

Block

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HUMAN GENETICS

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BLOCK 5 HUMAN GENETICS

Introduction

Genetics is the study of heredity – it is sometimes defined as the science that seeks to explain the similarities and differences that exist between organisms related by descent. Though genetics is a more inclusive science of biology, but geneticists also draw upon such related sciences as chemistry, mathematics and physics in their efforts to ferret out all of the complex reactions which are involved in the transmission of the inherited characteristics down through the generations.

Heredity plays an important role in the development of many human afflictions, and knowledge of heredity's exact role sometimes can be of great help in the prevention, diagnosis and treatment of disease. Closely related to the medical applications of genetics is the field of counseling. Most genetic counseling concerns human defects which lie in the field of medicine. Many court cases today rely on geneticists for valuable testimony. Questions of disputed parentage may often be solved by identification of the blood types of the persons in question.

A geneticist has various methods of study which he can use in investigations of problems of inheritance. Such investigations are done at the family level, through pedigree analysis, at the population level through statistical analysis, cytological studies for inherited abnormalities, and biochemical genetic studies at the family, pedigree and at the population level of different human population groups.

We will discuss about all these under Block 5, which covers four units. Before we discuss about human genetics in detail, we must understand the fundamental laws of inheritance. We will be able to understand human genetics and its principles in a better way if we have introductory knowledge about the structure and function of cell, chromosomes, cell division, and how the chromosome numbers are maintained in a population through generations, which will help us to understand the various types of inheritance based on autosomes and sex chromosomes is taken up in **Unit 1** on Human Genetics. **Unit 2** Methods of Human Genetics will discuss in some detail about the methods of inheritance study through pedigree, and the study of chromosomes on which genes are arranged in a linear fashion. We will also touch upon briefly about chromosome chemistry, and will discuss about the applications of genetic knowledge in human afflictions in diagnosis and in paternity disputes. **Unit 3** Population Genetics will discuss what are the proportions of different genotypes in a population, and how the proportions of genotypes existing in one generation be related to those in the next generations in human population groups, and the agents of change in genotype frequency. Though the movements and reactions of chromosomes during cell divisions are very exact, however, there are occasional deviations from the normal procedure and aberrant forms and arrangements of chromosomes results. We will discuss aberrations involving portions of chromosomes, entire chromosomes, and aberrations involving entire sets of chromosomes in **Unit 4** Chromosomal Aberrations in Man.

UNIT 1 HUMAN GENETICS

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- 1.1 Introduction
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Learning Objectives



Once you have studied this unit, you should be able to understand

- how a single gene or genes form the physical hereditary link between generations, from parent to offspring;
- the determination of sex and the relation of sex to inheritance, and sex related human traits; and
- the important factors of human diversity and ethnic variation.

1.1 INTRODUCTION

The field of anthropology is basically concerned with both biological and social/cultural evolution as well as diversity of human population throughout the ages. For understanding human genetics one needs to understand about physical anthropology or biological anthropology which deals with the study of human biology, evolution of the human organism, the relation between environment and human organism, and genetic variations between individuals and groups. The field of human genetics (of anthropological interest may be referred to as anthropological genetics which is concerned with human population variation study) uses pattern of genetic similarity and differences among different human populations throughout the human ancestry to infer the history of human evolution, migration, admixture and diversity. This would enable the scientists in explaining how the modern *Homo sapiens* evolved through the stages of *Homo habilis* and *Homo erectus* through the millennia to the modern man and the reasons behind many of the biological differences that we observe in different ethnic groups of the world.

Genetics is a branch of biology that deals with heredity or inherited variation of genetic traits. The science of genetics studies the phenotypic (visible) differences between individuals and attempts to relate them to underlying genic or chromosomal differences. The hereditary units that are transmitted through parent to offspring are called genes.

The word ‘gene’ is used frequently in genetics as a designation for each of the small units of heredity within a cell. Genetics has proved to have numerous practical applications because man has learned to use the discoveries in many different fields. It is being used in such diverse areas as plant and animal breeding, medical diagnosis, and genetic counseling, and even in cases of law. Genes are biochemical instructions that are supposed to determine those inherited traits that reside in the long molecules of deoxyribonucleic acid or DNA. Long polynucleotide molecules of *deoxyribonucleic acid*, called DNA, are intimately associated with chromosomes and are found exclusively in chromosomes. The chemical composition of chromosomes includes histones, proteins and deoxyribonucleic acid. The DNA is found only in chromosomes and is double stranded. The genes are then, sections of the DNA ladder-like molecules; different genes are different because they contain different sequence of the ‘letters’ A, T, C, and G. DNA in conjunction with protein matrix may form nucleoprotein and becomes organised as chromosomes that are found in the nucleus of the cell. DNA is a stable molecule, however, on rare occasions a change or heritable alteration may occur spontaneously, is called mutation which is the lead sources of biological variation. In the study of heredity, we must clearly distinguish between ‘genes’ and ‘traits’. Genes are at the bottom of development. On the other hand, traits, such as hair colour, eye colour, size, shape, etc. are end products of development. They require both the proper genes and proper environment for their development.

1.2 HISTORY, DEFINITION AND SCOPE

Human Genetics, as the name indicates, describes the study of inherited variation as it occurs in human beings. The inheritance of many traits, including human traits is at present fairly well known. The biochemical studies on the constituents of the chromosomes have given essentially the correct picture how heredity really works at the molecular level. Genes can be the common factor of the most inherited traits. Genes have become prominent in the nature versus nurture debate. Study of human genetics can be useful as it can answer questions about human nature, behaviour as well as understand the diseases and disease treatment, and genetics of human life.

The science of genetics emerged from the famous work of Father Gregor Mendel (1822-1884) while working at the Augustinian monastery of St Thomas at Bruno in Moravia with the common garden pea. He published the results of his studies in 1866 and thereby laid the foundation of modern genetics. In his paper, Mendel proposed some basic genetic principles — the law of segregation, and the law of independent assortment. The first one states that each parent contains two copies of a unit of inheritance (later called gene), however, any one of two genes (called allele) can be transmitted to the offspring through the gamete. Which allele in a parent’s pair of alleles is inherited is a matter of chance. The second principle states that the segregation of such gene pair (allele) occurs independently in respect of other gene pair, i.e. the paired genes (allelic pairs) separate from one

another and are distributed to different sex cells. The result is that new combinations of genes present in neither parent are possible. However, during his (Mendel) lifetime very few people realised the importance of his path breaking research. In 1901, Hugo de Vries, Carl Correns and Erich von Tschermak realised that Mendel's observations, conclusions and hypothesis have great importance in the field of genetics. During early 1900s, researchers noted that chromosomes behave like Mendel's traits and also inherited in random combinations. In 1909 Wilhelm Johansen renamed Mendel's characters as 'gene' and William Bateson coined the term 'genetics' to study genes. Thereafter researchers repeated and confirmed Mendel's hypothesis and his (Mendel) ideas on the inheritance of traits became more widely accepted and is now termed as Mendel's laws of inheritance.

Another milestone in the field of genetics is the discovery of the model for the structure of DNA as a genetic material by J.D. Watson and F.H.C. Crick in 1953. This was probably the key stone that unlocked an explosion in the field of human genetics as a form of molecular revolution.

Following are some of the fields where human genetics may contribute its knowledge for the betterment of the human society.

- To understand basic principles of inherited variation in man and to understand application of genetics in human life, and
- To answer questions about human nature, understand the diseases and development of effective disease treatment and health care.

