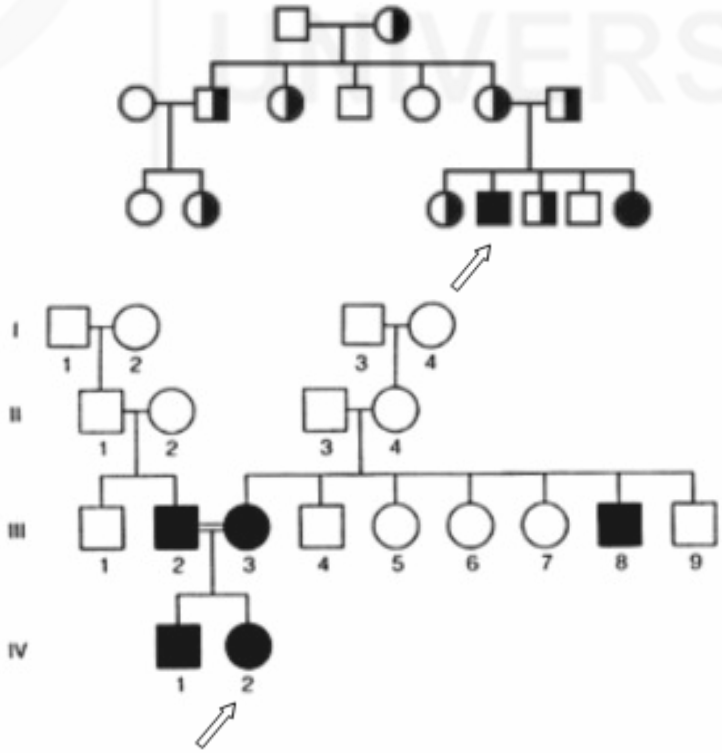


Examples: Huntington's chorea, Brachydactyly, Brown enamel, Hypercholesterolemia, Congenital cataract.

### Autosomal recessive inheritance

### Characteristic features

Parents of probands have normal phenotype but carry the mutant allele; both the sexes are equally affected; multiple sibs affected; increased incidence of parental consanguinity especially for rare case; pleiotropism observed; pseudodominance present when segregating in isolate groups.




Examples: All metabolic disorders, cystic fibrosis, some forms of congenital hearing impairment, retinitis pigmentosum (night blindness), corneal dystrophy, among others.

## X-linked inheritance

### Characteristic features

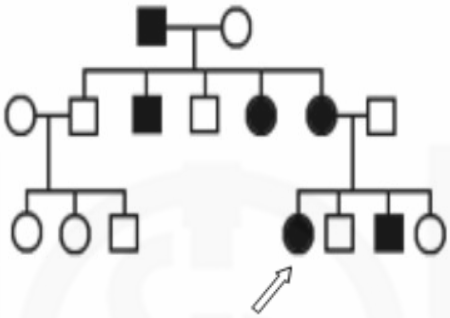
All the daughters of an affected male are affected; all sons and daughters of an affected woman will be affected.

Examples: Xg blood groups; Vitamin D resistant rickets; Rett's syndrome; Fragile X syndrome.

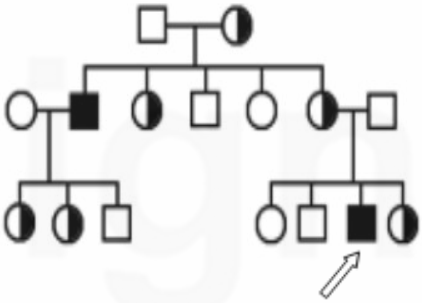
### Characteristic features of X-linked recessive inheritance

Absence of male to male transmission; gene in affected male is transmitted to his grandson through his daughter; criss-cross inheritance seen; 50% of sons of carrier woman are affected while 50% of daughters are carriers; when a male is affected the disease may be present in male relatives of his mother.

Examples: Colour blindness; haemophilia A and B; Duchenne and Becker's muscular dystrophies; G6PD deficiency; X-linked ichthyosis.



**X-linked dominant**



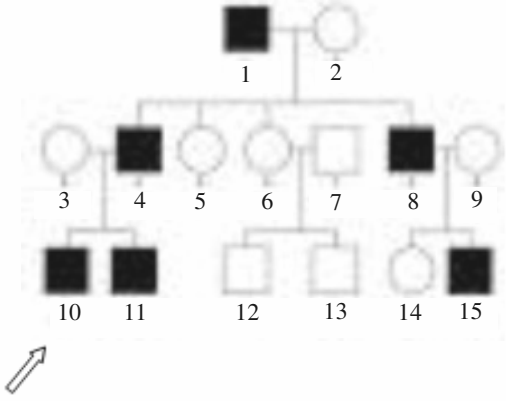
**X-linked recessive**

## Y-linked inheritance

### Characteristic features of Y-linked Inheritance

Y-linked genes are located on Y chromosome and are always transmitted from father to sons and not to daughters.

Examples: Male infertility (due to deletions in Y chromosome); Non-syndromic hearing impairment.



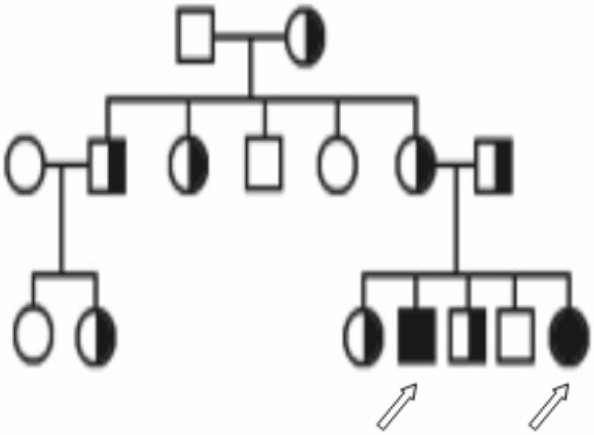

**Source: Desktopclass.com**

## Mitochondrial Inheritance

Characteristic features

The defect is transmitted to sons and daughters only through affected mothers; affected males do not transmit the disorder to his offspring.

Examples: Ptosis, neurological disorders, deafness and diabetes (DAD), Leber's hereditary optic neuropathy (LHON,Leigh syndrome, Myoclonic Epilepsy with Ragged Red Fibers.



The breakthrough in understanding the principles of biology was witnessed in the later part of 19th century when the nature and functions of the building blocks of life "the cells" and the stages of cell division and formation of daughter cells were discovered. At the same time plant and animal breeders tried to explain how the traits were passed on from the parents to their offspring. These studies and rediscovery of the propositions of laws of inheritance (Box 1.1) by George Mendel in 1900 motivated Sutton and Boveri in 1903 to propose independently the "Chromosomal Theory of Inheritance". They tried to draw one to one correlation between the stages of cell division leading to the formation of daughter cells and the segregations of characters from the parents to their offspring. They suggested that the hereditary factors or "genes" are located on the chromosomes and are transmitted along with the chromosomes to the daughter cells. This hypothesis helped in finding explanations to several other observations made in the following years.

The progress in the field of human genetics was rather slow because of 1) longer generation time (~30 yr) and 2) because unlike other animals, human matings cannot be performed at will. Therefore, human geneticists had to rely on the data collected from the already existing (retrospective) information on human pedigrees rather than plannnig prospective studies and following generations for the study of inheritance of the characters.

## 1.2 DEFINITION, SCOPE AND EMERGING TRENDS

Human genetics can be defined as a field of science that deals with the inheritance of traits that can be traced through generations. But the mechanisms governing the inheritance patterns are not simple always as they may sometimes involve interaction of genes with non-genetic and environmental factors as in the case of complex traits.

The growth of the field of human genetics witnessed several breakthroughs described under different branches of human genetics in the following. Development of advanced laboratory and analytical methods such as biostatistics and bioinformatics tools has helped in gaining more insights into the subject. The progress made in human genetics over the past fifty years has revolutionarised

the understanding of several concepts linked to health science, treatment of disease conditions, understanding the basic principles of biology, reasons for ethnic variations, evolution of living forms, including man, among others. Now it is being realized that almost every human disease has genetic basis and treating or managing any genetic condition is becoming more specific based on the genetic constitution of an individual. Thus the concepts of "personalised medicine" or "tailor made medicine" have been advanced.

## 1.3 BRANCHES OF HUMAN GENETICS

Like any other field, the subject of human genetics as it progressed led to the division into sub-specialties like cytogenetics, biochemical genetics, immunogenetics, pharmacogenetics, molecular genetics, somatic cell genetics, population genetics, genetic epidemiology, genomics and clinical genetics.

### 1.3.1 Cytogenetics

Cytogenetics can be defined as the study of chromosomes, the hereditary units. It has been an active field of research contributing to the understanding of organization of chromosomes and human genome. It is a discipline that matches phenotypes to detectable chromosomal abnormalities. In other words, you can correlate the abnormal changes occurring in the number (numerical aberrations like, monosomy, trisomy, nullisomy, triploidy) or structure (structural aberrations like chromosomal deletions, duplications, translocations and inversions) of chromosomes in an individual with the clinical features and symptoms (Table 1.1).

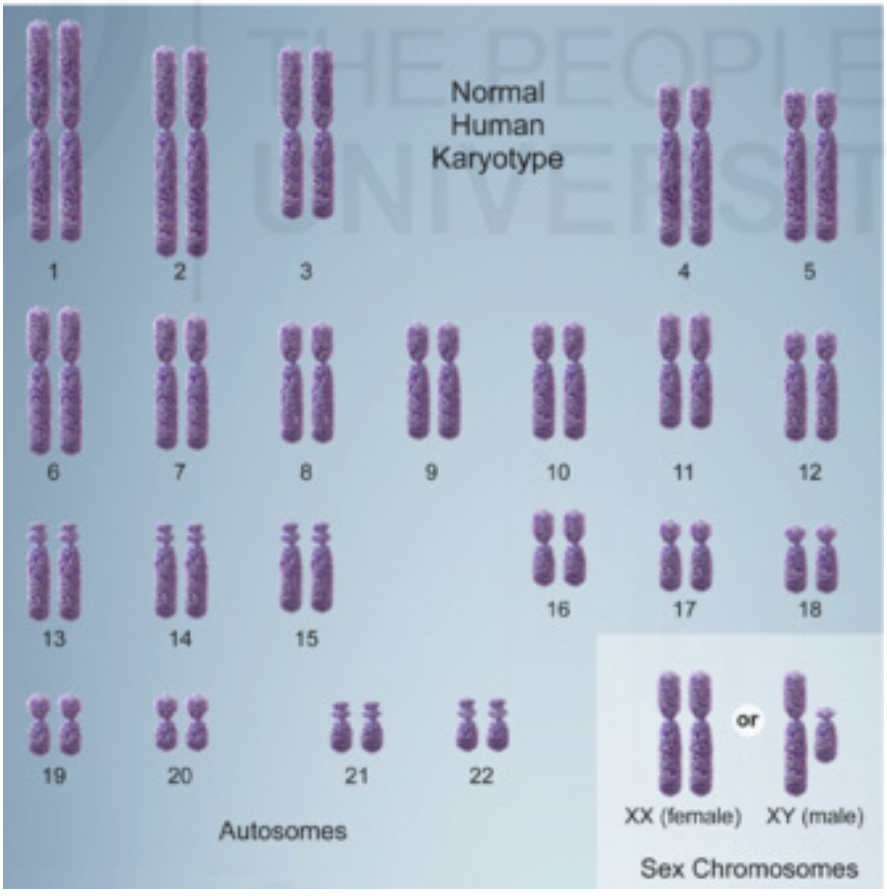
**Table 1.1: Common chromosomal aberrations in man and their clinical features**

| Chromosomal aberration | Chromosome complement | Clinical features |
|---|---|---|
| Down's syndrome | 47, trisomy 21 & t(21;13), t (21;14), t(21;15), t(21;22) | Mental retardation, moon face, simian crease, epicanthic fold. |
| Turner's syndrome | 45, XO | Female with short stature, webbed neck, infertility, swelling in the ankles and wrist. |
| Klinefelter's syndrome | 47, XXY | Male with tall stature, infertility, gynaecomastia (breast development). |
| Edward's syndrome | 47, trisomy 18 | Small face with micrognathia and a small chest. The ears are low set, overlapping fingers (clenched fist); digits 2 and 5 overlap 3 and 4. |
| Patau's syndrome | 47, trisomy 13 | Cleft lip, flexed fingers with polydactyly, ocular hypotelorism, bulbous nose, low-set and malformed ears, small abnormal skull, cerebral and cardiac malformation, microphthalmia, hypoplastic or absent ribs, visceral and genital anomalies. |
| Cri-du chat (Cat cry syndrome) | 46, deletion of 5p | Cry resembling that of a cat, flat face, receding chin, simian crease. |
| Philadelphia chromosome (Ph$^{-}$) | 46, deletion 21q & t (9;22) | Myeloid leukaemia. |

The foundation for cytogenetic studies was laid by the work of Arnold (1879) and Fleming (1882) who for the first time identified thread like structures called "chromosomes" during mitotic cell division by staining the preparations with certain dyes. In humans, the field of cytogenetics had its origin in the year 1956 when Tjio and Levan established the diploid chromosome number as 46. The preparation of human karyotype (Box 1.2) for the first time in 1959 led to the identification of numerical aberrations (changes in the number of chromosomes) in the following years associated with conditions like Down's syndrome (trisomy 21), Klinefelter's syndrome (XXY) and monosomy like Turner's syndrome (XO) which implied the need for routine screening for chromosomal anomalies in certain clinical conditions.

**Box 1.2**

Human body is composed of trillions of cells forming 200 different types of cells e.g. liver cells, brain cells, mucosal cells etc. Cells found in body parts are called somatic cells and cells found only in the gonads are referred to as germ cells. Each somatic cell comprises constant number of thread like structures called chromosomes that number 46, arranged in 23 pairs of which 22 pairs are autosomes and the remaining pair sex chromosomes. The autosomes and the sex chromosomes differ in their length, centromeric position and DNA content, among others. The homologous chromosomes of the sex chromosome pair are of the same type in females called X chromosomes while in males the pair of sex chromosomes comprises two different types of chromosomes referred as X and Y chromosomes. Thus, in the humans the normal chromosomal complement or karyotype in females is represented as 22, XX and in males as 22, XY.




Normal human karyotype with 22 pairs of autosomes and two X chromosomes in females and one X and Y chromosomes in males

In 1960 Moorehead and his colleagues published the chromosome preparations using short term lymphocyte cultures. Later Patau et al. and Edwards et al. reported trisomy 13 (Patau's syndrome) and trisomy 18 (Edward's syndrome), respectively, the affected infants showing congenital malformations. Nowell and Hungerford in the same year found deletion of chromosome 21, later referred to as Philadelphia chromosome (Ph$^{'}$), consistently in patients of chronic myelogenous leukaemia. This opened up new approach of screening for chromosmal variations such as deletions, duplications and translocations in patients with different types of tumors. Lejeune et al. (1963) reported a deletion syndrome called Cri-du-chat (cat cry syndrome). In the following years, Schroeder et al. (1964) and German et al. (1965) described chromosomal instability in conditions called Fanconi's anaemia and Bloom's syndrome, respectively. At the same time Jacobs and colleagues associated XYY chromosomal complement with criminal tendency.

The next significant breakthrough in human cytogenetics was the development of chromosomal banding techniques by Caspersson et al. (1968) who used quinacrine mustard to stain the chromosomes. This is referred to as quinacrine (Q) banding technique which yields fluorescent banding patterns that are specific for each chromosome. Thus, the technique permitted unequivocal identification of homologous human chromosomes of all autosomal pairs and sex chromosomes. Later other banding techniques such as giemsa (G) banding, reverse (R) banding, constitutive heterochromatin (C) banding and telomeric (T) banding were developed, of which G banding is most often used in clinical cytogenetic laboratories for diagnostic purposes. Further, studies of prometaphase chromosomes facilitated better identification of chromosomal variations with high resolution.

Later with the adoption of molecular biology techniques, especially the hybridisation technique, the field of cytogenetics transformed itself into the field of molecular cytogenetics. The discovery of DNA probes and their tagging with fluorescent dyes led to the development of a new technique called fluorescent *in situ* hybridisation (FISH) in early 1980s. This technique is used to detect and localize the presence or absence of specific DNA sequences on chromosomes to identify gain or loss of interstitial chromosomal regions such as microdeletions, duplications and several chromosomal structural changes that cannot be traced by the application of classical cytogenetic techniques. FISH can also be used to study interphase nuclei, cultured specimens and cells from specimens embedded in paraffin.

More recently the novel approach followed in molecular cytogenetics is the determination of overall genomic changes occurring in a given tissue by two types of comparative genomic hybridisation (CGH) techniques, referred to as metaphase CGH and array based CGH. These approaches enable the identification of copy number variations (CNV) in the genome with cells showing abnormal number of copies of DNA regions i.e. either deletions or duplications. These CNVs may show association with certain clinical conditions and help in diagnosis and risk prediction.

### 1.3.2 Biochemical Genetics

By definition, the field of bochemical genetics deals with the inheritance of genes that control the activity of an enzyme that catalyze the specific biochemical reaction in a metabolic pathway. When a gene becomes defective (due to

mutation), then a block is created in the biochemical pathways catalyzed by the particular enzyme. This leads to the accumulation of the product prior to the block and other reactions in the pathway will not proceed further. Sir Archibald Garrod, the father of biochemical genetics was the first to point out in 1902 that defects in the biochemical pathways can lead to inherited disorders like alkaptonuria, a rare condition in which urine of the patient turns black when exposed to atmospheric air; the black color being due to the accumulation of homogentisic acid caused by a block in the metabolic pathway of phenylalanine (Fig. 1.2). It is a harmless condition except that it causes arthritis in later life due to the accumulation of homogentisic acid in the joints. Garrod reported four families with eleven members affected and three of them were born to parents who were first cousins. It was later interpreted as an autosomal recessive condition and being rare is expected to show high incidence among offspring born to parents who are blood relatives (like cousins, uncle-niece and aunt-nephew). Parents who are cousins have greater chance of carrying the defective gene transmitted from their forefathers and both of them pass on the gene to their offspring who after receiving the defective gene in double dose (homozygous form) expresses the recessive disease.

The concept of genetic blocks in the metabolic pathways later received support by the proposition of "one-gene-one-enzyme hypothesis by three scientists namely, Avery, MacLeod and McCarty in 1944. Garrod also reported other genetic conditions called albinism, pentosuria and cystinuria arising due to defects in the respective metabolic pathways. The concept of gene controlling the activity of an enzyme involved in a biochemical pathway led to the detection of several inherited biochemical defects covering phenylalanine, amino acid, mucopolysaccharide, metal, carbohydrate, lipids, and purine and pyrimidine metabolisms. Each of these pathways may harbor several metabolic blocks leading to overlapping or distinct clinical conditions. For example, defects in phenylalanine metabolism may cause phenylketonuria, albinism, tyrosinosis and alkaptonuria (Fig. 1.2). In general, human metabolic disorders follow autosomal recessive pattern of inheritance, barring Hurler's syndrome and Lesch-Nyhan syndrome which follow sex linked recessive pattern.

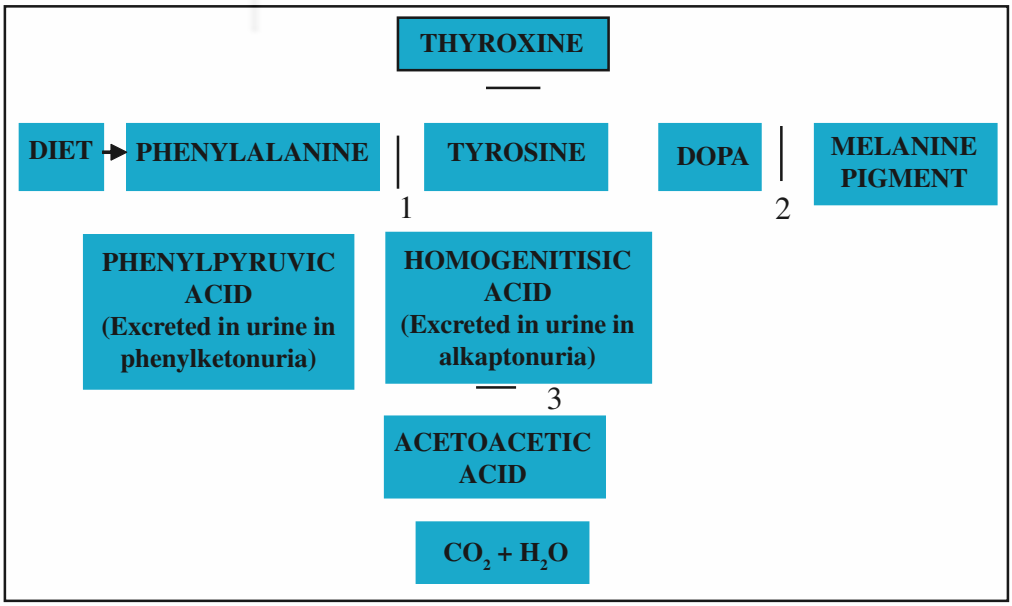



**Fig. 1.2: Diagram showing the sites of biochemical blocks in the pathway of phenylalanine metabolism. Metabolic blocks are indicated in red: 1- Phenylketonuria, 2- Albinism, 3- Alkaptonuria, 4- Congenital Thyroxine Deficiency (Cretinism)**

Another significant event in the history of human genetics was the discovery of sickle cell anaemia in which red blood cells in an affected individual become sickle shaped under reduced oxygen tension (Figs. 1.3 a, b). This disorder is inherited as a codominant condition along with normal haemoglobin. Pauling (1949) demonstrated change in elelectrophoretic pattern of sickle cell haemoglobin (HB S) implying chemical difference between normal (HB A) and mutant sickle haemoglobin . The cause of HB S was identified in 1957 by Ingram by protein fingerprinting as the substitution of glutamic acid by valine which are coded by the codon GAG and GTG, respectively.

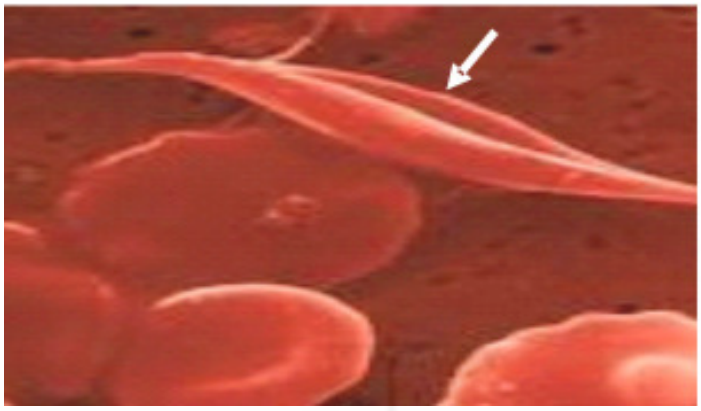


**Fig. 1.3a: Normal and sickle shaped red blood cells (indicated by arrow) (source: proargi.us).**

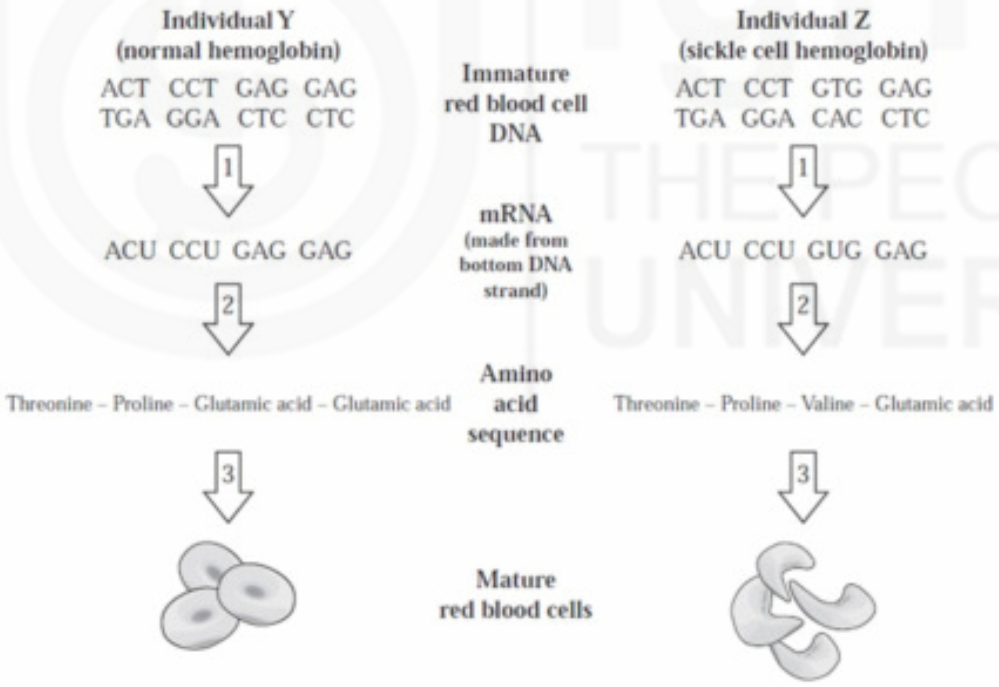



**Fig. 1.3b: Replacement of glutamic acid in the haemoglobin of normal individual (HB AA) by valine in the haemoglobin of sickle cell individual (HB SS).**

This was the beginning of identification of molecular basis for inherited diseases. Further, development of chromatography technique to check for the accumulated metabolites in urine and serum and gel electrophoresis for detecting polymorphic proteins and automated protein sequencing to identify abnormalities in the structure of serum and cellular proteins and enzymes enhanced the identification of several biochemical diseases with Mendelian inheritance.

### 1.3.3 Immunogenetics

Immunogenetics can be defined as the study that is concerned with the molecular and genetic basis of the immune response. The field of Immunogenetics has contributed a great deal in understanding certain disorders in recent times. You may say that the discovery of the ABO blood groups in 1900 by Landsteiner and the proof provided by von Dungern and Hirschfeld in 1911 that these blood groups are inherited formed the basis for the development of a separate field of immunogenetics in the following years.

The immune system consists of antigens and antibodies that distinguish self from nonself antigens. The immune reactions are highly specific and the antigens react only when they come in contact with specific antibodies and this specificity works like lock and key. ABO blood groups play an important role in blood transfusions because blood can be given from one person to other only when there is antigenic compatibility between the donor and recipient (Tables 2a,b).

**Table 1.2a: Determination of ABO blood groups, based on reaction to added antibodies**

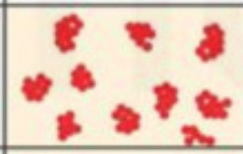
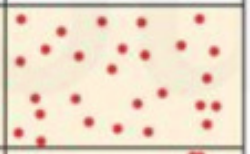
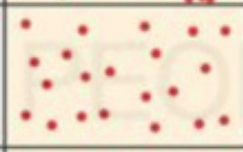
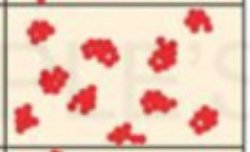
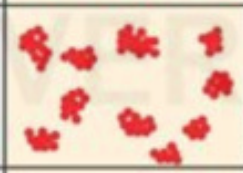
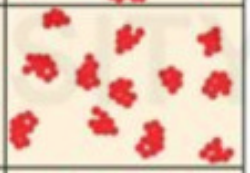
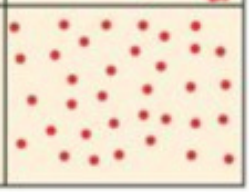
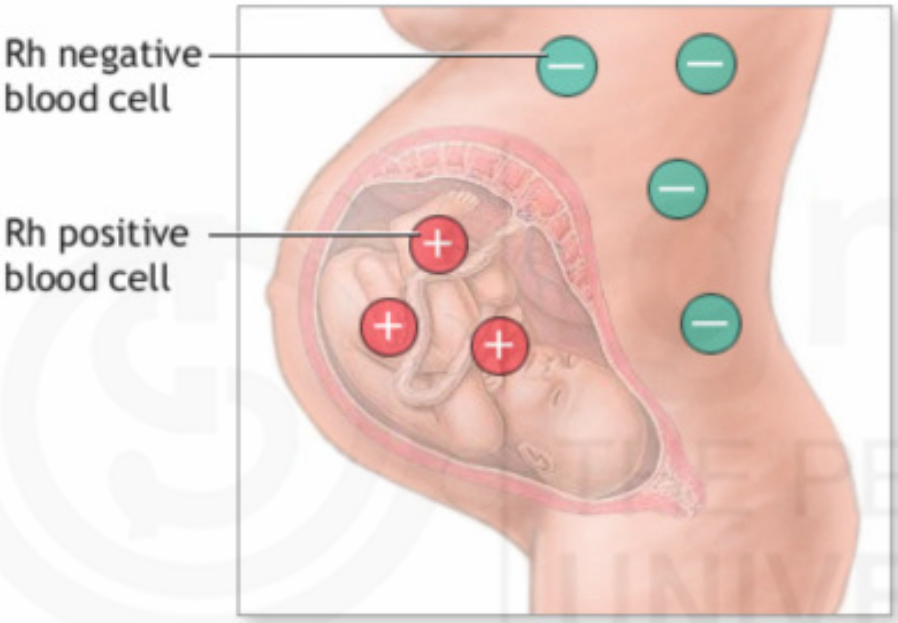
| Blood type of cells | Genotype | Antibodies made by body | Reaction to added antibodies | |
|---|---|---|---|---|
| | | | Anti-A | Anti-B |
| A | $I^AI^A$ or $I^Ai^O$ | Anti-B |  |  |
| B | $I^BI^B$ or $I^Bi^O$ | Anti-A |  |  |
| AB | $I^AI^B$ | Neither anti-A nor anti-B |  |  |
| O | $i^Oi^O$ | Both anti-A and anti-B |  |  |

**Table 1.2b: ABO blood groups that can be donated by the donors to the recipients**

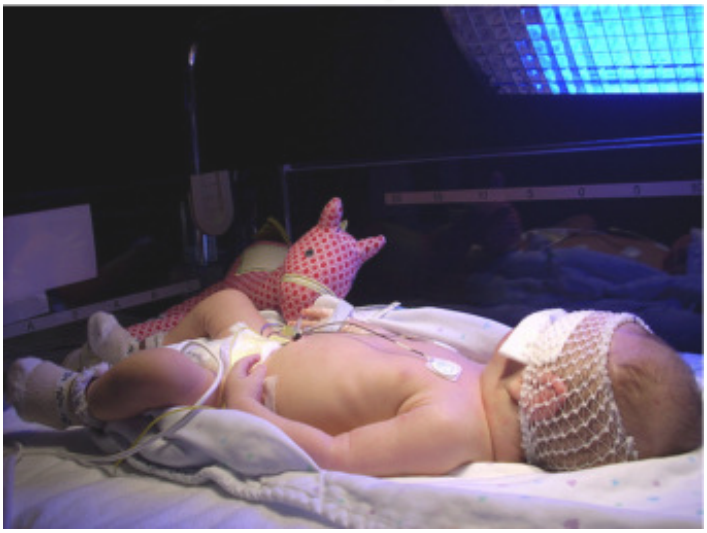
| Donor blood group | Recipient blood group | Possibility for transfusion |
|---|---|---|
| A | A and AB | Yes |
| A | B and O | No |
| B | B and AB | Yes |
| B | A and O | No |
| AB | AB | Yes |
| AB* | A, B and O | No |
| O** | A, B, AB and O | Yes |

* Universal recipient, ** Universal donor

Another blood group system important in transfusions is the Rh D blood groups which was discovered by the combined effort of Wiener, Levine and Landsteiner during the second world war. Blood of some wounded soldiers got agglutinated (clumped) when the antibodies raised in guinea pigs against the blood of rhesus monkeys was used. This means that the antigens reacting specifically with these antibodies are similar in man and the rhesus monkeys. The RH blood groups are important because they may cause haemolytic disease in the RH D+ babies born to RH D- mothers. This maternal fetal incompatibility leads to haemolytic anemia, jaundice resulting in premature birth and even death of the newborn. The affected offspring can be saved by giving exchange transfusion i.e. by slowly removing the blood from the infant on one side and replacing it with fresh RH D+ blood (Fig. 1.4, Table 1.3). In 1960 Clarke suggested a prophylactic (preventive) treatment which is being practiced now by administering anti-RH D antibodies just before delivery to RH D- mothers who are at risk.