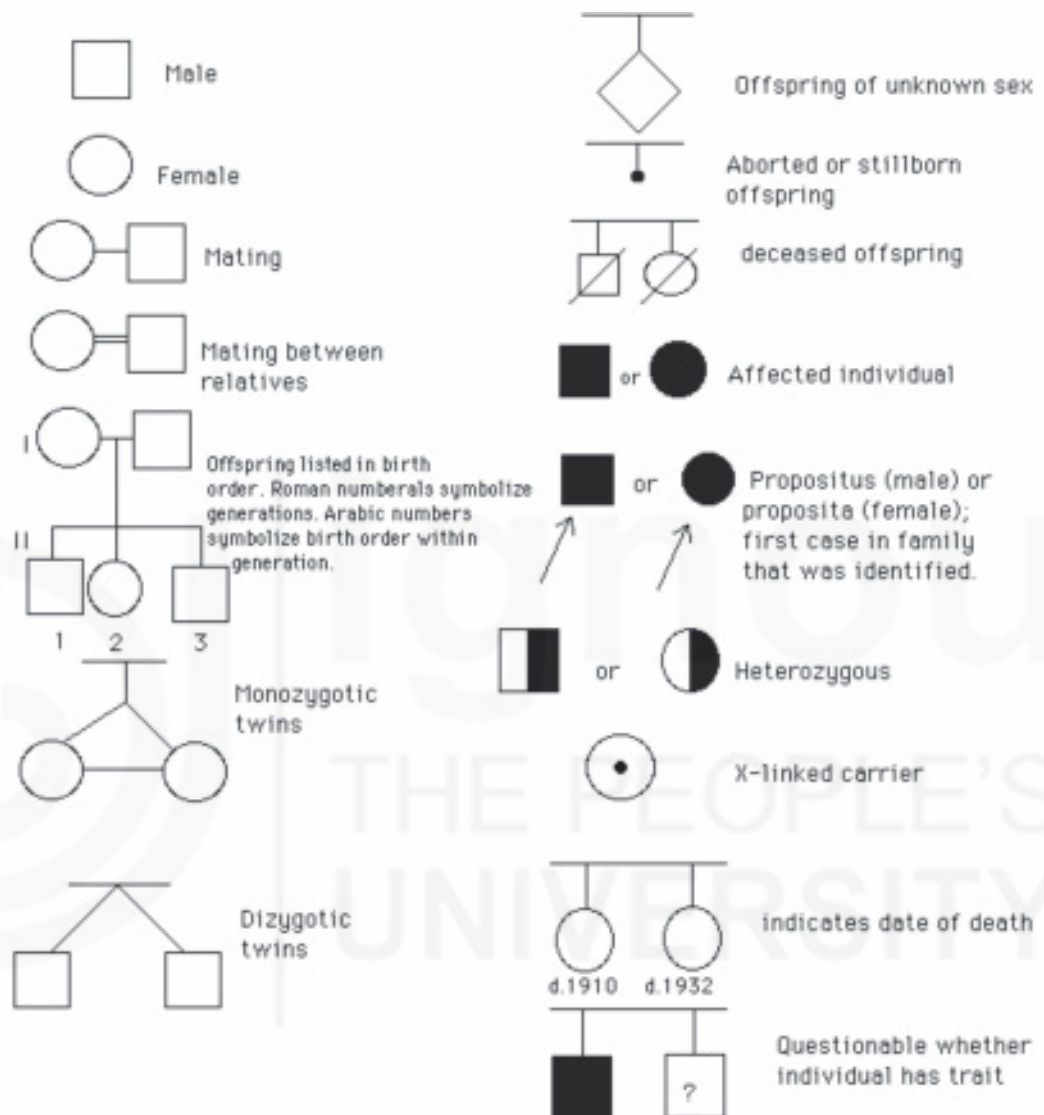
1.3 MENDELIAN INHERITANCE IN MAN

Mendelian traits or traits of simple inheritance are mainly discrete in nature and are controlled by alleles at single genetic locus. Therefore, in humans, traits or disorders that a single gene specifies are said to be Mendelian traits. Currently more than 4500 human traits are said to be inherited as per Mendelian principles; and another large conditions are suspected to be Mendelian traits. Many of the known Mendelian traits may be classified as disorders as per physical or mental disability. However, the most prevalent Mendelian disorders are very rare, usually affecting 1 in 10000 births or even less than that.

Human geneticist unlike others, who carried out experiment on plant or animal, can't have an access over experimental or controlled breeding. Hence they have to confine their study by observing the mode of inheritance in a pedigree. A Pedigree is a systematic drawing of the ancestral line of a given individual (both father and mother side) or family tree of a large number of individuals that depict blood relationship and transmission of inherited traits. A Pedigree can help to determine the genetic basis of a particular trait, especially in human, where experimental mating is not possible.

The term 'pedigree' (line of ancestors) is derived from French word '*pie de grue*' means crane's foot. The diagram of pedigree of large families with parents linked by curved lines to their offspring often resembled a bird's foot. You can tell a mode of inheritance just by looking at a pedigree. Pedigree is built of shapes connected by lines, vertical lines represent generations, horizontal lines that connect two or more shapes at their centers represent parents and vertical lines joined horizontally above them represent siblings. Matings are shown as

horizontal lines between two or more individuals. In case of shapes, *squares* indicate male, *circles* indicate female and *diamonds* for unknown sex. Different shades or colours can be added to the symbols to identify different phenotype — full coloured shapes for individuals who express the trait under study and half-filled for carriers. Each generation is listed on a separate row labeled with Roman numerals, whereas, individuals within a generation labeled by Arabic numerals.



Source: www.bio.classes.UCSC.edu

1.4 TYPES OF INHERITANCE

The patterns, in which Mendelian traits appear or transmitted in families, are called modes of inheritance. On the basis of chromosome where genes are located, you can find two types of inheritance - autosomal i.e. located on autosomes; and sex-chromosomal i.e. located on sex chromosomes, X or Y. Both autosomal and sex chromosomal inheritance may be subdivided as dominant or recessive inheritance on the basis of expression of alleles. However in respect of Y chromosome, there is no such subdivision like that described earlier. Hence, we have five modes of inheritance — autosomal recessive inheritance, autosomal dominant inheritance, X-linked recessive inheritance, X-linked dominant inheritance and Y-linked inheritance.

Mendel's observation of two different expressions of an inherited trait in a single locus (e.g. short or tall in respect of pea plant) narrates the facts that a gene can exist in alternate forms, usually called allele. An individual having two identical alleles is called homozygous, whereas the one with two different alleles is called heterozygous. Hence an individual may be homozygous either by two dominant alleles or two recessive alleles.

The allele that masks the effect of the other allele is called dominant (specifically completely dominant) and the masked one is called recessive. Whether the trait is dominant or recessive mostly depends upon the particular nature of the phenotype. Sometimes the heterozygous behave like an intermediate or a mix between homozygous dominant and homozygous recessive. Recessive disorders, in many cases, tend to be more severe or lethal and produce symptoms at an earlier age than dominant disorders.

If the genetic basis of a trait is known one can predict the outcomes of crosses. These are Punnett square method, forked line method and probability method. The ratios predicted from Mendel's law, apply to a new allele combination to each newly conceived offspring i.e. 50% chance of inheriting the allele, no matter what was the previous combination. You can compare the situation with tossing of coins; for first one the possibility of its being the head (or tail) is 50%. The same is true for second or any subsequent tossing. Therefore, if there is a 25% chance for a recessive disorder and first child is affected, there is no guaranty that next three will not be affected. The best way to calculate the probability of inherited traits was invented by Reginald Punnett and is called Punnett square. This is a simple graphical way to calculate all potential combinations of genotype for each time. You can start the same by drawing a grid of perpendicular lines. Now put the genotype of one parent across the top and other one down the left side. At last you can fill all the boxes by copying row and column letters (alleles).

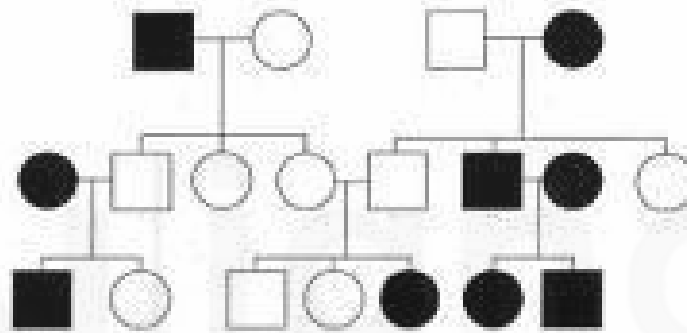


1.4.1 Autosomal Recessive Inheritance

Autosomal recessive trait can affect both sexes in equal proportions and can (but not necessarily) skip generation. The gene is carried on autosomes. For expression of recessive trait to be displayed, two copies of trait or allele needs to be present, which indicate that both the parents must be at least carrier for the specific traits. Therefore, a recessive trait can remain hidden for several generations without displaying the phenotype or diseases. The trait characteristically appears only in sibs, not in their parents, offspring or other relatives.

Sometimes a rare autosomal recessive trait may occur in families where the parents are close (blood) relatives, who are supposed to inherit the allele from a common ancestor. The situation is called consanguinity. Marriages between relatives - "consanguineous marriages", as they are often called, are important genetically.

Because closely related individuals have a higher chance of carrying the same alleles than less closely related individuals. The children from consanguineous marriages are more frequently homozygous for various alleles than are children from other marriages. In some ancient societies like the Pharaohs of ancient Egypt and the Incas of Peru favoured marriages of brothers and sisters of the ruling dynasties, to keep the 'royal blood' pure. These are extreme cases of consanguineous marriages. In some societies, more common types of close consanguinity are observed in cousin marriages. Examples of other consanguineous relations are those between uncle or aunt and nephew or niece (third degree), between cousins (fourth degree) and between second cousins (sixth degree). Consanguinity relations are identified by the number of steps from a common ancestor to only one of the related individuals, namely, the one more remote from him.



Source: www.migeneticsconnection.org

Some important characteristic features are:

- Occurrence and transmission is not influenced by sex;
- Traits can express only in homozygous condition;
- In a pedigree you can find the trait only in siblings, not in their parents;
- On average $\frac{1}{4}$ th of the sibs of the proband are affected;
- In the instance of a rare disease, affected individuals have normal parents;
- Ratio of affected, carrier and non-affected is 1:2:1 (in sibs); and
- Parents of an affected child, in many cases, are close blood relatives.

Results from each of the six possible crosses are summarized in Table 1.1

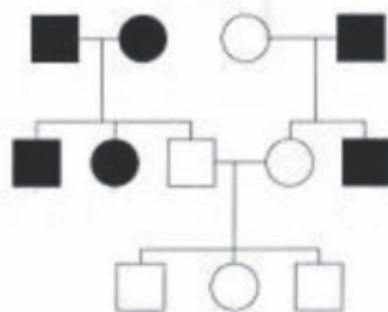
Table 1.1: Summary of Autosomal Recessive inheritance

Parents	Offspring
One parent homozygous Normal Other parent homozygous Normal	All the offspring will be homozygous normal
One parent homozygous Normal Other parent heterozygous Normal (Carrier)	50% probability that offspring will be homozygous normal 50% probability that offspring will be heterozygous normal (Carrier)

One parent heterozygous Normal (Carrier) Other parent heterozygous Normal (Carrier)	25% probability that offspring will be homozygous normal 50% probability that offspring will be heterozygous normal (Carrier) 25% probability that offspring will be affected
One parent homozygous Normal Other parent affected	All the offspring will be heterozygous normal (Carrier)
One parent heterozygous Normal (Carrier) Other parent affected	50% probability that offspring will be heterozygous normal (Carrier) 50% probability that offspring will be affected
One parent affected Other parent affected	All the offspring will be affected

1.4.2 Autosomal Dominant Inheritance

Autosomal dominant trait, like autosomal recessive traits, can affect both sexes in equal proportions; the gene is carried on autosomes but unlike previous one does not skip generations. If no offspring inherits the trait in any generation its transmission stops. The trait is called “dominant” because a single copy of the trait, inherited from either parent, is enough to cause this trait to appear; the dominant allele masks the recessive one. Hence both homozygous dominant and heterozygous individual can express the trait. This often means that at least one parent must have the trait to transmit; otherwise it may appear because of mutation. Unaffected family members do not transmit the trait to their children. Dominance and recessiveness are obviously developmental phenomena resulting from genic action. They refer to the effect of a combination of differing alleles as compared to the effect of a homozygous combination.



Source: www.migeneticsconnection.org

Some important characteristic features are:

- Occurrence and transmission is not influenced by sex;
- Traits can express in both homozygous and heterozygous condition;
- You can find the trait in every generation of a pedigree;
- Affected individuals are usually born of normal parents;
- Affected individuals are always the product of a parent carrier of the same character;

- Trait always transmitted by an affected person (if heterozygous he/she is supposed to transmit the trait to half of the children and if homozygous to all the children); and
- All children of a normal individual will be normal i.e. unaffected family members do not transmit the trait to their children.

Results from each of the six possible crosses are summarized in Table 1.2

Table 1.2: Summary of Autosomal Dominant inheritance

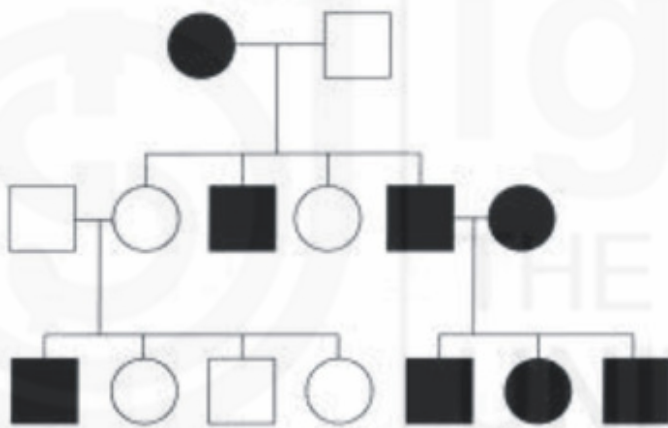
Parents	Offspring
One parent homozygous affected Other parent homozygous affected	All the offspring will be homozygous affected 50% probability that offspring will be homozygous affected 50% probability that offspring will be heterozygous affected
One parent homozygous affected Other parent heterozygous affected	25% probability that offspring will be homozygous affected 50% probability that offspring will be heterozygous affected 25% probability that offspring will be normal
One parent heterozygous affected Other parent heterozygous affected	All the offspring will be heterozygous affected
One parent homozygous affected Other parent normal One parent heterozygous affected Other parent normal	50% probability that offspring will be heterozygous affected 50% probability that offspring will be normal
One parent normal Other parent normal	All the offspring will be normal

Sex-Linkage: In the human species, the sex-chromosomes contain many more genes than those concerned with sex-determination. These affect the widest range of characters and bear no relation to sex. Genes carried in the same chromosome are said to be 'linked' because they are assorted together. Haemophilia is due to the operation of a recessive sex-linked gene. A woman, heterozygous for it is therefore unaffected, since she carries the haemophilia gene (*h*) in one X-chromosome, and its normal allelomorph (*H*) in the other. Normal women can transmit haemophilia while a normal man cannot do so.

Sex-linked Inheritance: Colour blindness is an example of sex-linked inheritance in man. Women are much less often colour blind than men. But if a woman does happen to be colour blind, and if she marries a normal man, all of her sons are colour blind but none of her daughters are.

1.4.3 X-linked Recessive Inheritance

Sex-linkage was first discovered by Thomas H. Morgan (father of modern genetics) in 1910. Sex-linked traits affect male and female differently. As human male is hemizygous for X-linked traits, any gene on a male's X chromosome is expressed in his phenotype because there is no such second allele to mask its expression. Therefore, the condition of dominant and recessive trait is limited to female only. Females express X-linked traits or disorders when they are homozygous for the disorder and become carriers when they are heterozygous. Therefore female can transmit the trait as affected if her father is affected and mother at least carrier. However male can transmit the trait if any of the parents is affected or carrier (for mother). Therefore, the incidence is much higher in males than females. These patterns of inheritance are also called crisscross inheritance or skip generation inheritance, in which a character is inherited to the second generation through the carrier of first generation. X-linked (both recessive and dominant) traits are always passed on by the X chromosome from mother to son or from either parent to daughter. The trait never passed from father to son. The human male is hemizygous in respect of X-linked inheritance as they have single copy of X chromosome.



Source: www.migeneticsconnection.org

Some important characteristic features are:

- Occurrence and transmission is influenced by sex; males are more affected than females;
- Affected male does not transmit the trait to his sons but always transmits to all his daughters;
- Carrier female can transmit the trait to half of her children of either sex;
- The trait is transmitted from affected male through all his daughters to half of his grandsons; and
- The trait may be transmitted through a series of carrier females; carrier shows variable expression of the trait.

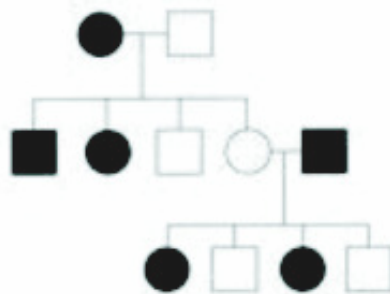
Results from each of the six possible crosses are summarized in Table 1.3

Table 1.3: Summary of X linked Recessive inheritance

Parents	Offspring
Mother homozygous Normal Father Normal	All the offspring will be homozygous normal
Mother homozygous Normal Father affected	All the daughters will be heterozygous normal (carrier) All the sons will be normal
Mother heterozygous Normal (carrier) Father Normal	50% probability that daughter will be homozygous normal 50% probability that daughter will be heterozygous normal (carrier) 50% probability that son will be normal 50% probability that son will be affected 50% probability that daughter will be heterozygous normal (carrier) 50% probability that daughter will be affected
Mother heterozygous Normal (carrier) Father affected	50% probability that son will be normal 50% probability that son will be affected
Mother affected Father normal	All the daughters will be heterozygous normal (carrier) All the sons will be affected
Mother affected Father affected	All the offspring will be affected

1.4.4 X-linked Dominant Inheritance

X-linked dominant inheritance shows the same phenotype as a heterozygote and homozygote. In case of an X-linked dominant inheritance, male to male transmission is not there. This also makes it distinct from autosomal traits. X-linked dominant cannot be distinguished from Autosomal Dominant by progeny of affected females, but only from the progeny of affected males. Affected females are more common than affected males (but heterozygous females have milder expression); on the other hand the traits (especially disorder) are more severe in males than their female counterparts.



Source: www.migeneticsconnection.org

Some important characteristic features are-

- Occurrence and transmission is influenced by sex; females are more affected than males but may be with variable expressions;
- Homozygous female transmitted the trait to all the children;
- Male transmitted the trait to all the daughters but never to a son;
- Affected males have no normal daughter;
- Affected heterozygous females transmit the trait to half of their children of either sex. Affected homozygous females transmit the trait to all their children; and
- X linked dominant cannot distinguish from Autosomal Dominant by progeny of affected females, but only from the progeny of affected males.