**a) RH D - mother with RhH D + fetus (source: mifrah.com)**



**b) Exchange transfusion of blood given to a new born baby with haemolytic anaemia (source: pathologystudent.com)**

**Fig. 1.4: Haemolytic anaemia of the new born**

**Table 1.3: Maternal-fetal incompatibility for RH D blood group system**

| Father's blood group | Mother's blood group | Fetus blood group | Condition of the baby |
|---|---|---|---|
| RH D+ | RH D+ | RH D+ | Normal |
| RH D- | RH D+ | RH D+ | Normal |
| RH D- | RH D- | RH D- | Normal |
| RH D+ | RH D- | RH D+ | Haemolytic anaemia |

Similar to red cell antigens, leucocyte (white blood cell) antigens play an important role in kidney and other organ transplantations. The histocompatibility antigens (HLA) comprising HLA A, B, C, D and D loci with several hundred alleles at each locus have only two of these alleles (one derived from the father and another from the mother) present in an individual. Therefore, it is difficult to identify a donor with compatible genotypes for the HLA alleles that match with that of the recipient requiring organ transplantation.

Now many abnormalities of the immune mechanisms involving immunoglobulins, cellular immunity, complement and polymorphonuclear function are identified which form group of autoimmune disorders. Research conducted at varied levels using techniques like immuno precipitation, immunoelectrophoresis and hybridoma, among others, are expected to solve some of the problems of immune system disorders.

### 1.3.4 Pharmacogenetics

Pharmacogenetics is a growing field and is defined as the discipline that deals with inheritance of drug sensitivity in humans. The classical example that can be quoted is the sensitivity in humans to taste the chemical phenylthiocarbamide (PTC) or the related compound phenylthio- urea (PTU) which is inherited as an autosomal dominant trait. Individuals who can taste such compounds at micro levels are called tasters (about 70% of the population) and those who can not taste are called non-tasters (about 30% of the population). Thus the ability to taste PTC is considered to be dominant over the non-tasting of it. The non-tasters are found to be at higher risk for developing the condition called gout.

Another classical example that fits into pharmacogenetics is the sensitivity of G6PD (glucose-6-phosphate dehydrogenase) enzyme deficient individuals to anti-malarial and several other drugs including those with naphthalene component. WHO has listed the chemicals or drugs to which the G6PD deficient individuals are sensitive. G6PD deficiency is an X-linked recessive condition and leads to haemolytic anaemia and death when deficient individuals are exposed to anti-malarial and other drugs. Several other situations that can be considered under pharmacogenetics are now known and correlating them with genome sequence (nucleotide sequence) in an individual may provide more information about the reasons for sensitivity and variations caused among individuals.

### 1.3.5 Molecular Genetics

Molecular Genetics can be defined as the field that deals with any genetic condition that occurs due to changes in the nucleotide sequence of DNA representing a gene. Such conditions are identified by applying molecular biology

tools. Study of genetic diseases at molecular or DNA level has been accelerated in mid 1970s after the development of recombinant DNA technolgy in which a normal or desired gene sequence is introduced into the genome of a vector (virus, liposomes etc., that act as carriers of introduced DNA sequence/gene) and the recombinant molecule with the vector and introduced gene sequence is multiplied inside a host, mostly a bacterium or artifial chromosomes of yeast (YACs), bacteria (BACs) or of mammals (MACs).

The first human gene to be cloned and completely seuqenced was the beta globin gene of haemoglobin. Now hundreds of genes are cloned that help in the treatment of diseases (e.g. human insulin used to treat diabetes mellitus). Further rapid growth of sensitive techniques enabled manipulation of DNA, RNA and proteins which touched every aspect of human genetics, especially clinical diagnosis and treatment aspects.

The development of several thousands of polymorphic markers (Box 1.3), has helped a great deal to identify the risk causing genes and their use in preclinical/ presymptomatic diagnosis. If the extent of risk is known, one can try to prevent or delay the onset of fatal compliactions associated with the disease condition like in diabetes or hypetension that are associated with heart attack, kidney failure and retinal damage, among others.

**Box 1.3**

**Genetic Polymorphisms**

The proteins and enzymes are encoded by genes with stretches of DNA having hundreds/thousands of nucleotide base pairs. Alteration/mutation of even a single nucleotide in the stretch can affect structure and function of the encoded protein/enzyme. The mutations occurring in the same gene sequence represent the alleles. When such alleles exist more frequently in a given normal/patient population, they are referred as polymorphic alleles.. Polymorphism is defind as the occurrence of two or more alleles of a gene in a population such that frequency of the rarest of the alleles is =1.0%. In a given individual only two of the alleles can be present, one inherited from the father and other from the mother). Thus differences or variations between individuals in a population are found based on the combination of alleles they possess. If a gene has four alleles, individuals with ten different allelic combinations are expected. Red cell antigen polymorphisms (like ABO, RH D blood groups), leucocyte antigen polymorphisms (HLA system), serum protein polymorphisms (like HP, TF),, red cell enzyme polymorphisms (like PGM, AK) and DNA polymorphisms (like, restriction fragment length polymorphisms (RFLPs), variable number of tandem repeats (VNTRs), di and tri nucleotide polymorphisms and single nucleotide polymorphisms (SNPs)) represent polymorphic genetic systems in man.

Molecular biology techniques are being used extensively to map genes to specific chromosomal regions; understand the clustering of SNPs on a homologue as a group (i.e. haplotypes); linkage disequilibrium (i.e. non random association of genes/markers present on same or different chromosomes), epistatic or non allelic interaction between genetic loci influencing severity of diseases, exploring population diversity in terms of genic/allelic distribution; to predict risk of a disease in association with genetic marker/ environmental/ epidemiological factors.

Since molecular analysis generates huge data, improved analytical biometric and bioinformatics tools were developed to draw reliable inferences. Generation of super computers is expected to simpilfy the study of differences between individuals for several thousands of SNPs that helps to understand mainly the population diveristy, origin of races and communities and also evaluation of drug effects on disease and drug designing, among others.

### 1.3.6 Somatic Cell Genetics

Somatic cell genetics can be defined as the branch of genetics that deals with fusion of somatic cells of different species to conduct genetic studies by testing the hybrid cells. The introduction of somatic cell genetics in 1960s was a major breakthrough as the technology bypasses the need to wait for next generation (~20-25 yr of generation time) to trace the inheritance of traits from parents to the offspring. The technology in few weeks can help identifying mutations, detecting inheritance patterns, mapping genes to specific chromosomal regions using panel of hybrid cells and molecular markers.

Barski et al. (1960) were the first to demonstrate spontaneous fusion of two different but related tumor cells. Ephrussi et al. (1961) showed that large genetic differences did not affect the cell fusions. Littlefield (1964) used HAT Medium with hypoxanthine, aminopterine and thymidine- which selects the hybrid cells from other cells in culture. The two mutant genes located at two different loci complement with each other in hybrid cells which grow in the minimal medium. Later Ephrussi and Weiss in 1965 fused mouse and rat cells for the first time indicating that interspecific barrier does not affect cell fusions. In the same year Okada, Harris and Watkin enhanced the frequency of cell fusions by adding inactivated Sendai virus to the cell cultures. Later several chemicals were also tried and of them polyethylene glycol (PEG) gave good results. Use of Sendai virus, PEG and HAT medium together yields greater success in somatic cell fusions.

### 1.3.7 Population Genetics

A population can be defined as a group of interbreeding individuals and their offspring. Population genetics deals with frequencies of different alleles in different groups of populations and exploration of mechanisms causing genetic diversity between them. The primary generalization of population genetics was first focused by Penrose in 1904 which was clearly formulated by Hardy, a British mathematician, and Weinberg, a German medical doctor, in 1908. They independently set out the fundamental theorem of population genetics popularly known as Hardy-Weinberg Law (equilibrium) which states that the gene and genotypic frequencies remain constant through generations in a large random mating population in the absence of natural selection, genetic drift, mutation and migration. The data pertaining to any study on polymorphism is tested for deviations from the equilibrium and when significant deviations are observed proper explanations are sought for. Weinberg also studied Mendelian inheritance in small pedigrees and by analysis of twins reared,apart, suggested methods for resolving bias ascertainment of recessive inheritance. Haldane too developed statistical tests to deal with biased human data. He in 1919 formulated the relation between recombination frequency and linkage map distance and coined the term centimorgan. In 1925, Bernstein through family studies identified multiple allelic inheritance for ABO blood groups. Around 1930-32 Haldane, Fisher and Wright

established the principles of population genetics. In 1935 Haldane determined the spontaneous mutation rates of a human gene. After two decades, in 1955 Morton developed lod score method to determine linkage between two loci using likelihood ratio method. Today genetic analysis of any condition is carried out at population level to understand the distribution and dynamics of the genes studied in those populations.

With the realization of the importance of population studies in genetics, another field i.e. genetic epidemiology emerged that uses advanced analytical tools. Genetic epidemiology deals with knowledge on prevalence of a condition/disease, modes of inheritance, heterogeneity and mutation rates of hereditary diseases. In 1940s and 1950s, T. Kemp's institute from Copenhagen, J.V. Neel's institute from Michigan, A.C. Stevenson's from North Ireland contributed a great deal to the understanding of genetic epidemiology. In recent years, complex analysis of common diseases like diabetes, hypertension, coronary artery disease and neurological and affective disorders is being carried out to predict risk for a condition based on its association with epidemiological parameters and genes implicated in its etiology.

### 1.3.8 Genomics

Genomics can be defined as the structural and functional studies of genome that represents the total content of DNA within an organism or cell, including nuclear and mitochondrial DNA. The human genome comprises of 3.2 billion nucleotides and about 20,000 genes along with spaces between them. Under Human Genome Project (HGP) entire DNA in human genome was sequenced in April 2003. The sequence derived is being annotated to obtain complete map of human genome. The organization of the human genome that has coding and non-coding sequences, unique and repeated sequences, etc., is shown in the flow diagram (Fig. 1.5).

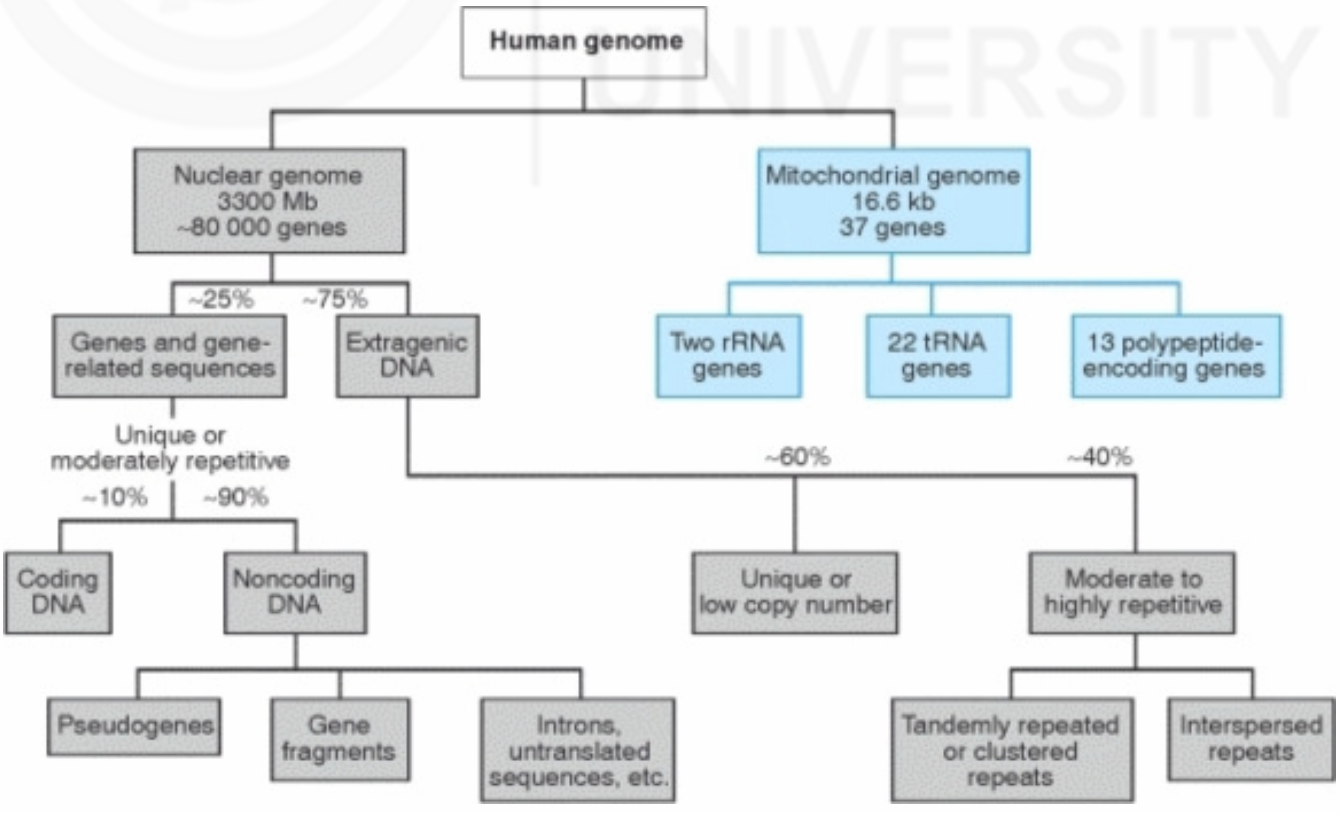



**Fig. 1.5: Organisation of Human Genome**

### 1.3.9 Clinical Genetics

Clinical genetics can be defined as the branch of genetics that deals with evaluation of genetic involvement in a disease/disorder and its treatment and management. Three cardinal principles viz. genetic heterogeneity, pleiotropism and variability should be essentially observed in the practice of clinical genetics. In simple terms, genetic heterogeneity can be defined as occurrence of one and the same or nearly the same phenotype having different modes of inheritance. This naturally has different implication in genetic counseling.

Pleiotropism is defined as multiple end effects of the same gene and in some conditions may result in a syndrome. A syndrome is defined as a collection of symptoms arising due to a single gene defect. Pleiotropism is important to clinical medicine because certain of the multiple effects of a given gene may provide valuable clues in the diagnosis of serious internal diseases. Variability in the expression of any disease is another important factor in clinical medicine. If the expression of the condition is mild, the presence of the mutant gene can not be recognized by the phenotypic appearance. In such cases the gene is said to be non penetrant and such an individual, when present in a family the pedigree, shows irregular dominant pattern of inheritance. Dominant genes are often associated with penetrance while recessive genes are often associated with varied expression of the condition.

#### 1.3.9.1 Genetic Diagnosis

Genetic diagnosis can be defined as the determination of genetic cause underlying a disease/disorder. Genetic diagnosis is carried out at chromosomal and gene level including pedigree analysis, screening for known mutations using biochemical, immunological and molecular markers. Other diagnostic tools include ultrasound, X-rays, magnetic resonance imaging (MRI), echocardiograms, angiograms etc. Simple investigations using blood biochemistry may become useful in confirming the diagnosis like estimation of blood sugar levels in diabetes.

For certain conditions like birth defects and malformations (spina bifida, anencephaly, cleft lip, skeletal abnormalities and some syndromes) prenatal diagnosis even before the birth of the offspring can be performed through ultrasound, fetoscopy and measurement of serum alpha protein levels etc. Screening for metabolic defects like phenylketonuria and galactosaemia etc. and mutations in genes causing congenital defects like in certain cases of blindness and deaf mutism can also be performed using amniotic fluid and fetal cells. By culturing foetal cells and chorionic villi it is possible to diagnose the chromosomal disorders at early stage of pregnancy (4-16 weeks) and terminate the same, if needed.

Genetic diagnosis can also be performed in the adult population using molecular and other diagnostic tests as in prospective cases of Huntigton's disease, myotonic dystrophy and lipedemias etc. which are expressed in later years of life. Screening of populations for carriers of the genetic cases is recommended to identify persons at risk so that steps for proper management can be adopted.

#### 1.3.9.2 Management of Genetic Conditions

Once the genetic diagnosis is available, one can look for the prognosis for improving quality of patient's life by using proper treatment. There are various

methods of treating genetic disorders right from using planned diet, supplementation of missing gene products, use of vaccinations, antibiotics and drugs and surgical interventions etc. If this is not possible then extent of risks for complication in the patient and recurrence of the condition in relatives can be estimated. This preventive strategy is important to reduce the occurrence of the condition in the population and burden to the society at large.