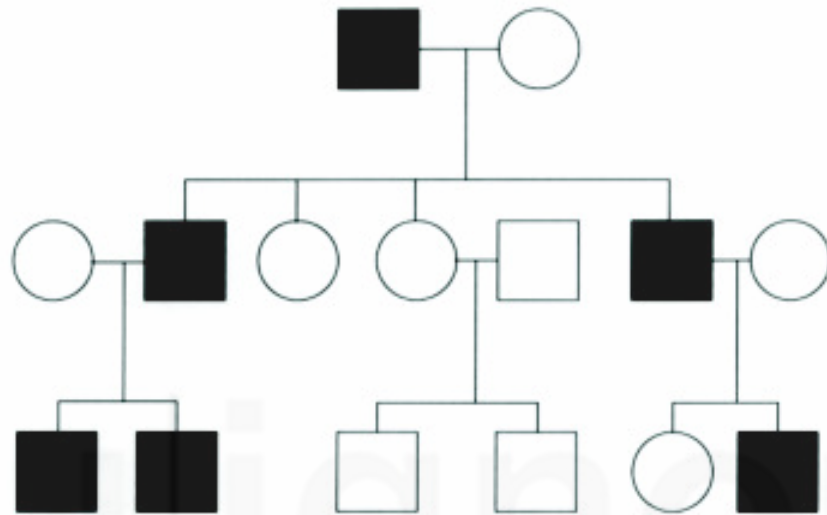
Results from each of the six possible crosses are summarized in Table 1.4

Table 1.4: Summary of X linked Dominant inheritance

Parents	Offspring
Mother homozygous affected Father affected	All the offspring will be homozygous affected
Mother homozygous affected Father normal	All the daughters will be heterozygous affected All the sons will be affected
Mother heterozygous affected Father affected	50% probability that daughter will be homozygous affected 50% probability that daughter will be heterozygous affected 50% probability that son will be affected 50% probability that son will be normal
Mother heterozygous affected Father normal	50% probability that daughter will be heterozygous affected 50% probability that daughter will be normal 50% probability that son will be affected 50% probability that son will be normal
Mother normal Father affected	All the daughters will be heterozygous affected All the sons will be normal
Mother normal Father normal	All the offspring will be normal

1.4.5 Y-linked Inheritance

The genes located on the Y chromosome, whose alleles are absent on the X chromosome are Y-linked genes or holandric genes (also hemizygous). Y-linked inheritance occurs when a gene is transmitted through the Y chromosome. Since Y chromosomes can only be found in males, hence Y linked genes are only passed on from father to son and never appear in females. Therefore, there is no skipping of generation and affected males have all affected sons, no females are said to be affected for the trait (www.sakshieducation.com).



Source: www.migeneticsconnection.org

Some important characteristic features are-

- In pedigree, only males are affected;
- Affected male transmitted the trait to all his sons but never to his daughter; and
- No skipping of generations.

Results from each of the two possible crosses are summarized in table 1.5

Table 1.5: Summary of Y-linked inheritance

Father	Offspring
Father affected	All the sons will be affected
Father normal	All the sons will be normal

1.5 EXAMPLES

Traits/ Description	Autosomal Recessive	Autosomal Dominant
Albinism: is a form of hypopigmentary congenital disorder, characterised by a partial or total lack of melanin pigment in the eyes, skin and hair (or more rarely the eyes alone).	Albinism	Normal pigmentation

Thalassemia: Human haemoglobin molecule consists of two alpha and two beta globin chains conjugated with heme. In alpha Thalassemia alpha chain is missing or defective and in beta Thalassemia beta chain is absent which leads to iron overload and anemia.	Thalassemia	Normal
Cystic Fibrosis: Cystic fibrosis is an inherited disease that causes thick, sticky mucus to be built up in the lungs and digestive tract. It is one of the most common chronic lung diseases in children and young adults, and may result in early death.	Cystic Fibrosis	Normal
Tay-Sachs disease: Tay-Sachs disease is caused by a mutation on chromosome 15. Tay-Sachs disease occurs when the body lacks hexosaminidase A, a protein that helps break down a chemical found in nerve tissue called gangliosides.	Tay-Sachs disease	Normal
Xeroderma pigmentosum: A disruption of affected person's DNA's ability to repair damage caused by ultraviolet radiation of sunlight.	Xeroderma pigmentosum	Normal
Hitchhiker's thumb: More formally known as "distal hyper extensibility of the thumb" can extend the top of the thumb backwards nearly 90° when the thumb is extended in a "thumbs-up" position.	Hitchhiker's thumb	Straight thumb
Dentinogenesis imperfecta: Pulp chambers and root canals of teeth are obliterated with abnormal dentin. There is also an increased constriction and junction between the crowns and the roots of the molar.	Normal teeth	Dentinogenesis imperfecta
Cleft Chin: It is a Y-shaped fissure on the chin with an underlying bony peculiarity.	No Cleft Chin	Cleft Chin
Brachydactyly: Better known as clubbed thumb, is a condition where the thumbs are shorter and stubbier than normal. Brachydactyly is a genetically inherited trait that is often dominant.	Normal thumb	Brachydactyly

PTC taste sensitivity: Phenylthio-carbamide also known as PTC is anorganosulfur thiourea containing a phenyl ring. A crystalline compound, $C_6H_5NHCSNH_2$, that tastes intensely bitter to people with a specific dominant gene and tasteless to others.	Non-taster	Taster
Achondroplasia: Characterized by prominent forehead, low nasal root, redundant folds in arms and legs accompanied by short-limbed dwarfism.	Normal	Achondroplasia
Familial Hypercholesterolemia: Characterized by high LDL in blood resulting to deposition of cholesterol in arteries, tendons, skin, etc., which may leads to coronary artery diseases.	Normal	Familial Hypercholesterolemia

Traits/ Description	X-linked Recessive	X-linked Dominant
Duchene muscular dystrophy: It is an inherited disorder that involves rapidly worsening muscle weakness.	Affected	Normal
Haemophilia A: Occurs due to the deficiency of factor VIII in blood. Affected persons are unable to produce a factor needed for blood clotting, therefore the cuts, wounds, etc., of haemophilic persons continue to bleed and sometimes (if not stopped by clotting factors) leads to death.	Haemophilia A	Normal
Red green color blindness: Colour perception is mediated by light absorbing protein in the cone cells of the retina in the eye. Colour blindness is caused by an abnormality in any of the receptor protein. Red green colour blindness is the ability to perceive the colour green and red.	Red green color blindness	Normal vision
G6PD deficiency: It is an inherited disorder in which the body doesn't have enough enzyme glucose-6-phosphate dehydrogenase, or G6PD, which helps red blood cells (RBCs) function normally, and deficiency may cause hemolytic anemia.	G6PD deficiency	Normal

Incontinentia pigmenti: Incontinentia pigmenti is a genetic defect on X chromosome which leads to unusual blistering and changes in skin color.	Normal	Incontinentia pigmenti
Fragile X syndrome: Fragile X syndrome is a genetic condition involving changes in part of the X chromosome resulting in mental retardation.	Normal	Fragile X syndrome
Congenital generalized hypertrichosis: Person has more hair follicles which lead to dense and more abundant terminal hair. Generally, it causes excess facial and upper body hair that covers extensive areas of skin.	Normal	Congenital generalized hypertrichosis

Y-linked traits
Hypertrichosis of ear: growth of hair on the rim of pinna
Testis determining factor (TDF)

Note: You can find out more examples from NCBI databases OMIM: Online Mendelian Inheritance in Man

Sex-limited and Sex-controlled Traits

So far we have been discussing about sex-linked traits, but there are some such genes which are sex-limited in their effect, that is, they are expressed phenotypically in one sex only. In man sex-limited expression of genes occurs in uterine (in female) and prostate (in male) cancer. Anatomical and physiological properties of the female sex, such as width of pelvis or age of onset of menstruation is a sex-limited expression. Similarly, sex-limited male characters such as type of beard growth or amount and distribution of body hair, probably depend on genes common to both sexes, but the penetrance and expressivity of the genes are more limited to males. Sex-limitation is only the extreme example of control of the expression of certain genotypes by sex.

When a genotype is expressed in both sexes but in a different manner in each, we speak of sex-controlled, or sex-modified, genic expression. Sex-controlled dominance has been suggested as an explanation of the pattern of inheritance of baldness in man. Both sexes may be affected, but the high relative frequency of affected males is notable. Some of these traits are controlled by the sexual constitution of the individual and thus are under the influence of sex hormones.

1.6 SUMMARY

Mendel considered a single gene to be responsible for a single trait, but after the discovery of other types of non-Mendelian inheritance it is now clear that many genes may be involved for the production of single or many traits. Mendel's

laws also incorporate many of the modern discoveries which enriched these laws. For example, chromosome or meiosis was discovered after Mendel's work. Now we can correlate that Mendel's first law i.e. law of segregation is about anaphase-I where homologous chromosomes segregate from each other. Similarly as per second law, segregation of alleles for one character follow independently of the segregation of allele of other character because each pair of homologous behaves like an independent unit during meiosis. Again, especially after modern discovery, we can understand that it is the gene and not the trait (as per Mendel) that are inherited.

Since Mendel's time, understanding of the mechanisms of genetic inheritance has grown immeasurably. The simple rules of Mendelian inheritance do not apply in elucidating many of the inheritance patterns, and are understood to be non-Mendelian inheritance patterns.

1.7 GLOSSARY

Allele	: an alternate form of gene that determine alternate traits or characteristics.
Autosomal dominant	: the inheritance pattern of a dominant allele on autosomes.
Autosomal recessive	: the inheritance pattern of a recessive allele on autosomes.
Autosomes	: a non-sex determining chromosome. Human has 22 pairs of autosomes.
Carriers	: a heterozygous individual who possess a deleterious recessive allele which is suppressed by dominant normal allele.
Chromosome	: a structure within a cell's nucleus that carries gene and consists of a continuous molecule of DNA and proteins.
Consanguineous	: relating to or denoting people descended from the same ancestor.
Dominant trait	: the trait that is expressed in the F_1 generation.
DNA	: a long linear polymer found in the nucleus of a cell, formed from nucleotides and shaped like a double helix; generally associated with the transmission of genetic information.
Gene	: a sequence of DNA that instructs a cell to produce a particular protein.
Genetics	: branch of biology that concerned with heredity and variation.
Heterozygous	: having two different alleles of a gene at a single locus and produces different kinds of gametes.
Homozygous	: having two identical alleles of a gene single locus and produces only one kind of gamete.

Mutant	: an allele that differs from wild type allele, altering the phenotype.
Mutation	: any event that changes genetic structure; any alteration in the inherited nucleic acid sequence of the genotype of an organism.
Pedigree	: a chart consisting of symbols for individuals connected by lines that depict blood relationships and transmission of inherited traits.
Probability	: probability is a way of expressing mathematical knowledge that an event will occur or has occurred.
Proband	: proband, or propositus, is a term used most often in genetics to denote a particular subject (person in human genetics) being studied or reported on.
Protein	: a type of macromolecule that is the direct product of genetic information.
Recessive trait	: the trait that is masked in the F_1 hybrids.
Sex cells	: sex cells are the cells that give rise to the gametes of organisms that reproduce sexually.
Sex Chromosome	: a chromosome containing genes that specify sex.
Sex linked	: genes that are part of a sex chromosome.
Variable expression	: a genotype producing phenotype that varies among individuals.
X linked dominant	: the inheritance pattern of a dominant allele on X chromosome.
X linked recessive	: the inheritance pattern of a recessive allele on X chromosome.
Y linked	: the inheritance pattern of a gene on Y chromosome.

Suggested Reading

Cummings, M. R. 1997. *Human Heredity: Principles and Issues*. Belmont, Wadsworth.

Gardner, E. J., Simmons, M.J. and Snustad, D.P. 1991. *Principles of Genetics*. New York, John Willey & Sons.

Lewis, R. 2003. *Human Genetics: Concepts and Applications 5th edition*. Boston, WCB McGraw Hill.

Stern, C. 1960. *Principles of Human Genetics* (2nd Edition). San Francisco and London, W. H. Freeman and Company.

Strickberger, M. W. 2003. *Genetics 3rd edition*. New Delhi, Prentice Hall.

Website

Mendel Web: www.mendelweb.org

National Center for Biotechnology Information: Online Mendelian Inheritance in Man: www.ncbi.nih.gov

www.sakshieducation.com

Sample Questions

- 1) What is autosomal recessive trait? From marriages between normally pigmented carrier people and albinos what proportion of children would be expected to be albino and normal? What is the chance in a family of three children that one would be normal and two albinos?
- 2) What do you mean by X linked recessive trait? From marriage between carrier female and affected male what proportion of children would be expected to be Haemophilic?
- 3) What do you mean by Human Genetics? Write a brief note on Mendelian genetics in Man.
- 4) What are X linked traits? How does X linked dominant trait is differentiated from Autosomal dominant trait?
- 5) What is Pedigree? Draw a pedigree of X linked recessive traits in Man.



UNIT 2 METHODS OF HUMAN GENETIC STUDY

Contents

- 2.1 Introduction
- 2.2 Pedigree
- 2.3 Chromosome Analysis
- 2.4 Karyotype Analysis
- 2.5 Cytogenetic Methods
- 2.6 DNA and Recombinant Technology
- 2.7 Biochemical Methods
- 2.8 Paternity Testing
- 2.9 Twin Studies
- 2.10 Immunological Methods
- 2.11 Summary
- References
- Suggested Reading
- Sample Questions



Learning Objectives

Once you have read the unit, you will understand that, there are:

- various classical and modern techniques developed for human genetics study;
- techniques aimed to put light on various processes that help to understand and identify some specific diseases and disorders;
- classical genetic methods like pedigree studies and twin studies are very important to understand the role of heredity and the environment in the manifestation of some physical traits in man, and some physiological and pathological conditions, and diseases like tuberculosis, cancer, etc.; and
- twin study methods help us to understand how much the variability observed between different individuals, or individuals of the same familial group, is due to hereditary differences and how much differences due to environmental factors.

2.1 INTRODUCTION

At first sight, man appears to be an unfavourable object for genetic study. Plant and animal geneticists use breeding methods to raise successive generations under similar environmental conditions.

In man, however, the genetic diversity of individuals is great and uncontrolled, and biological and social environment vary greatly. In man, as we cannot do experimental crossing, so the studies on inheritance pattern are based on a series of generations.

For human genetical study, the observer, that is the geneticist, and the object of his observation, a family, or pedigree, of say three to four generations, is restricted, as the duration of a generation is alike in the observer and in the object of observation. Many factors affecting transmission of hereditary traits obey statistical laws and are best studied when large numbers of offspring are available. In man, these numbers are always small, even large human families fall far short of the size desirable for statistical deductions.

Genetic differences between two individuals may consist of differences between the alleles at a single pair of loci or between those at more than one pair of loci. An example of a 'single factor inheritance' showing simple dominant inheritance was found in an extensive pedigree of a rare type of unusually woolly hair in Norwegian kindred, reported in the year 1932. It has been propagated for at least five generations. So we find pedigree studies help us to understand the nature of inheritance of a specific familial trait.

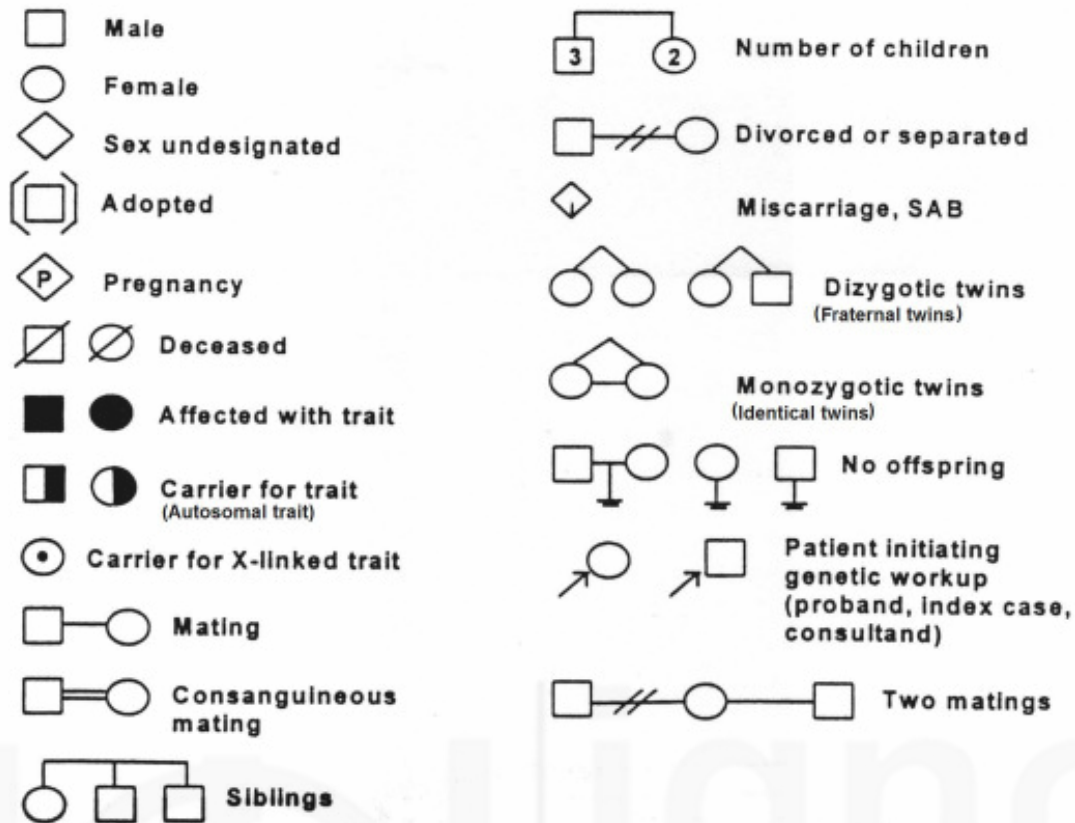
Through the statistical analysis of covariance and discriminant analysis of morphological and anatomical traits the study of human diversity has been greatly advanced.