Advanced technologies like gene therapy that involves replacement of defective gene with normal gene sequence, use of embryonic and adult stem cells to regenerate the damaged tissues or organs (such as damaged heart muscles), use of nano particles to deliver efficiently the normal genes or drugs to the target sites are the most recent approaches that have revolutionarised the practice of clinical genetics

## 1.4 SUMMARY

Human genetics is a branch of science that deals with the inheritance of characters (traits) and diseases/disorders through generations from parents to offspring. Genetic diseases may be caused by numerical or structural chromosomal abnormalities (like trisomies, monosomies, translocations, deletions, duplications and inversions) due to mutations or variations in DNA. These may follow autosomal dominant, autosomal recessive, X-linked dominant, X-linked recessive or mitochondrial (maternal) pattern of inheritance. Genes sometimes interact with demographic and environmental factors and thus cause difficulty in interpreting the mode of inheritance.

The dedicated work of scientists in the past led to the steady growth of the subject of human genetics. Biochemical defects, mutations in DNA sequence, differences in immune responses and abnormal chromosome complements were identified as reasons for several diseases/ disorders. This led to the subdivision of the subject of human genetics into branches like cytogenetics, biochemical genetics, immunogenetics, pharmacogenetics, molecular genetics, somatic cell genetics, population genetics, genomics, clinical genetics, genetic diagnosis and counseling. Rapid progress in the subject, especially during the past five decades, has opened several avenues for improving quality of human health and thereby longevity. Today, differences between the individuals can be identified at single nucleotide level and based on this information specific drugs can be used for treatment to suit the genetic makeup of the individual.

**Suggested Readings**

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Strachan, T. and Read, A. P.2004. *Human Molecular Genetics*, 3rd edition. New York: Garland Science.

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**Glossary**

| | | |
|---|---|---|
| Allele | : | Alternative form of a gene at a locus, each of which is a viable DNA sequence occupying a given position, or locus on a chromosome. |
| Autosome | : | A chromosome not involved in sex determination. |
| Chromosomal theory of inheritance | : | The chromosomal theory of inheritance is the idea that genes, the units of heredity, are physical in nature and are found in the chromosomes. |
| Consanguinity | : | Consanguineous individuals have at least one common ancestor in the preceding few generations. |
| Deoxyribose nucleic acid (DNA) | : | DNA is a double-stranded molecule that encodes genetic information. |
| Domianant gene | : | Alleles that determine the phenotype displayed in a heterozygote with another (recessive) allele. |
| Empiric risk | : | The chance that a disease will occur in a family based upon experience (past history, medical records, etc.) rather than theory. |
| Epistasis | : | A circumstance where the expression of one gene is affected by the expression of one or more independently inherited genes. |
| Expresivity | : | A term used in genetics to refer to variations in a phenotype among individuals carrying a particular genotype. |
| Gene | : | The fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule). |
| Genetic counseling | : | The educational process that helps individuals, couples, or families to understand genetic information and issues that may have an impact on them. |
| Genome | : | All the genetic material in the chromosomes of a particular organism; its size is generally given as its total number of base pairs. |
| Genomics | : | Refers to the study of the entire genome of an organism. |

| | | |
|---|---|---|
| Genotype | : | Genetic constitution of an individual |
| Heterozygote | : | An individual having two different alleles at a locus in a pair of homologous chromosomes. |
| Heterozygote detection | : | Identification of genetic carriers for a given trait. |
| Homozygote | : | An individual having two identical alleles at a locus in a pair of homologous chromosomes. |
| Hardy–Weinberg equilibrium (HWE) | : | HWE states that both allele and genotype frequencies in a population remain constant, that is, they are in equilibrium from generation to generation unless specific disturbing influences such as drift, mutation, selection, among others, are introduced. |
| Idiogram | : | A diagrammatic representation of a karyotype showing the number, relative sizes, and morphologic characteristics of the chromosomes of a species, individual, or cell. |
| Inbreeding coefficient | : | The probability that the two genes present at a locus in an individual are identical by descent. |
| Incomplete dominance | : | A form of intermediate inheritance in which one allele for a specific trait is not completely dominant over the other allele. This results in a combined phenotype. |
| Karyotype | : | Arrangement of chromosomes according to their size (from largest to smallest), position of centromere and banding patterns (to identify homologous pairs). |
| Locus | : | Site for the location of genes on a chromosome. |
| Multifactorial condition: | | A characteristic influenced in its expression by many factors, both genetic and environmental. |
| Mutation | : | Process by which genes undergo a structural change or any heritable change in DNA sequence. |
| Nucleotide | : | A subunit of DNA or RNA consisting of a nitrogenous base (adenine, guanine, thymine, or cytosine in DNA; adenine, guanine, uracil, or cytosine in RNA), a phosphate molecule, and a pentose sugar molecule (deoxyribose in DNA and ribose in RNA). |
| Pedigree | : | A genetic representation of a family tree that diagrams the inheritance of a trait or disease though several generations. |
| Penetrance | : | The proportion of individuals carrying a particular variant of a gene (allele or genotype) that also express an associated trait (phenotype). |
| Phenotype | : | Observable characteristics of an organism produced by the organism's genotype interacting with the environment. |

| | | |
|---|---|---|
| Pleiotropism | : | A single gene affects a number of phenotypic traits in the same organism. |
| Polymorphism | : | Genetic variations in DNA sequence occurring in =1% of a population. |
| Prenatal diagnosis | : | Testing performed during pregnancy to determine if a fetus is affected with a particular disorder. |
| Recessive gene | : | A gene that is phenotypically manifest in the homozygous state but is masked in the presence of a dominant allele. |
| RNA | : | One of the two types of nucleic acids and a single stranded molecule found in all cells which transmits genetic information from DNA to proteins produced by the cell. |
| Sex chromosomes | : | The X and Y chromosomes in human beings that determine the sex of an individual. Females have two X chromosomes in diploid cells; males have an X and a Y chromosome. |
| Stem cells | : | A stem cell is a cell with the potential to form many of the different cell types found in the body. |
| Ultrasound | : | The visualization of deep structures of the body by recording the reflections of echoes of pulses of ultrasonic waves directed into the tissues. |
| X-linked dominant | : | Describes a dominant trait or disorder caused by a mutation in a gene on the X chromosome. |
| X-linked recessive gene | : | A mutation in a gene on the X chromosome that causes the phenotype to be expressed in males who are hemizygous for the gene mutation (i.e., they have only one X chromosome) and in females who are homozygous for the gene mutation (i.e., they have a copy of the gene mutation on each of their two X chromosomes). |

**Sample Questions**

1) Define human genetics? Briefly discuss the different branches of human genetics.
2) Define the following terms

   a) Human genetics, b) Genomics, c) Polymorphism and d) Pharmacogenetics.
3) What do you understand by somatic cell genetics? Mention its applications.
4) What is meant by Hardy-Weinberg equilibrium? Define.
5) What are cardinal features to be observed while practicing clinical genetics and why?
6) Briefly describe the terms a) Gene therapy and b) Genetic counseling.
7) Describe briefly the organization of human genome.
8) What do you understand by polymorphism? Explain.

# UNIT 2 BIOLOGICAL BASIS OF HUMAN HEREDITY

**Contents**



**Learning Objectives**

After reading this unit, you will be able to:

- understand cell, its structure and other cellular components;
- discuss mitotic and meiotic cellular divisions and the differences between them; and
- explain the genetic basis of human variation.

## 2.1 INTRODUCTION

Earlier biologists and geneticists viewed heredity and inheritance in a different way, some of which are presented here to widen your understanding in this unit. Galton's theory of blending inheritance states that the hereditary characteristics of the parents are irreversibly mixed in the progeny. Weismann (1892) put forth his theory of germplasm inheritance according to which germplasm was considered immortal and formed the bridge of life passing from generation to generation. The blood theory of inheritance states that blood acts as a vehicle for the transmission of characters from parents to offspring. All these views have been rendered void after Mendel's discovery of laws of inheritance. Currently, the principle of chromosomal theory of inheritance is the valid concept to understand heredity.

> Hereditary mechanisms keep populations similar and stable from generation to generation. But we know populations do change over time. Such changes may be understood by studying the factors that alter the hereditary mechanisms of populations.
>
> William C. Boyd

## 2.2 ORGANIZATION OF VARIOUS CELLULAR COMPONENTS

### Historical Background

Robert Hook (1665) observed the cell for the first time with the help of his primitive microscope. The material that he observed was a piece of cork. This structure of cell is now known as the unit of life. There is really no **'**typical**'** cell in which we can see all the features of the cell. Living things are composed of material structural units called cells. A cell is the fundamental unit of structure and function in an organism. It is that unit of organism which is delimited by plasma membrane and is capable of self-reproduction (Loewy and Siekevitz, 1963). Sir Frederick Gowland Hopkins called cells as theaters of life. All cells carry out the same biological function. They perform metabolic and reproductive functions and maintain cellular integrity for our life. Cells combine to form colonies (Functional Association) and form tissues (Facultative Association).

### Cell Theory

The cell theory is a concept proposed by Schwann and Schleiden (1838-39) and Rudolf Virchow (1858). This theory states that:

All organisms are made up of cells.

Cells are organisms.

Cells arise from pre-existing cells.

The activities of organisms are the outcome of individual cells.

### Cell Types

Living organisms on earth provide us high degree of cellular diversity in reference to cell types. There are two principle cell types' namely unicellular simple prokaryotes and multi cellular complex eukaryotes. The former shows the absence of well-organized nucleus and nuclear membrane and the latter shows the presence of them. The examples of prokaryotes (e.g. bacterial cell) and of eukaryotes (e.g. human) are listed below:

Reproductive cells e.g. sperm, egg.

Somatic cells e.g. nerve cells.

Intestinal cells e.g. mucosa.

Columnar epithelial cells e.g. gut.

Goblet cells e.g. lumen of gut.

Connective tissue cells e.g. collagen fibre.

Muscle cells e.g. smooth muscle cell.

Unicellular organisms e.g. amoeba.

Prokaryotic cell e.g. bacterium.

Eukaryotic plant cell e.g. onion peel cell.

Eukaryotic cell e.g. human cheek epithetical.

## Cell Structure

The cell consists of three principle components. They are: 1) Plasma membrane 2) Cytoplasm and 3) Nucleus, and all of them are combinely known as protoplasm. The nucleus controls all the activities of the cell (Fig. 2.1). Besides this, the cytoplasm possesses many organelles and inclusions. For example, endoplasmic reticulum and mitochondrion are organelles while vacuoles and vesicles are inclusions. The cell has two types of membranes: 1) cytoplasmic membrane which regulates internal environment and 2) internal membrane which encloses organelles and perform metabolic functions such as mitochondrial ATP synthesis. There are many organelles present inside the cell. The nucleus and chromosomes take active part in the hereditary transmission of characters so we will examine them in greater detail in the following.

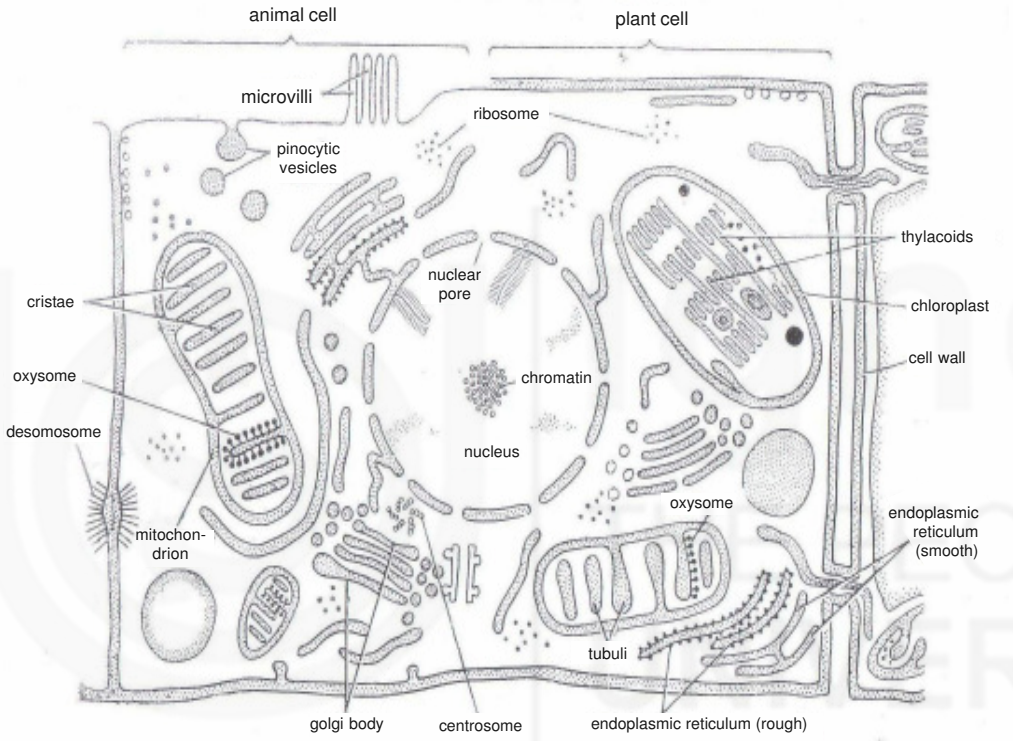



**Fig 2.1: Diagrammatic representation of cell structure showing differences in animal and plant cells (Source: Gupta (1974).**

## The Nucleus

Nucleus is the most vital part of the cell. It controls all the activities of cell and can be called as manager of the cellular factory. It was first discovered by Robert Brown in 1831. It is defined as any formation surrounded by cytoplasm from which chromosomes arise during cell division. Nucleus is present in all cells. However, it is absent in human red blood corpuscles (RBC) and in some lens cells.

The nucleus is bounded by a double layer of membranes called nuclear membrane. A thread like material can be seen within nucleus called chromatin which consists of DNA and proteins. The nucleus is filled with a transparent substance called nuclear sap in which nucleolus and chromatin threads remain enclosed.

The nucleus consists of nucleolus proteins and nucleic acids. The nucleic acids are of two types - DNA (deoxyribonucleic acid and RNA (ribonucleic acid). DNA is present in chromatin network and RNA is present in nucleolus.

The most significant role of the nucleus is to store and transmit hereditary information from generation to generation of cells.

## The Chromosomes

Chromosomes are self-reproducing thread like structures located inside the nucleus. The word chromosome (chromo = colour, soma = body) means coloured bodies. They can be easily stained with dyes. Hofmeister in 1848 discovered chromosomes. They are the vehicles of heredity and serve as our horoscope. The chromosome number varies from species to species. But it remains constant between the members of the same species.

Humans have 46 chromosomes in 23 pairs: 22 pairs are called autosomes and one pair is the sex chromosomes X and Y. These chromosomes are divided into 7 (A-G) groups as per Denver- London System of classification. From cytogenetic point of view, males are characterized by (22 autosomes + XY) and females are characterized by 22 autosomes + XX. The presence of barr body is characteristic of females and sex determination in humans. Males with 22 autosomes + XY are heterogametic producing two types of gametes, while females with 22 autosomes + XX are homogametic producing one type of gamete (Fig. 2.2).

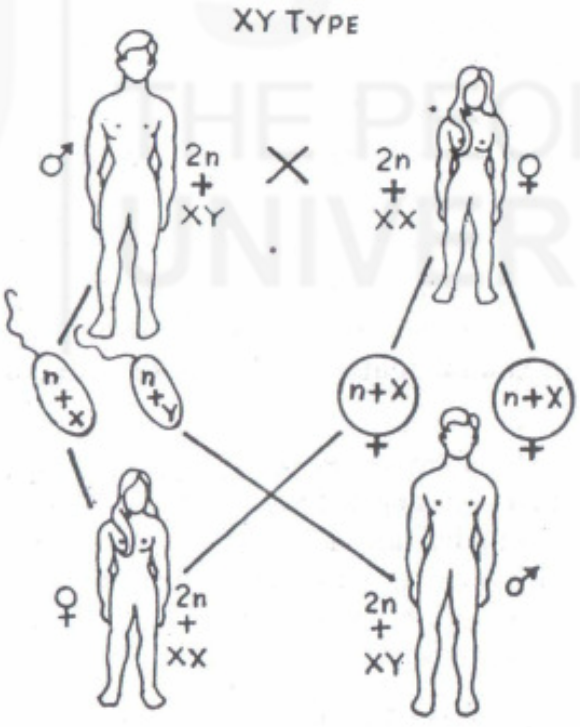



**Fig. 2.2: Sex determination (Source: Sabanayagam, 1990).**

The principle of chromosomal basis of hereditary transmission clearly states that genes we have with their unique features form an integral part of the chromosome of each cell. Sexual reproduction mediates the transmission of chromosomes (genes) from generation to generation. The chromosomal

constitution of an individual, a species or race is called karyotype which is an arrangement of chromosomes according to their size and position of centromere.