Methods of human genetic studies may be taken up at the family / pedigree level by simple or clinical observation, while at the cellular level through chromosomal studies of particular cases in families. At the population level for understanding human variation of different morphological anthropometric traits, dermatoglyphics and other anatomical traits, population sero-genetical markers like blood groups, PTC, ABH secretion etc., and biochemical traits like G6PD, haptoglobin and transferrin, and other red cell enzyme polymorphisms through electrophoretic methods are being conducted. Lately DNA fingerprinting techniques are being used to assess migration and population affinities of different ethnic groups and their biochemical relationship at different levels. These are highly specialised methods of study of human population groups at the genic level.

We will discuss briefly about all these methods of human genetic studies at the family and population level, so as to make you aware about the different methods of human genetic studies now normally being used by human geneticists.

2.2 PEDIGREE

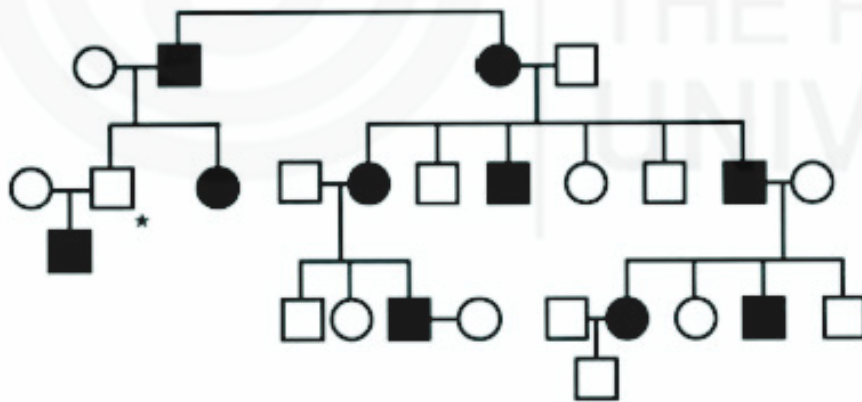
A pedigree is a diagram of family relationships in which symbols are used to represent people, and lines are used to represent genetic relationships. These diagrams make it easier to visualize the relationships within the families, particularly large extended families. Pedigrees are also often used to determine the mode of inheritance of genetic diseases (Strachan and Read. 1999).



(Adapted from: www.uic.edu)

We can use pedigree to study different modes of inheritance:

Autosomal Dominant inheritance

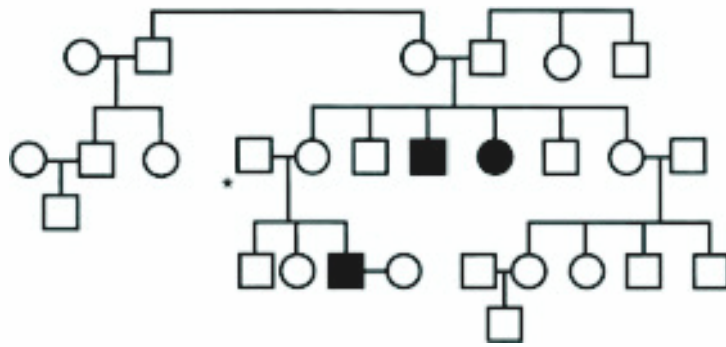


(p= proband)

(Adapted from www.bios.niu.edu/johns/genetics)

The major characteristics are following:

- It manifests in the heterozygous state i.e. in a person possessing both an abnormal and normal allele,
- Gene is located on autosome,
- Both males and females are equally affected, and
- Vertical family history may be seen and male to male transmission is possible.
Example: Marfan syndrome, Huntington's disease.

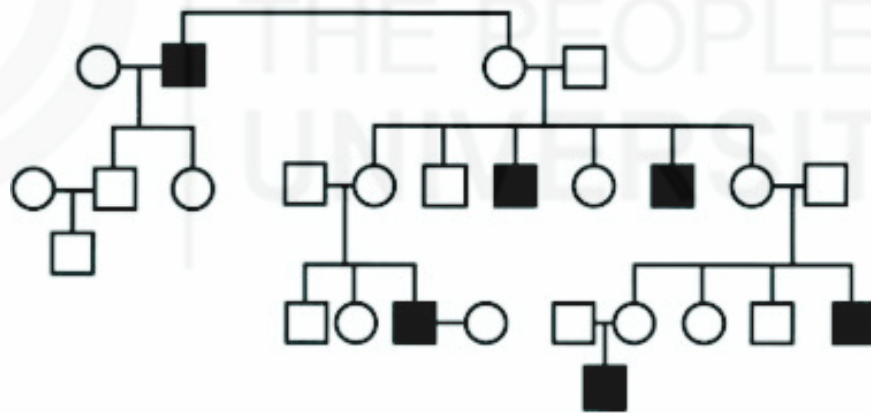
Autosomal recessive inheritance

(Adapted from www.bios.niu.edu/johns/genetics)

The major characteristics are the following:

- The gene is located on autosome,
- Two copies of the mutant gene is necessary for phenotypic manifestations,
- Males and females are equally affected,
- Pedigree may show several sibs and cousins affected in the same generation indicating a horizontal transmission, and
- Consanguinity is often present.

Example: Phenylketonuria, Homocystinuria, Cystic fibrosis

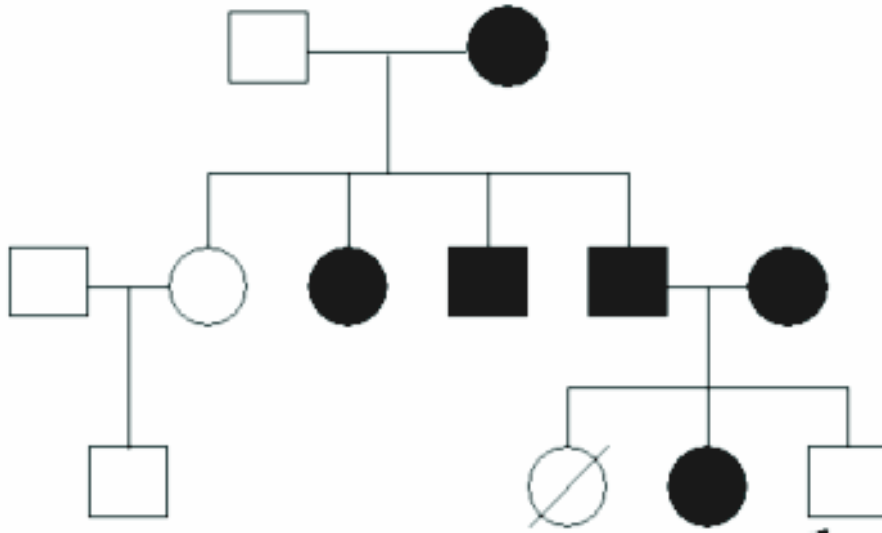
X-linked recessive inheritance

(Adapted from www.bios.niu.edu/johns/genetics)

The major characteristics are the following:

- The mutant gene is on the X-chromosome,
- One copy of mutant gene in males and two copies of mutant gene in females are needed for phenotypic effect,
- Usually males are affected and transmission is through heterozygous (carrier) females,
- No male to male transmission, and
- All daughters of affected males will be carriers.

Example: Duchenne's muscular dystrophy (DMD), hemophilia, color blindness



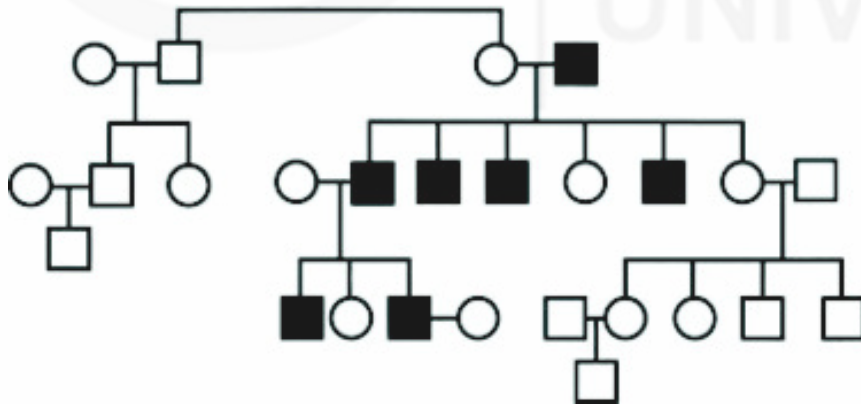
(Adapted from www.bios.niu.edu/johns/genetics)

The major characteristics are the following:

- Affected males have no normal daughters and no affected sons,
- The pattern of inheritance resembles autosomal dominant,
- No male to male transmission, and
- Affected heterozygous females transmit the condition to half of their children of either sex and affected homozygous females transmit to all their children.

Example: Vitamin D resistant rickets, orofacial digital syndrome.

Y-linked inheritance

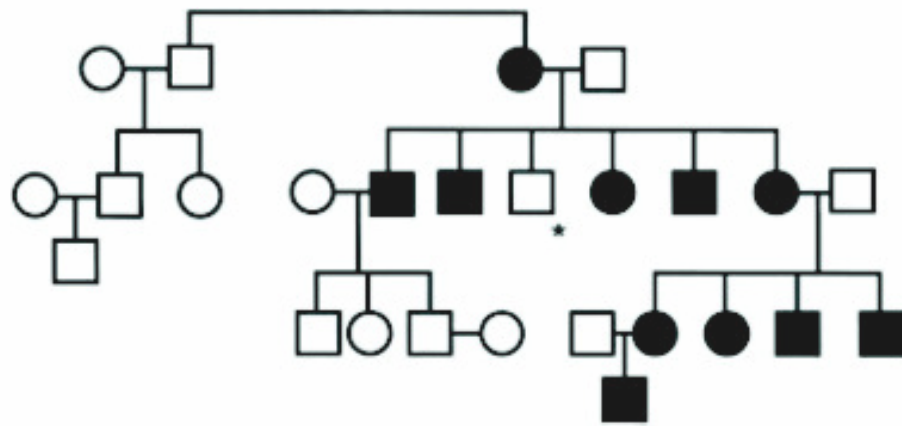


(Adapted from www.bios.niu.edu/johns/genetics)

The major characteristics are the following:

- Only males are affected, and
- Affected males must transmit the disorder to their sons.

Example: Male infertility.



(Adapted from www.bios.niu.edu/johns/genetics)

- Trait is transmitted through affected females, and
- Affected males give rise to unaffected offspring.

Example: Inherited blindness (Leber's hereditary optic neuropathy) and a type of deafness (Muller and Young, 2001).

2.3 CHROMOSOME ANALYSIS

Genes form the physical hereditary link between generations. A typical human body cell contains about 40,000 genes. The genes do not exist as a separate unit, but are arranged in a linear order on thread like bodies known as chromosomes, within the nucleus of a cell. Chromosomes become shortened and thickened during cell division and can be seen clearly under the microscope.

Chromosomes are microscopic filamentous structures that contain an individual's genetic material. This genetic material serves as the "instruction manual" for the body, containing the "directions" the body needs in order to form and function properly. Human cells have a total of 46 chromosomes, which are arranged into 23 pairs. We inherit one member of each pair from our biological mother, and the other member of each pair from our biological father. The first 22 pairs of chromosomes are called "autosomes" and the last pair is called the "sex chromosomes". Females typically have two "X" sex chromosomes, while males typically have one "X" and one "Y" sex chromosome (Tseng, 1995).

Let us know what is a chromosome analysis?

Chromosome analysis is a study of the number and general structure of all 46 chromosomes, it is also known as a karyotype. In a standard karyotype, chromosomes from cells in the body are counted to ensure that the cells have the correct number of chromosomes, and their structure is analysed to ensure that there are no large pieces of material that are missing (deleted), extra (duplicated), or rearranged in any way. It is important to realise that standard chromosome analysis may not be able to detect tiny deletions or duplications of genetic material and will not be able to detect single gene conditions, such as sickle cell disease. Hundreds of different types of chromosome abnormalities causing well described syndromes have been reported in humans. They fall into two categories:

- ✓ Numerical Chromosome Abnormality means that a person has a total number of chromosomes different from 46; usually 47 or sometimes 45 chromosomes, in each cell of their body, respectively. An example of a numerical chromosome abnormality is Down syndrome, which is caused by having an entire extra chromosome 21, for a total of three copies of chromosome 21 instead of two (www.genetics.emory.edu).
- ✓ Structural Chromosome Abnormality means that a portion of the genetic material has been rearranged in some way; for example, a piece of one chromosome may be attached to another chromosome (translocation), or a piece of a chromosome may be turned upside down (inversion). A rearrangement may or may not result in obvious health problems. This depends on whether the structural problem ultimately results in a net gain or loss of chromosome material. If the chromosome material is simply in a rearranged fashion, but all of the genetic information is present, the person may have no symptoms and this is known as a balanced rearrangement (www.genetics.emory.edu).

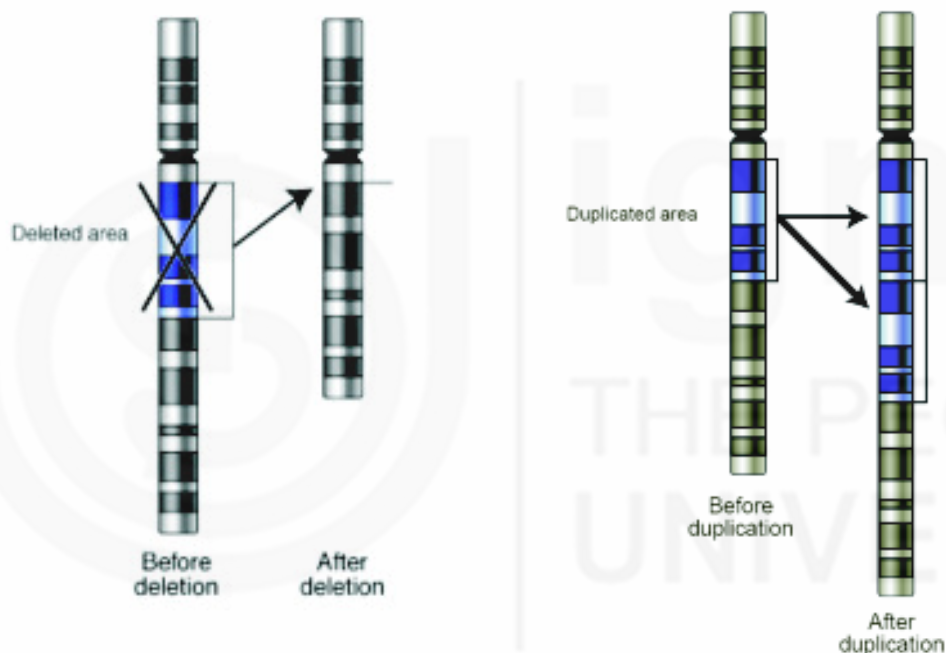


Fig. 2.1: Deletion and Duplication (Adapted from www.ghr.nlm.nih.gov)

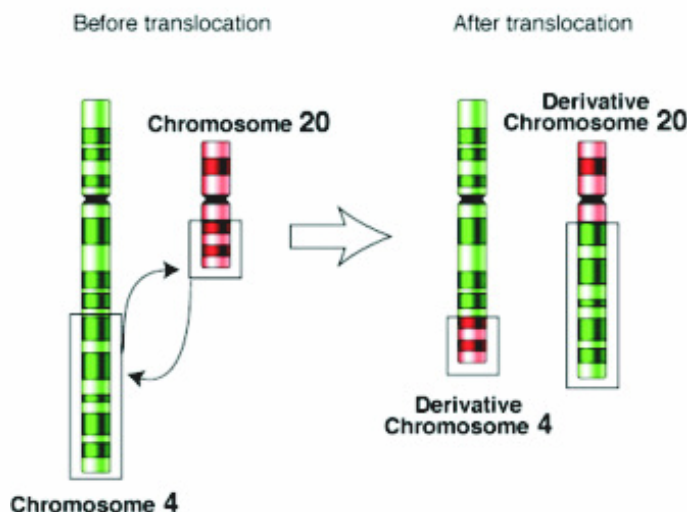


Fig.2.2: Translocation between chromosome 20 and 4 (Adapted from www.ghr.nlm.nih.gov)

Requirement for chromosome analysis:

Chromosome analysis is recommended as a routine diagnostic procedure for a number of indications, including the following:

- Problems noted during early growth/development,
- Stillbirths and neonatal deaths,
- Fertility problems,
- Pregnancy in women 35 years or older at the time of delivery, and
- Family History (Rowley. 2001).