There are 4 types of chromosomes (Fig.2.3): metacentric, sub-metacentric, acrocentric (with satellites), acrocentric (without satellites) and telocentric (absent in man). However, acentric chromosomes without centromere can also be found.

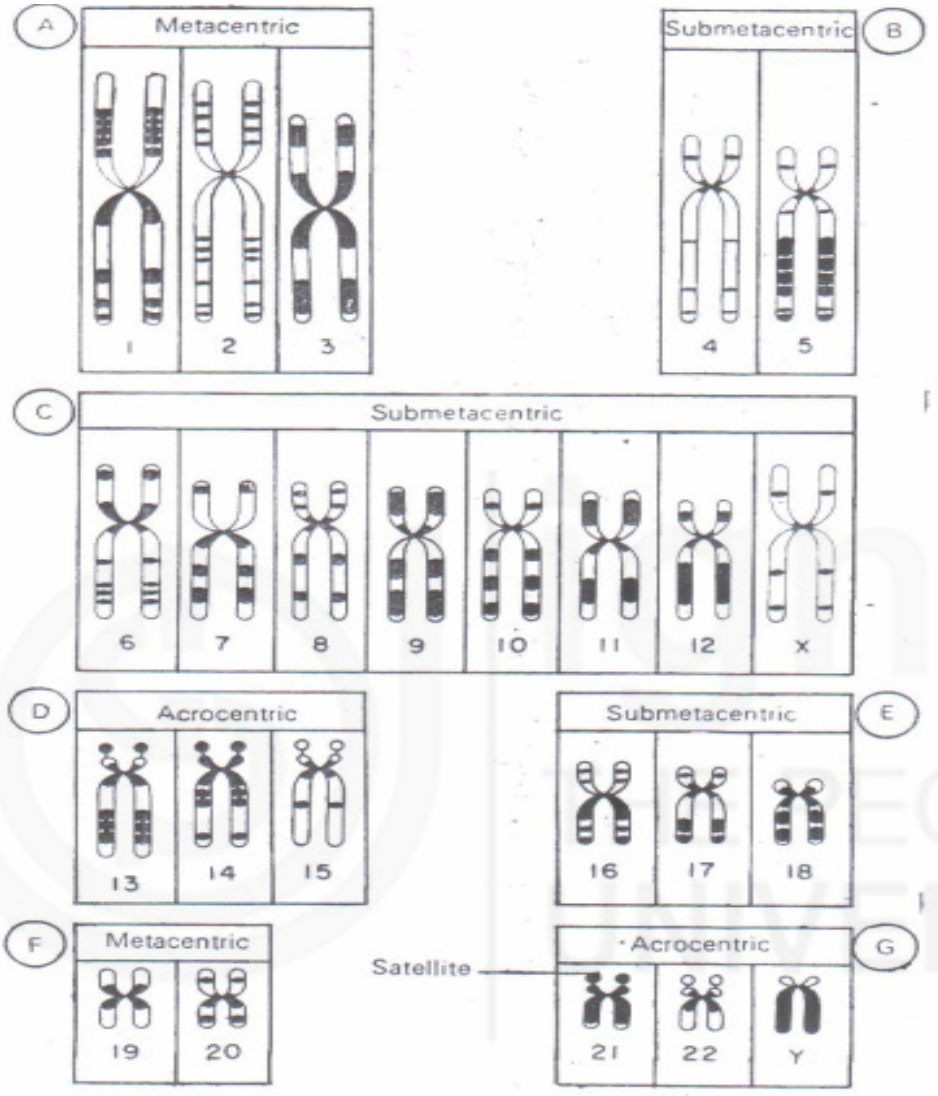
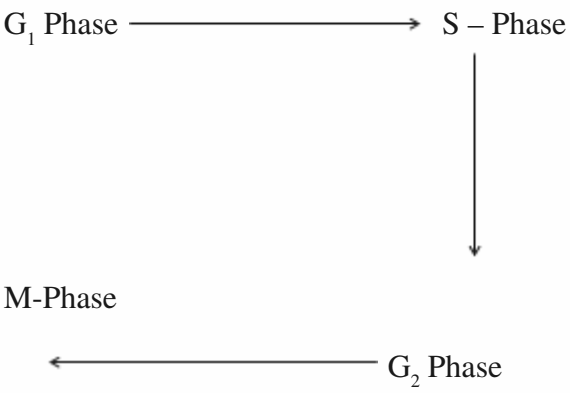



**Fig 2.3: Human chromosomes, one member of each homologous pair, shown in groups A to G , and in numerical order of Denver London classification. Banding pattern indicated. The sex chromosomes X and Y are shown in groups C and G, respectively (Source: Bhatnagar et al., 1977).**

## The Cell Cycle

Living organisms are characterized by two important features, growth and reproduction. Each cell grows to a definite size and then it undergoes self-reproduction to give daughter cells.

There are two phases/periods in the life of a cell. They are N (inter phase or period of non-division) and M (phase or period of division). The longest phase in cell cycle is the inter phase (89 hours). The cycle shows 4 distinct phases.




$G_1$ - Gap (1st Growth)

S = Synthesis

$G_2$ = 2nd Growth

M = Mitosis

The M phase consists of the following two sub phases.

Karyokinesis – division of nucleus into two daughter nuclei.

Cytokinesis – division of cytoplasm into two daughter cells.

## 2.3 CELL DIVISION

Organisms show two types of cell division viz., mitosis and meiosis. Following is the brief account of cell divisions with their genetic significance.

### 2.3.1 Mitosis

Mitosis is essentially somatic cell division and was first discovered by Fleming in 1879. It is defined as that cell division which gives rise to two identical daughter cells, each with nucleus containing the same amount of DNA and same genes as the parent cell. Mitosis is necessary for growth and reproduction of all living organisms.

Following are the types of mitosis.

Intra nuclear mitosis: It occurs within the nucleus (cell division).

Extra nuclear mitosis: It occurs outside nucleus but in cytoplasm.

Endomitosis: Chromosomes multiply without cell division e.g. polytene chromosome.

*Mechanism of Mitosis*

The mitotic division takes place in following two stages.

Karyokinesis – the division of nucleus into two daughter nuclei

Cytokinesis – division of cytoplasm into two daughter cells.

The former cell division takes place in four stages. They are prophase, metaphase, anaphase and telophase (Figs. 2.4, 2.5). We will examine in brief these changes in each phase.

1) Prophase – It is the first phase of mitosis in which chromosomes become short and thick; each chromosome is formed of two chromatids and are connected by centromere.

2) Metaphase – Chromosomes are arranged in the equatorial plane and chromosomal fibers are formed.

3) Anaphase – The chromatids of each chromosome are separated to form two daughter chromosomes which move to opposite poles of the cell.

4) Telophase – It is the last stage in cell division in which chromosomes uncoil and lengthen, nucleolus appears, spindle fibers are dissolved into cytoplasm and two daughter nuclei are formed.

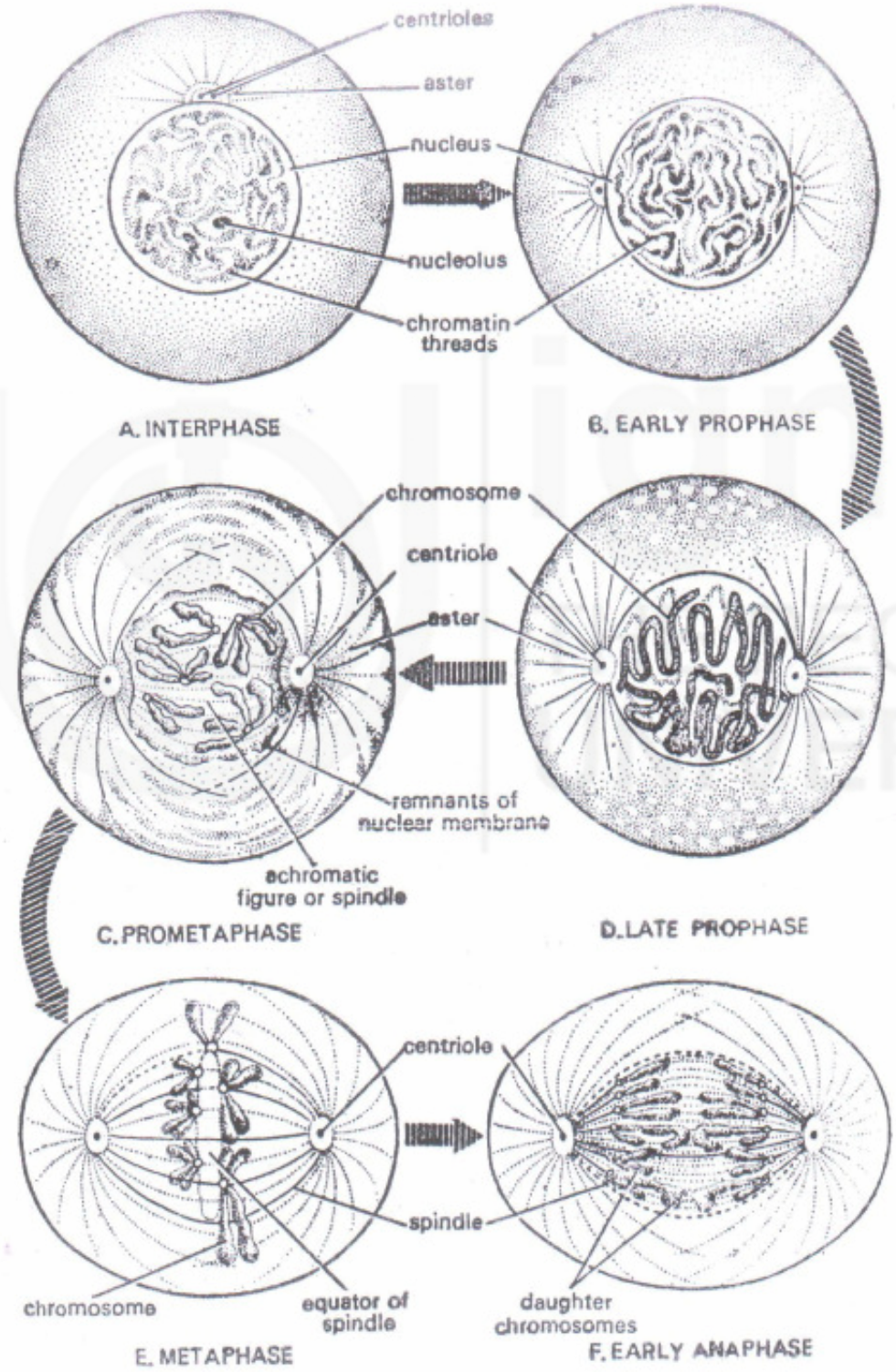



**Fig. 2.4: Some early stages of mitosis (after King, 1965) (Source: Verma and Agarwal, 1982).**

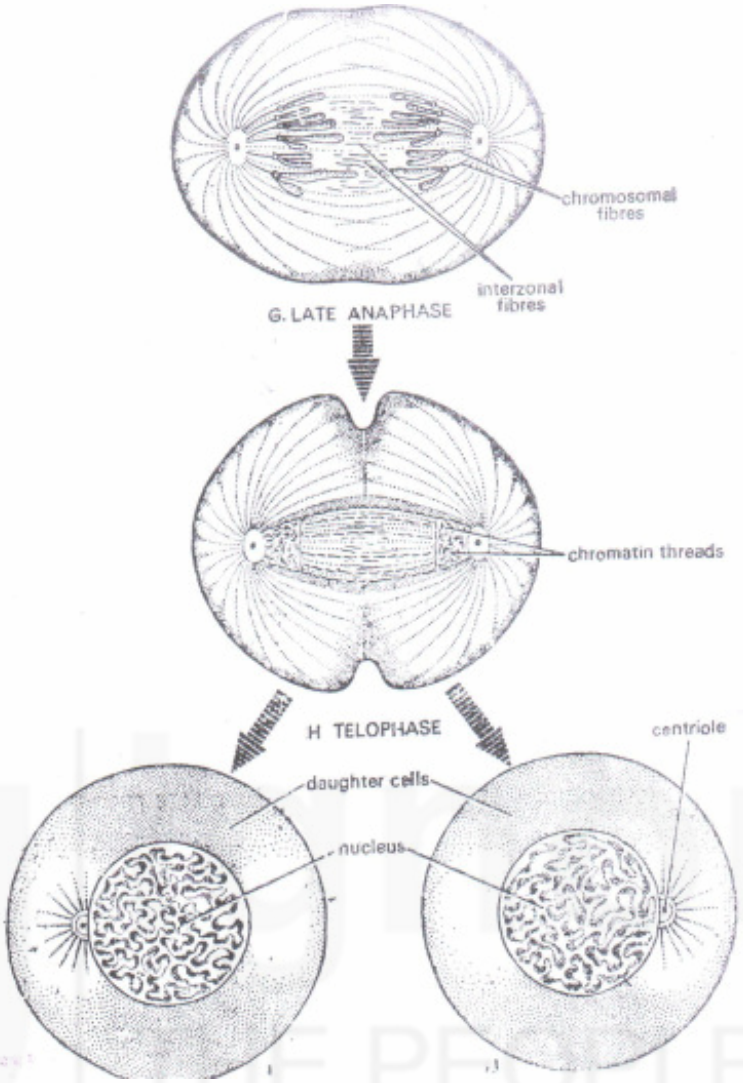



**Fig. 2.5: Late stages of mitosis (after King, 1965) (Source: Verma and Agarwal, 1982).**

### Genetic significance of Mitosis

The mitotic cell division ensures equitable distribution of nucleus and cytoplasm between the daughter cells. The number of chromosomes in the parent cell is the same in daughter cells. Therefore, the structural, functional and hereditary potentialities of both daughter cells are same as that of the parent.

## 2.3.2 Meiosis

Meiosis cell division was discovered by Farmer in 1905. It is also called as reduction division or reproductive division because the diploid (2n) chromosomes are reduced to haploid (n). It occurs only in reproductive (germ) cells. The cell in which meiosis takes place is called meiocytes. It is more complex than mitosis. Meiosis has two stages as follows.

1) Heterotypic division (First Meiotic Division): The diploid cell is divided into 2 haploid cells.

2) Homotypic division (Second Meiotic division): During this, the two haploid cells of I$^{st}$ division divide into 4 haploid cells. The daughter cells are similar to parent cell in chromosome number.

The important point to note here that during the first meiotic division, the centromere does not divide causing the reduction in the number of chromosomes. During second meiotic division, the centromeres divide and not the chromatids.

Meiosis – First stage (Prophase) is represented in the Fig. 2.6 and is comprised of 5 different stages as follows.

1) First Prophase

   i) Leptotene – The diploid chromosome appear in the nucleus.

   ii) Zygotene – The identical chromosomes come close to each other and undergo pairing whole length. This is called synopsis. The paired chromosomes become Bivalent condition.

   iii) Pachytene – The bivalent chromosomes coil around one another and get shortened, chromosomes are haploid.

   iv) Diplotene: The longitudinal split of chromosome give rise to 2 chromatids.

   v) Diakinesis: Chromosomes coil and become further short. They remain distributed in the Nucleus.

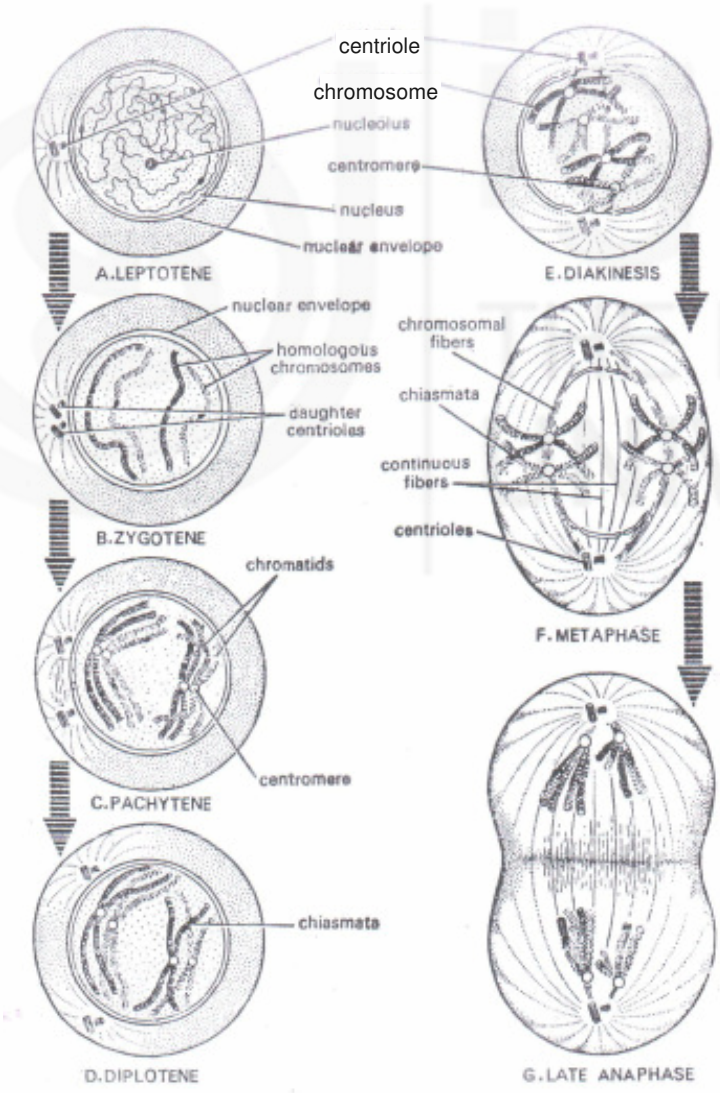



**Fig. 2.6: The mechanism of distribution of chromosomes during meiosis first (after King, 1965) (Source: Verma and Agarwal, 1982).**

Further stage of Meiotic division is known as Meiosis II and is represented in Figure 2.7. In addition to First Prophase, Meiosis consists of the following stages.

1) First Metaphase: Nuclear membrane disappears, nucleolus vanishes, nuclear spindle develops and bivalent chromosomes move towards equatorial plane. Each chromosome has 2 centromeres and attached to spindle fibers.

2) First Anaphase: The two pairs now get separated and move to opposite poles.

3) First Telophase: Two daughter nuclei each with a pair of chromatids formed at the poles. The nuclei are haploid.

4) Second Metaphase: The paired chromatids are widely separated and point of attachment is at centromere.

5) Second Anaphase: The chromatids separate in opposite poles.

6) Second Telophase: 4 daughter nuclei are formed each with haploid (N) number of chromosomes.

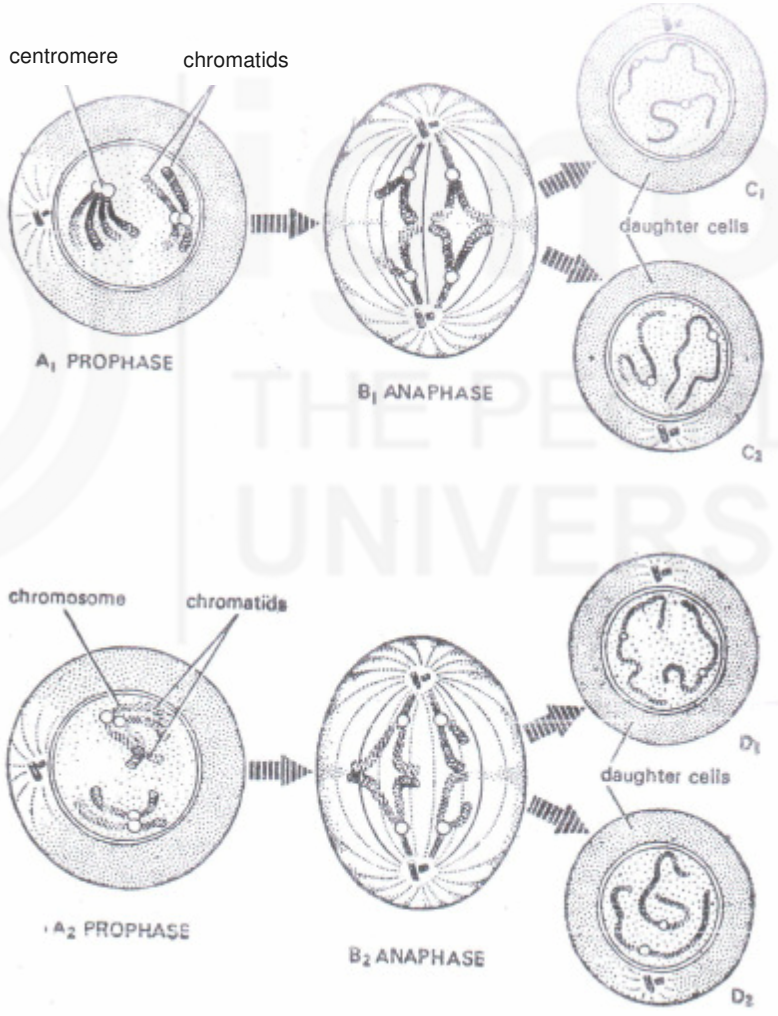



**Fig. 2.7: The different stages of meiosis (after King, 1965) (Source: Verma and Agarwal, 1982).**

*Genetic significance of Meiosis*

1) Gametes are produced by meiosis and are essential units of sexual reproduction.

2) Meiosis reduces diploid (2n) chromosomes characteristic of somatic cells to the haploid number (n) characteristic of gametes.

3) Meiosis prevents in the duplication of chromosomes in the zygote which otherwise would be abnormal.

4) The constant number of chromosomes is maintained by meiosis in a given species.

5) Meiosis provides new combination of genetic material due to crossing over. The hereditary factors (genes) from males and females get mixed causing genetic variations among species. Variations are the principle source for evolution.

6) Meiotic drive refers to disturbance in 1:1sex ratio.

## 2.4 MAJOR DIFFERENCES BETWEEN MITOSIS AND MEIOSIS

The following are some of the major differences between mitosis and meiosis.

| Mitosis | Meiosis |
|---|---|
| 1. It is a simple cell division. | 1. It is a complex cell division. |
| 2. It takes place in somatic (body) cells. | 2. It takes place in reproductive (germ) cells. |
| 3. It helps for the growth of organism. | 3. It is concerned with reproduction. |
| 4. It is a single step cell division. | 4. It is a multiple step cell division. |
| 5. It produces two cells. | 5. It produces four cells. |
| 6. Similarity between daughter cells and parent cells is observed. | 6. No similarity between daughter cells and parent cells is observed. |
| 7. Chromosome number of daughter cells is same as parents i.e. if parents are 2N each, the daughter cells are also 2N. | 7. Chromosome number of daughter cells is reduced to half i.e. if parents are 2N each, the daughter cells are N each. |
| 8. Daughter cells further divide and grow. | 8. Daughter cells do not divide further. |
| 9. Prophase is short and simple. | 9. Prophase is long and complex. |
| 10. No pairing of homologous chromosomes occurs. | 10. Pairing of homologous chromosomes Occurs. |
| 11. No chiasmata and crossing over occurs. | 11. Chaismata is formed due to crossing over of chromosomes. |
| 12. Absence of crossing over and absence of exchange of genes. | 12. Crossing over and of exchange of genes occur. |
| 13. Centromere position is towards equator and arms towards poles. | 13. Opposite situation is observed in meiosis. |
| 14. The size of chromosomes is thin and large. | 14. The size of chromosomes is short and thick. |
| 15. Telophase occurs. | 15. Telophase may be absent. |
| 16. Karyokinesis (nuclear division) is followed by cytokinesis. | 16. Cytokinesis may be absent. |

## 2.5 BIOCHEMICAL BASIS OF CELL DIVISION

The biochemical basis of cell division is not very simple and straight as we believe. It involves various highly sensitive cellular interactions and based on enzymes. Cell biologists are currently involved in unraveling the mystery of cell divisions through intensive current research. Recent advances in cell biology genetics and molecular biology have shown new insights into cell division. All higher organisms possess $B_1$ type of cyclins. Mitotic cyclins play a vital role in cell division. They are accumulated; activated and destroyed during cell division. When cellular proteins are phosphorylated to high degree the cell enters Mitosis. When they are dephosphorylated the cell leaves Mitosis.

## 2.6 GENETIC BASIS OF HUMAN VARIATION

Genetic variability is a universal feature of all breeding populations. It forms a pre-requisite condition for evolution.

Human body with all its physical attributes is the product of heredity and environment. Variation is due to heredity and environment says Galton. Variation forms the principal source for evolution. When variation within a population is converted into variation between population evolutions occurs (Lewontin, 1967).

The Mendelian school and Darwinian school differ in their very outlook of variations. The former look at variations upward from the genes, while later looks at variation downward from the phenotype. Variations refer to dynamic study of gene differences in the population to understand evolutionary changes. The greater genetic diversity in man is due to combination of alleles. Besides this, mutations play a vital role in the maintenance of genetic variability.

*How Variations originate in the Biological System*

We have good constancy in the operation of various biological systems. For example

1) Precise transcription of DNA

2) Precise pattern of chromosome movement

3) Strong sugar–phosphate backbone of DNA that maintains correct transmission of hereditary information.

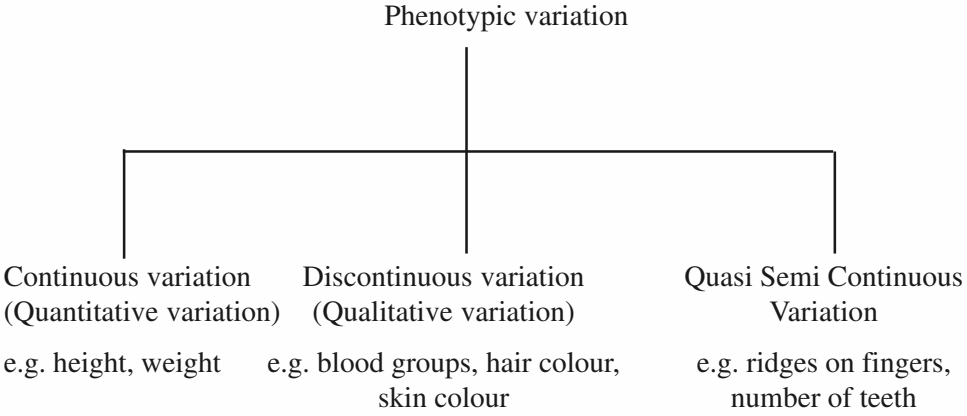
4) Mitosis ensures identical genetic content in daughter cells

With all the above mechanisms of constancy, biological systems generate new information or combination of new information. At the backdrop of above constancy, all biological systems have to play following two games of chance to play.

1) Errors in the replication of DNA (mutations).

2) Random assortment of chromosomes pair (meiosis).

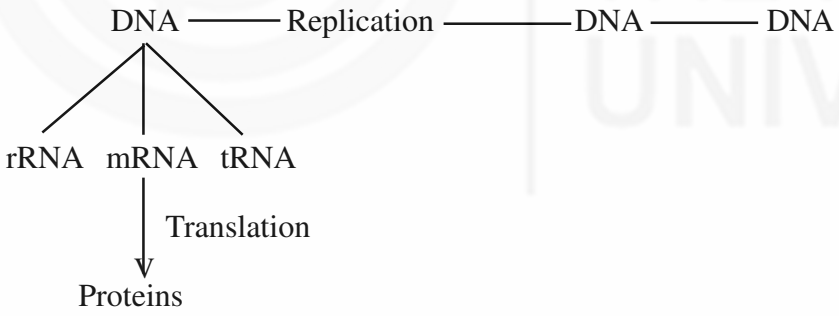
A) Phenotypic variation




B) Genotypic variation ($V_G$)

It is that portion of phenotypic variation which is entirely due to genes. This is called H (heritability). If H is 100% then all variations are genetic. In other words, it means absence of environmental variation. As environmental variation increases, heritability decreases. The remarkable genetic diversity which sets each person apart is a unique phenomenon in nature. There is a definite genetic basis of this variation. Even among MZ (monozygotic) identical twins variations are bound to occur due to intra – uterine environment. It is often said that there are as many genotypes as many individuals in the world.

Genes (hereditary factors) play a very important role in causing variation. At cellular level, DNA has a definite role to play in genetics as shown in the following diagram.




Genes are located in linear fashion on the chromosomes which are made up of DNA and proteins. Thus DNA segments are genes. It is the germ cells which carry genes from one generation to another. Life itself is an eternal journey from cell to cell.

The gene is made up of 4 functional units namely Codon, Recon, Muton and Cistron. Gene is a segment of DNA molecule that codes polypeptide.

## 2.7 SUMMARY

This unit provides a comprehensive picture on various aspects, heredity, inheritance, biological and genetic basis of transmission of hereditary characters in man. Besides this, this unit is endowed with good coverage of all basic points in reference to cell, cell structure, cell types, structural components of cell, mitosis and meiosis their major differences and genetic basis of human variation.

## Glossary

| | | |
|---|---|---|
| Phenotype | : | Observable hereditary characteristic of an individual. |
| Genotype | : | Characteristic present in an individual. |
| Karyokinesis | : | Division of nucleus. |
| Cytokinesis | : | Division of cytoplasm. |
| Diploid | : | The double state of all chromosomes in somatic cells (2N). |
| Somatic cells | : | Cells of the body. |
| Reproductive cells | : | Germ cells e.g. egg, sperm. |
| Homogametic | : | Produce one type of gametes (females). |
| Heterogametic | : | Two types of gametes are produced (males). |
| Gene | : | A segment of DNA that codes for one polypeptide. |
| Prokaryotes | : | Unicellular primitive organisms. |
| Eukaryotes | : | Multicellular organisms. |
| Karyotype | : | The chromosome set of a somatic cell. It is also called idiograph. |
| Locus | : | The site of location of the gene on chromosome. |
| Centromere | : | The constricted portion of the chromosome. |
| Chromatid | : | One of the two identical longitudinal half of chromosome. |
| Crossing over | : | Exchange of genetic material between two homologous chromosomes during meiosis. |
| Codon | : | A triplet of 3 successive bases in a DNA or RNA molecule that code for single amino acid. |
| Cistron | : | The smallest structural and functional unit of the gene which specifies the coding of a particular polypeptide. |
| Muton | : | Smallest sub unit of cistron that brings mutation in the genetic material, as small as one nucleotide pair. |
| Recon | : | The smallest unit of sub unit of cistron that is capable of recombination equals one nucleotide pair. |
| Allele | : | An alternate form of a gene occurring at a locus. |
| Meiotic drive | : | Refers to disturbance in 1:1 sex ratio. |
| Acentric chromosome | : | Chromosomes without centromere. |

## Suggested Readings

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## Sample Questions

1) What is the difference between prokaryotes and eukaryotes in their cell structure?
2) What is cell theory? Who proposed it? Explain the theory.
3) What is the composition of a gene? How many functional units are present in it?
4) Explain transcription, translation and replication with reference to DNA.
5) Define mitosis. Briefly comment on various stages of cell division.
6) Define meiosis and list various stages involved in this cell division.
7) What are the major differences between mitosis and meiosis. What is genetic significance of cell division.
8) What is karyotype?
9) What are the three principle components of a cell? Elaborate.
10) Explain in brief various earlier theories of heredity and inheritance.

# UNIT 3 FORMAL GENETICS

**Contents**



**Learning Objectives**

After having studied the contents of this unit, you should be in a position to:

- understand the classical concepts of inheritance in man;
- explain the different types of simple factor human inheritance; and
- discuss the different types of complex types of human inheritance.

## 3.1 INTRODUCTION

Formal genetics deals with the study of Mendel's laws of inheritance, suggesting the transmission of single gene characters in the families, along with more complex types of inheritance such as multi-factorial or polygenic inheritance. This unit also deals with multiple allelic inheritance, which is an extension of single genic inheritance. Further, other exceptions like epistasis are also dealt with here. Under single genic inheritance, autosomal dominant and autosomal recessive inheritance and sex-linked inheritance (X-linked inheritance and Y-linked inheritance) are covered. Inheritance of sex-limited and sex influenced characters is also described.

## 3.2 MENDEL'S LAWS OF INHERITANCE

Gregor Johann Mendel was born on July 22, 1822 to peasant parents in a small agrarian town in Czechoslovakia. He is considered as the father of genetics. Through his hybridization experiments on garden pea plant (Pisum sativum), in the year 1865 he presented some basic ideas on inheritance in a research paper. This remarkable piece of work unfortunately remained unrecognized for 34 long years. In the year 1900, Mendel's work was rediscovered by three botanists namely Hugo de Vries, Carl Correns and Erich Von Tschermak. Interestingly, it was not Mendel but Correns, one of the discoverers of Mendel's work, who proposed this work as Mendelian laws of Inheritance. These laws of heredity are listed below.

1) Law of uniformity.
2) Law of segregation or Law of purity of gametes.
3) Law of independent assortment or Law of free recombination.

From the monohybrid crosses, in which crosses were made between parents, each of which exhibited one of two contrasting forms of the characters, Mendel suggested as follows.

Genetic characters are controlled by unit factors (later called genes) that occur in pairs on homologous chromosomes in individual organism.

When two unlike unit factors responsible for a single character are present in a single individual, one unit factor may be dominant over the other, which is referred to as recessive.

### 3.2.1 Law of Uniformity

Mendel's first law states that when plants with two contrasting characters are crossed (mated), the characters do not blend. If any character does not express in the first generation, it may reappear without any change in subsequent generations.

### 3.2.2 Law of Segregation

The second law states that in a heterozygote the dominant and recessive factors (genes or alleles) remain together throughout life without contaminating or mixing with each other and finally separate or segregate from one another so that each gamete receives only one factor either dominant or recessive. For explanation, see the following figures.

**Monohybrid cross in garden pea plants**

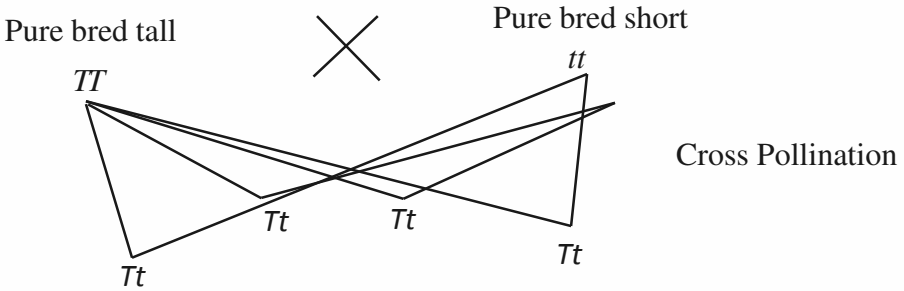



**Fig. 3.1: All the plants of $F_1$ generation are genetically *Tt*.**

To determine the types and frequencies of various offspring expected we normally use squares called Punnett Squares in genetics.

| | | Gametes of pure bred tall plant | |
|---|---|---|---|
| | | *T* | *T* |
| Gametes of pure bred short plant | *t* | *Tt* | *Tt* |
| | *t* | *Tt* | *Tt* |

**Fig. 3.2: The Punnett's square showing genetic constitution of offspring resulted due to the mating between pure short and pure tall plants.**

Monohybrid cross in humans

Normal Skin Colour (with Melanin) × Albinism (without melanin skin pigment)

*AA* ↓ *aa*

$F_1$ Generation *Aa* (all hybrid individuals are genetically normal)

*A* = Normal dominant

*a* = Abnormal recessive

**Fig. 3.3: Monohybrid cross (mating) for skin colour in Man.**

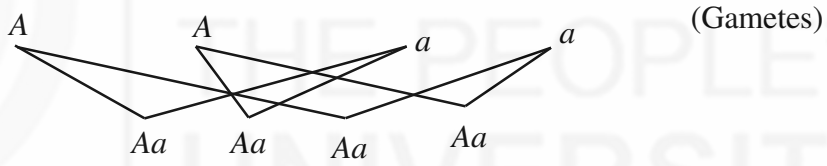



**Fig. 3.4: All the individuals of F1 generation are genetically hybrid.**

| | | Gametes of pure bred normal individuals | |
|---|---|---|---|
| | | *A* | *A* |
| Gametes of pure bred albinos | *a* | *Aa* | *Aa* |
| | *a* | *Aa* | *Aa* |

**Fig. 3.5: The punnett squares showing the genetic contribution of the offspring resulted from mating between pure normal and pure albino individuals.**

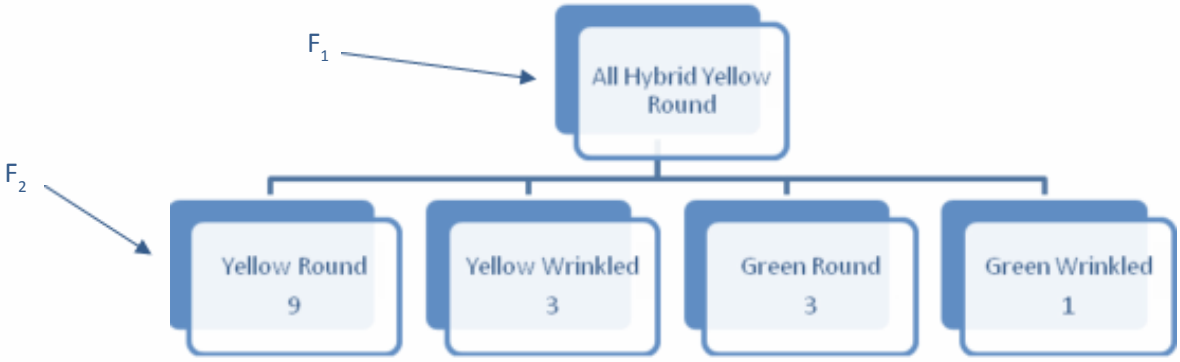
### 3.2.3 Law of Independent Assortment

The law of independent assortment or recombination states that the members of different pairs of factors (genes) assort independently of each other when the gametes are formed. Because of that new combinations (or all possible combinations) of characters are produced in the offspring.

For explanation see the following figures.

Di hybrid cross in pea plants having yellow, round, green and wrinkled seeds.

| | | | |
|---|---|---|---|
| *YR* | X | *yr* | Corss |
| Pure bred | | Prue bred | Pollination |
| yellow round | | green wrinkled | |




Checker Board

Genotype *YyRr*

Phenotype Yellow Round

| | *YR* | *YR* |
|---|---|---|
| *Yr* | *YyRr* | *YyRr* |
| *Yr* | *YyRr* | *YyRr* |

**Fig. 3.6a: Di hybrid cross $F_1$ generation.**

| | *YR* | *Yr* | *yR* | *yr* |
|---|---|---|---|---|
| *YR* | *YRYR* | *YRYr* | *YRyR* | *YRyr* |
| *Yr* | *YrYR* | *YrYr* | *YryR* | *Yryr* |
| *yR* | *yRYR* | *yRYr* | *yRyR* | *yRyr* |
| *yr* | *yrYR* | *yrYr* | *yryR* | *Yryr* |

**Fig. 3.6b: Di hybrid cross $F_2$ generation.**

Genotypes: 9 different combinations.

Phenotypes: 9 Yellow Round : 3 Yellow Wrinkled : 3 Green Round : 1 Green Wrinkled.

In case of di hybrid cross, when mating takes place in humans showing different contrasting pairs of characters, it will be observed that assortment of genes of one pair will be independent of the other pair.

From the above figure it is revealed that each pair of contrasting characters behaves independently and bears no association with a particular character.

In the ABO blood group system of human beings, *ABO*A* and *ABO*B* are codominant and both are dominant over *ABO*O* which is recessive, while in the Rhesus blood group system, *RH*D* is dominant over *RH*d*. If an individual with A blood group (*ABO*A ABO*A)* and RHD+ factor (*RH*D RH*D* ) marries a person possessing O blood group (*ABO*O ABO*O)* and RHD- factor (*RH*d RH*d)*, then due to the independent assortment of the two blood group systems 9:3:3:1 dihybrid ratio is observed in the offspring.

*ABO*A ABO*A RH*D RH*D* — A blood group RH*D+ — X — O blood group RH*D- — *ABO*O ABO*O RH*d RH*d*

Gametes *ABO*A RH*D* × *ABO*O RH*d*

$F_1$ : *ABO*A ABO*O RH*D RH*d* i.e. A blood group, RH*D+

**Fig. 3.7: Dihybrid cross $F_1$ generation.**

## Punnett's checker board

### $F_1$ generation

Genotype
*ABO*A ABO*O* RH*D *RH*d*

Phenotype
All A-blood group RH*D+

| Sperm \ Ova | *ABO*A RH*D* | *ABO*A RH*D* |
|---|---|---|
| *ABO*O* RH*D | *ABO*A ABO*O RH*D RH*d* | *ABO*A ABO*O RH*D RH*d* |
| *ABO*O RH*D* | *ABO*A ABO*O RH*D RH*d* | *ABO*A ABO*O* RH*D *RH*d* |

### $F_2$ generation

Gametes *ABO*A* RH*D, *ABO*O* RH*D, *ABO*A RH*d, ABO*O RH*d*

| | *ABO*A RH*D* | *ABO*A RH*d* | *ABO*O RH*D* | *ABO*O RH*d* |
|---|---|---|---|---|
| *ABO*A RH*D* | *ABO*A ABO*A RH*DRH*D* | *ABO*A ABO*A RH*D RH*d* | *ABO*A ABO*O RH*DRH*D* | *ABO*A ABO*O RH*D RH*d* |
| *ABO*A RH*d* | *ABO*A RH*d ABO*A RH*D* | *ABO*A RH*d ABO*A RH*d* | *ABO*A RH*d ABO*O RH*D* | *ABO*A RH*d ABO*O RH*d* |
| *ABO*O RH*D* | *ABO*O RH*D ABO*A RH*D* | *ABO*O RH*D ABO*A RH*d* | *ABO*O ABO*O RH*DRH*D* | *ABO*O RH*D ABO*O RH*d* |
| *ABO*O RH*d* | *ABO*O RH*d ABO*A RH*D* | *ABO*O RH*d ABO*A RH*d* | *ABO*O RH*d ABO*O RH*D* | *ABO*O RH*d ABO*O RH*d* |

Genotype 9-different combinations.

Phenotype

Dyhybrid cross: F2 generation

9 A Blood group RH*D+

3 A Blood group RH*D-

3 O Blood group RH*D+

1 O Blood group RH*D-

### 3.2.4 Back Cross and Test Cross

When F1 individuals are crossed with one of the parents from which they are obtained, such cross is called back cross. In such back crosses, when F1 is back crossed to the parent with dominant phenotype, no recessive individuals are derived in the offspring. But when F1 progeny is back crossed with its recessive parent, both phenotypes (i.e. dominant and recessive) appear in the progeny. While both of these crosses are back crossed, only the cross with the recessive parent is called Test Cross.

**Examples**

I) **Monohybrid Test Cross**

In a monohybrid cross of homozygous tall (*DD*) and homozygous dwarf (*dd*) plant is crossed either with its dominant parent to perform a back cross or with its recessive parent to perform a test cross the following results are obtained

$P_1$

Homozygous tall (*DD*) X Homozygous dwarf (*dd*)

Heterozygous Tall

*Dd*

A) **Back Cross**

$F_1$ Tall (*Dd*) X $P_1$ Tall (*DD*)

*½ DD* *½ Dd*

Back Cross Progeny: Homozygous Tall (All Tall) Heterozygous Tall

B) **Test Cross**

$F_1$ Tall (*Dd*) X $P_1$ Dwarf (*dd*)

*½ Dd* *½ dd*

Test Cross Progeny: Homozygous Tall Homozygous Dwarf

Or Test Cross ratio = 1:1

II) **Di hybrid Test Cross**

The test cross of heterozygous yellow round (*YyRr*) seeded pea plant with a double parent recessive parent (green wrinkled *yyrr*) yields a test cross genotypic ratio of 1 : 1 : 1 : 1 as follows.

$P_1$

| | | |
|---|---|---|
| Yellow, Round | X | Green, Wrinkled |
| (Heterozygous) | | (Homozygous) |
| *YyRr* | X | *yyrr* |

$F_1$

| | | |
|---|---|---|
| 1*YyRr* | : 1*Yyrr* | : 1 *yyRr* : 1 *yyrr* |
| | (Or) | |

¼ Yellow round : ¼ yellow wrinkled : ¼ green round : ¼ green wrinkled

## 3.3 INHERITANCE PATTERNS IN MAN

It is necessary to know the patterns of inheritance in man, before understanding the features of any genetic disease for the following reasons.

- For the precise diagnosis of genetic disorders.
- To estimate the risk of genetic disease (recurring risk) appearing in the offspring.
- To identify the means to prevent the genetic disease.

The inheritance of common traits will broadly fall in the following categories.

- Monogenic (single gene) or Mendelian Inheritance.
- Polygenic or multi-factorial inheritance.

### 3.3.1 Monogenic Inheritance

In monogenic (also referred to as single gene or Mendelian) inheritance, the trait or character is determined by single gene and it follows Mendel's laws of inheritance. This single gene inheritance is further classified as follows.

Autosomal inheritance

Sex-linked inheritance

Autosomal inheritance is due to the gene present on autosome while sex-linked inheritance is determined by gene present on sex chromosome (X or Y). The autosomal inheritance is further classified into autosomal dominant and autosomal recessive. In case of autosomal dominant inheritance, the gene manifests itself even in single dose (heterozygous state) while an autosomal recessive inheritance the trait is expressed only when the gene is present in double dose (homozygous state). Sex-linked inheritance is determined by a gene present on the sex chromosome (X or Y) i.e. it could be X-linked or Y-linked.

*Pedigree Chart*

A pedigree diagram is used to follow the transmission of the character in the families, over different generations using certain symbols as listed below.

- Squares represent males and circles represent females.
- Affected persons (proband / propositus / index case) for male and female are shown by solid squares or solid circles, respectively.

- The position of affected person(s) in the family tree is indicated by arrow.
- Mating is represented by horizontal line.
- The order of birth of children is shown from left to right.
- The successive generations are shown by roman numerals. e. g. I, II, III and IV etc.

### 3.3.2 Autosomal Dominant Inheritance

The genes responsible for autosomal dominant characters are present on autosomes and can express the trait even in single dose (heterozygous state). Following are some of the examples.

| Trait | Characteristic features |
|---|---|
| Achondroplasia | Dwarfism with short limbs, normal size head and trunk. |
| Hypercholesterolemia | Very high serum cholesterol levels, heart disease. |
| Polydactyly | Extra fingers and/or toes. |
| Huntington disease | Progressive uncontrollable movements and personality changes, beginning in middle age. |

Characteristic features of autosomal dominant inheritance are listed below:

1) A trait can appear in either sex because an autosome carries the gene.
2) The trait does not skip generations.
3) An affected person will always have an affected parent.
4) Normal children do not transmit the trait to the next generation as they do not have the abnormal gene.

*Affected heterozygous parent (Aa)*

Gametes 1:1

*A*: Mutant gene

*a*: Normal gene

*Aa* = 50% (Heterozygous affected)

*aa* = 50% (Homozygous normal)

Affected Heterozygous Parent

(*Aa*)

Gametes1:1 *A* *a*

When affected heterozygous parent *(Aa)* marries unaffected parent *(aa)*

*Aa* (50% Heterozygous affected)

*aa* (50% Homozygous normal/ unaffected)

*Aa* X *aa*

| Gamete | *A* | *a* |
|---|---|---|
| *a* | *Aa* | *aa* |
| *a* | *Aa* | *aa* |

**Fig. 3.8: Autosomal dominant Inheritance**

Some of the exceptions like pleiotrophy, variable expressivity of gene, incomplete penetrance, co-dominance and intermediate inheritance are discussed here in detail in the following.

**Pleiotrophy**

Usually an autosomal dominant gene has one effect and thus involves only one organ or part of the body. However, when single gene disorder produces multiple phenotypic effects then it is called pleiotrophy. For example, in case of osteogenesis imperfecta the mutant gene is responsible for defect in the synthesis of collagen. However, the formation of defective collagen leads to many other defects like osteosclerosis, blue sclera and brittle bone etc.

**Variable expressivity of gene**

The phenotypic expression of an autosomal dominant gene can vary from person to person. In clinical terms the expression of gene may be in mild, moderate or severe form of the trait. One common example is polydactyly (extra finger). In some individuals this extra finger may be fully formed while in other individuals it may be very small.

**Incomplete penetrance**

It is the extreme end of variable expressivity. In this condition a person who is heterozygous for a dominant disorder fails to manifest a disorder clinically. Thus it may appear as if the disorder has skipped the generation. The penetrance of a gene in any generation is expressed in terms of percentage (%) which is calculated from the number of offspring showing the trait as compared to the expected.

The cause of reduced penetrance or the variation in the expression of gene may be due to influence of genes at other loci. It may be also due to the difference in environmental factors.

**Codominance**

When both the traits are expressed fully in heterozygous state they are called codominant. For example, a person with blood group AB shows both A and B antigens on his red blood cells. The allelic genes *ABO*A* and *ABO*B*, which are present near the tip of long arm of chromosome 9, are therefore codominant.

**Intermediate Inheritance**

In the heterozygous condition of a recessive trait, abnormal (mutant) allele is unable to express itself. However, when in heterozygous condition if it shows intermediate expression between abnormal heterozygous and normal heterozygous then this is known as intermediate inheritance.

## 3.3.3 Autosomal Recessive Inheritance

For the manifestation of this trait, the gene should be in homozygous state (double dose). Following are some examples.

| Trait | Characteristic features |
|---|---|
| Phenylketonuria | Mental retardation, fair skin |
| Cystic fibrosis | Lung infection and congestion, poor fat digestion, male infertility, poor weight gain, salty sweat |

Following are the characteristic features of autosomal recessive inheritance

1) The trait can also appear in either sex.
2) Affected individuals have homozygous recessive genotype, while the heterozygotes, called carriers, are quite healthy.
3) The trait can skip generations.
4) Parents of the affected individual are either heterozygous carriers or have the trait.
5) Consanguinity among parents can increase the recurrence risk of the disease.

*Aa* X *Aa*

Mating between carrier parents

| | | Normal but carrier parent (*Aa*) | |
|---|---|---|---|
| | | *A* | *a* |
| Normal but carrier parent (*Aa*) | *A* | *AA* | *Aa* |
| | *a* | *Aa* | *Aa* |

*A*= mutant gene, *a* =Nomal gene

*AA* = 25% normal *Aa* = 50% normal but carrier *aa* = 25% affected

Genotypic ratio 1:2:1

Phenotypic ratio 3:1

**Fig. 3.9: Autosomal recessive inheritance.**

### 3.3.4 Sex Linked Inheritance

This type of inheritance depends on the genes present on X or Y chromosome; chiefly it is one of the following two kinds.

1) X-linked inheritance
2) Y-linked inheritance

X-linked Inheritance may be dominant or recessive.

#### 3.3.4.1 X-Linked Dominant Inheritance

This disorder is due to the presence of mutant gene on X chromosome. As the gene is dominant, it expresses in heterozygous females as well as in males. This type of inheritance resembles that of an autosomal dominant inheritance but can be distinguished owing to the fact that an affected male passes on this trait to all his daughters but to none of his sons. Therefore, to distinguish this character from autosomal inheritance one has to observe the offspring of affected males.

Further, gene expression of X-linked dominant allele is different in two sexes. A female who inherits dominant X –linked allele has the associated trait or illness, but a male who inherits the allele is more severely affected because he is hemizygous for X chromosome and therefore has no other allele to offset the effect of the dominant allele.

The children of a normal male and female with a dominant disease causing gene on the X chromosome bear the risk as shown in the following figure.

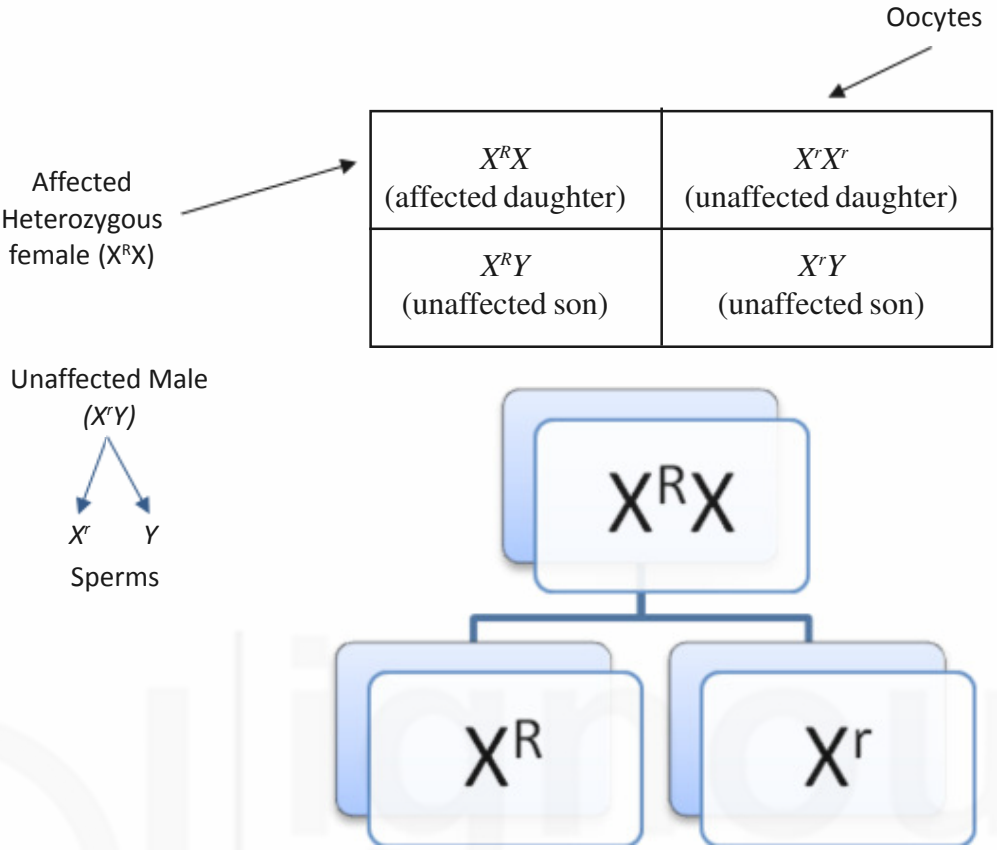



**Fig. 3.10: X-Linked Dominant Inheritance**

A woman who is a carrier of X-linked dominant trait transmits it to sons with a probability of 1 in 2 and to a carrier daughter with same chance.

Following are some examples of X-linked dominant traits in man.

| Trait | Characteristic features |
|---|---|
| Hypophosphatemia | Vitamin-D resistant rickets. |
| Incontinentia pigmenti | Swirls of skin color, hair loss, seizures, abnormal teeth. |
| Xg blood groups | Normal character. |

### 3.3.4.2 X-Linked Recessive Inheritance

An X-linked recessive trait is expressed in females if genes for it are present in two copies i.e. homozygous state (since in females there are two X-chromosomes). Because X-linked recessive genes are rare, possibility of an X-linked recessive trait in females is rarer.

A common situation is for an X-linked trait to pass from a heterozygous mother to an unaffected son. Since male is having only one X-chromosome, he can express the trait even in heterozygous state referred to as hemizygous state in this context. The affected male will transmit this gene to all his daughters who will become carriers and will transmit the triat to 50% of his grandsons.

Following are some of the examples of X-linked recessive traits in man.

| Trait | Characteristic features |
|---|---|
| Haemophilia | Absence of clotting due to factor VIII. |
| Red green colour blindness | Abnormal red cone pigments in retina. |
| Muscular dystrophy | Progressive muscle weakness. |

Characteristic features of X-linked recessive traits are as follows:

1) Predominantly males are affected.
2) The trait is transmitted through unaffected carrier females (and also affected homozygous females) to their sons.
3) Affected female has an affected father and a mother who is affected or a carrier.
4) The affected males cannot transmit the disorder to their sons as the gene is not present on Y chromosome.
5) Affected males usually have normal parents as the mutant gene on X chromosome is received through normal carrier mother.

Carrier female (mother)

Normal male (father)

| Gamete | $X^H$ | $X^h$ |
|---|---|---|
| $X^H$ | $X^HX^H$ | $X^HX^h$ |
| $Y$ | $X^HY$ | $X^hY$ |

$X^H$ = Normal gene, $X^h$ = Abnormal gene

25% $X^HX^H$ Normal daughter

25% $X^HX^h$ Carrier daughter

25% $X^HY$ Normal son

25% $X^hY$ Son with haemophilia

**Fig. 3.11: A mating between normal male ($X^HY$) and carrier female ($X^HX^h$) for haemophilia.**

### 3.3.4.3 Y-Linked Inheritance

The only one gene known as SRY (sex determining region-Y) is identified on Y-chromosome. The SRY gene encodes a type of protein called transcription factor which controls other genes involved in male development. An affected male transmits Y-linked trait to all his sons but to none of his daughters (as an affected male transmits X chromosome to the daughters).

Characteristic features of Y-linked inheritance are listed below:

1) Only males are affected.
2) All sons of affected males are affected.
3) Females never get the trait or transmit it.

### 3.3.5 Extranuclear Inheritance

Extranuclear inheritance, also referred to as mitochondrial or maternal inheritance, is defined as non-mendelian inheritance, usually involing DNA in self-replicating cytoplasmic oraganell mitochondrion. Mitichondria contain DNA that is autonomous outside the nuclear genome. Mitochondria in human cells contain several copies of a 'mini chromosome' that carries just 37 genes. Sometimes it is called the twenty fifth chromosome. The inheritance of these genes is variously referred to as extranuclear, mitochondrial, maternal or cytoplasmic inheritance. The basis of the Mendel's law of segregation is that both parents contribute equally to progeny. This is not the case for genes present in mitochondria.

The hereditary patterns and mutation rates for the mitochondrial genes differ from those for genes in the nucleus. Mitochondrial genes are maternally inherited. They are passed only from an individual's mother because sperms almost never contribute to mitochondria when they fertilize an oocyte. Pedigrees that follow mitochondrial genes show a woman transmitting the trait to all her children, while a male cannot pass this trait to any of his children.

Unlike DNA in the nucleus, mitochondrial DNA (mt DNA) mutates faster because it lacks DNA repair enzyme and mitochondria is the site of energy reactions that produce oxygen free radicals that damage DNA. Also unlike nuclear DNA, mitochondrial DNA is not wrapped in histone proteins and nor are genes interrupted by DNA sequences that do not encode proteins called introns. Inheritance of mitochondrial genes differs from inheritance of nuclear genes simply because a cell has one nucleus but many mitochondria and each mitochondrium harbours several copies of its chromosome. Mitochondria with different alleles for the same gene can reside in the same cell.

Some examples of mitochondrial disorders in humans are given below.

| Trait | Characteristic features |
|---|---|
| Mitochondrial myopathies | Weak and placid muscles and intolerance to exercise. |
| Leber's hereditary optic neuropathy (LHON) | Impairs vision. |

## 3.4 SEX LIMITED CHARACTERS

Here the expression of character is limited to one sex. In humans, beard growth in males and breast development in females are sex limited traits. A woman does not grow a beard because she does not produce the hormones required for facial hair growth. She, can, however pass to her sons the genes specifying heavy beard growth. Such a gene may be sex-linked or autosomal.

Due to anatomical differences between males and females, intrauterine or testicular defects constitute other examples of sex limited characters. Another inherited condition known as preeclampsia that arises during pregnancy is also a good example of sex limited trait. Since males do not get pregnancy, preeclampsia in females leads to a sudden increase in blood pressure that occurs in pregnant woman as the birth approaches.

## 3.5 SEX INFLUENCED CHARACTERS

A trait is said to be sex influenced when it expresses differently in males and females because an allele is dominant in one sex but recessive in the other. Again such a gene may be X-linked or autosomal. The difference in expression can be caused by hormonal differences between the sexes. For example, the expression of common baldness is different in males and females. It is an autosomal dominant trait in males and hence very common. While it is autosomal recessive in females hence they are rarely seen bald. Female heterozygote can transmit the trait to their offspring but do not manifest it. Females display the trait only when they inherit two copies of the gene, i.e. when they are homozygous recessive. Even then, they are more likely to display marked thinning of the hair, rather than complete baldness whereas an affected male may be completely hairless on the top of the head.

## 3.6 MULTIPLE ALLELES

The concept of multiple alleles is simply an extension of single gene inheritance. Mendel's short and tall pea plants seem much simpler. New mutations at a single locus would complicate the correlation between phenotype and genotypes. An individual possesses two alleles for any autosomal gene (one allele for each homologous chromosome) but a gene can exist in more than two allelic forms in a population on account of new mutations producing variations in phenotype.

For instance, the ABO blood groups are determined by the presence of three alleles (alternative form of the gene) at a single locus and hence are examples of multiple alleles. These alleles are designated as *ABO*A, ABO*B* and *ABO*O;* the former two are dominant over the latter. A person can have any two of these alleles present on the homologous chromosomes.

| Genotype | Phenotype (Blood group) |
|---|---|
| *ABO*A ABO*A/ABO*A ABO*O* | A |
| *ABO*B ABO*B/ABO*B ABO*O* | B |
| *ABO*A ABO*B* | AB |
| *ABO*O ABO*O* | O |

The *ABO*A* and *ABO*B* alleles are dominant over *ABO*O* allele, which is recessive. When *ABO*A* and *ABO*B* are present together, both are expressed and this phenomenon is called co-dominance.

## 3.7 POLYGENIC OR MULTI-FACTORIAL INHERITANCE

There are many common characters and disorders which do not follow simple Mendelian (single gene) inheritance. Common traits like intelligence, blood pressure, height, weight, hair colour, eye color and facial appearance have more

complex genetic basis. If height were to be determined by a pair of genes (as is the case of Mendelian inheritance) then this would result in only two types of persons i.e. tall and short. (If we represent tallness as 'T' and shortness 't' then tall individual will be '*TT*' or '*Tt*' and short ones will be '*tt*'). However, in each family we get individuals whose height shows quantitative variation from one extreme to other. All the aforementioned traits cannot be distinctly classified into two groups but are measured quantitatively and therefore are called as continuous or quantitative traits.

Similarly, the following disorders do not follow Mendelian (single gene) inheritance. However these disorders cannot be measured as height or blood pressure. These disorders are either present or absent. These are called threshold traits. Threshold traits are present or absent e.g. a person is diabetic or non-diabetic. Following are examples of threshold traits in man.

| **Congenital malformation** | **Adult onset disease** |
|---|---|
| Neural tube defects | Diabetes mellitus |
| Pyloric stenosis | Epilepsy |
| Cleft lip | Hypertension |
| Cleft palate | Ischemic heart disease |
| Heart defects | Schizophrenia |
| | Glaucoma |

The above mentioned threshold traits are considered to be determined by actions of many genes which are situated at different loci on chromosomes, each of which exerts an equal additive effect. This kind of inheritance is called polygenic inheritance. Thus in polygenic inheritance the genes do not behave as dominant or recessive but have an additive or cumulative effect on the trait.

It is also believed that these common physical traits, disorders or congenital malformations are not entirely determined by the action of many genes but are to be resulted from interaction of environmental and genetic factors. Many environmental factors like diet (in case of weight), sunlight (in case of skin colour), disease, chemicals and radiation, among others, may influence the action of genes. Thus polygenic inheritance is also called as multi-factorial inheritance.

## 3.8 SUMMARY

A bird's eye view of the contents mentioned in the above unit will give you an overall picture of the classical concepts of formal genetics in man, the different modes of the simple and complex inheritances along with illustrations, with a focus on related topics dealing with certain situations of exceptions, which we come across while studying the inheritance patterns in man.

**Suggested Readings**

Lewis, R. 2003. *Human Genetics*, 5th Edition. New York: McGraw-Hill Publications.

Verma, P.S and Agarwal, V.K. 2009. *Genetics*. New Delhi: S. Chand & Company Ltd.

Jorde L.B, Carey J.C, Bamshad M.J, and White R.L 2000. *Medical Genetics*, 2nd Edition. St. Louis: Mosby.

Barua, S. 2002. *Human Genetics. An Anthropological Perspective*. Kolkata: Classsique Books.

**Sample Questions**

1) Describe the Mendel's laws of inheritance. Illustrate your answers with suitable examples.
2) Distinguish between multiple alleles and polygenic inheritance. Illustrate your answer with appropriate examples.
3) Differentiate between the autosomal dominant and X-linked dominant modes of inheritance giving examples.
4) Give an account of mitochondrial inheritance as differentiated from nuclear inheritance.
5) How can you distinguish mitochondrial inheritance from nuclear inheritance?
6) Write short notes on the following.
   a) Pleiotropism
   b) Sex limited traits
   c) Sex influenced traits
   d) Variable expressivity of gene
   e) Y-linked inheritance
   f) Red green colour blindness
   g) Albinism
   h) Test cross