2.4 KARYOTYPE ANALYSIS

Karyotype is the number and appearance of chromosomes in the nucleus of a eukaryotic cell. The term is also used for the complete set of chromosomes in a species, or an individual. Karyotype analysis involves visualization of chromosomes under a microscope. Cells are collected from an individual, induced to divide, and then arrested at metaphase. The chromosomes are stained with certain dyes that show a pattern of light and dark bands (called the banding pattern). The banding pattern for each chromosome is specific and consistent allowing identification of each of the 24 chromosomes (Comai, 2005).

Karyotype analysis can be performed on virtually any population of rapidly dividing cells either grown in tissue culture or extracted from tumors. Chromosomes derived from peripheral blood lymphocytes are ideal because they can be analysed three days after they are cultured. Lymphocytes can be induced to proliferate using a mitogen (a drug that induces mitosis) like phytohemagglutinin. The cultured cells are treated with colcemid, a drug that disrupts the mitotic spindle apparatus to prevent the completion of mitosis and arrests the cells in metaphase. The harvested cells are treated briefly with a hypotonic solution. This causes the nuclei to swell making it easier for technicians to identify each chromosome. The cells are fixed, dropped on a microscope slide, dried, and stained. The most common stain used is the Giemsa dye. Other dyes, such as fluorescent dyes, can also be used to produce banding patterns (www.bookrags.com).

Chromosome spreads can be photographed, cut out, and assigned into the appropriate chromosome number or they can be digitally imaged using a computer. The chromosomes can be divided into seven groups (A-G) based on descending order of size and position of the centromere. The standard nomenclature for describing a karyotype is based on the International System for Human Cytogenetic Nomenclature (ISCN) (www.science.jrank.org).

Genetic counselors rely on karyotypes to diagnose abnormal pregnancies. Amniocentesis is a routine procedure used in prenatal screening that involves removing amniotic fluid for karyotype analysis. It also can be helpful in certain cases to obtain karyotypes from parents to determine carrier status, which can be relevant to recurrence risks in future pregnancies. Karyotype also may help determine the cause of infertility in patients having reproductive difficulties (www.bookrags.com).

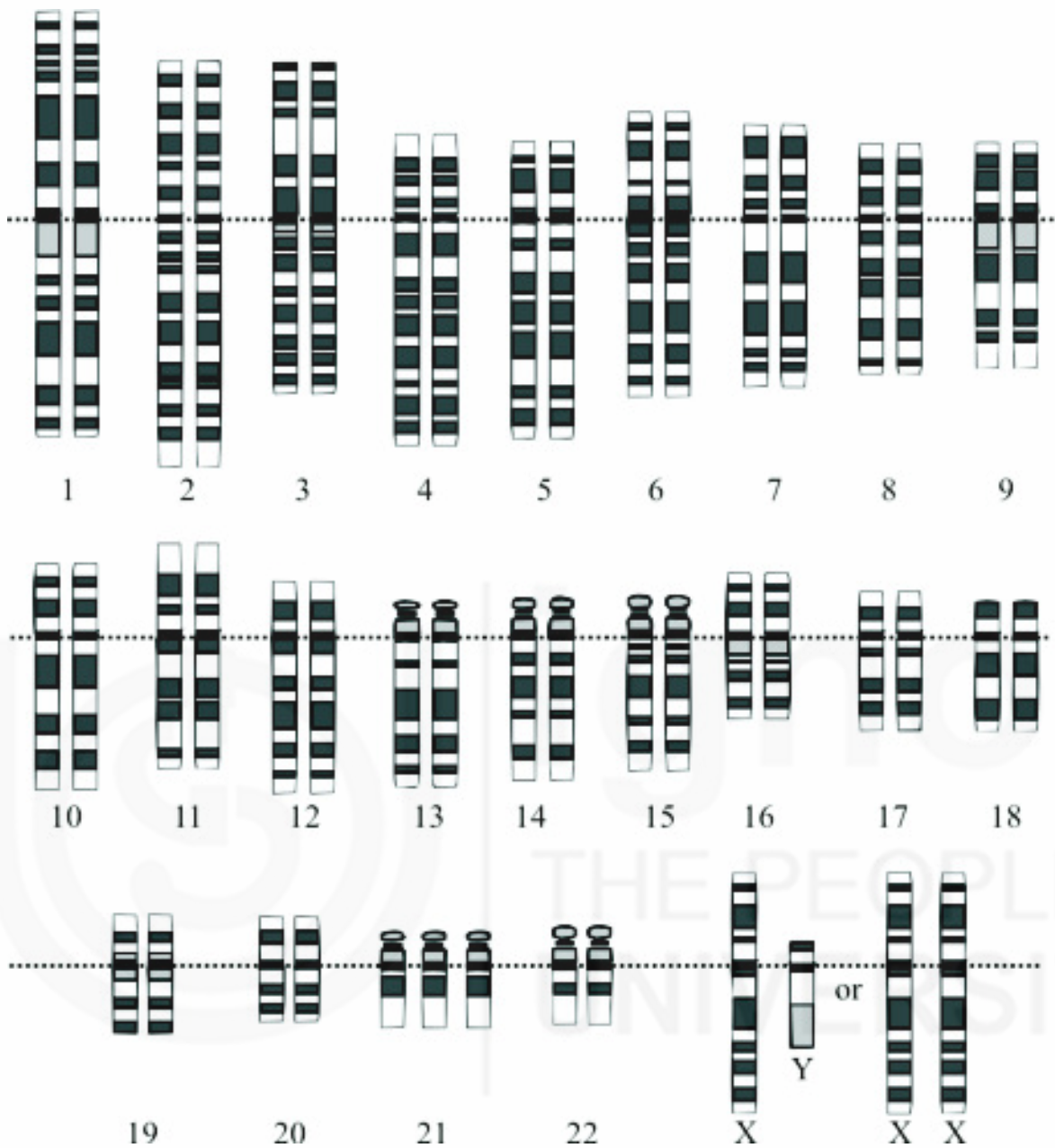


Fig.2.3: Trisomy 21 (Down syndrome)

(Adapted from Human Genome Project)

Trisomy 21 is the presence of 3 chromosome 21 and causes the condition commonly known as Down syndrome

Klinefelter syndrome

A male with the genotype 47, XXY with extra X chromosome leads which to features of the condition commonly known as Klinefelter syndrome.



Fig.2.4: Klinefelter's Syndrome

(Adapted from www.trueknowledge.com)

Turner's syndrome: A female with genotype (45, X), with one X chromosome missing

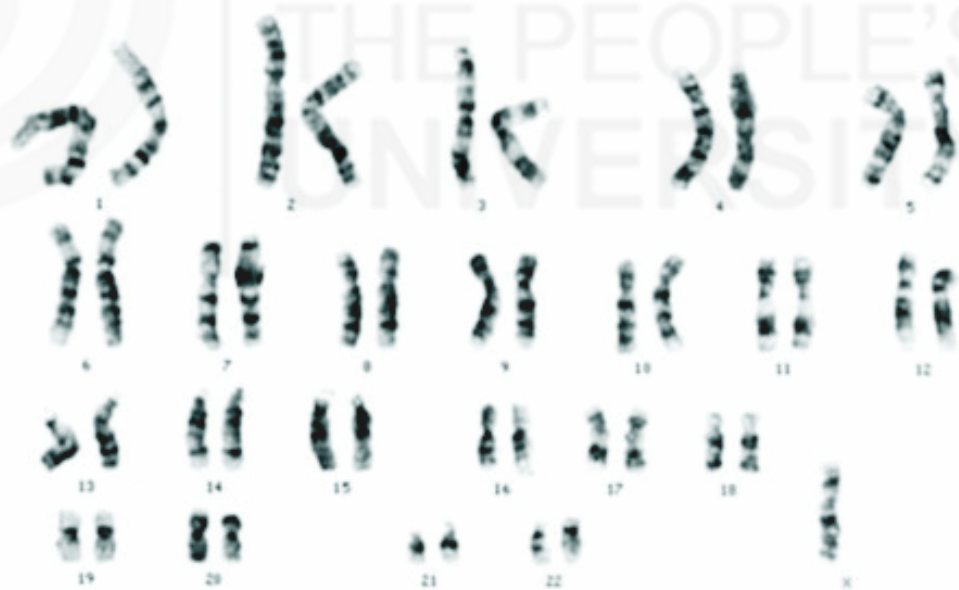


Fig.2.5: Turner's Syndrome

(Adapted from www.powerofthegene.com)

2.5 CYTOGENETIC METHODS

Cytogenetics is a branch of genetics that is concerned with the structural and functional studies of the cell, especially the chromosomes. It includes routine analysis of G-banded chromosomes, other cytogenetic banding techniques, as well as molecular cytogenetics such as fluorescent in situ hybridization (FISH) and comparative genomic hybridization (CGH).

(www.doctorsmedicalopinion.com).

Chromosome banding

Different staining methods can be utilised to identify individual chromosomes:

G (Giemsa) banding: This is the most commonly used method. The chromosomes are treated with trypsin to denature their protein content and then stained with a DNA binding dye known as Giemsa which gives each chromosome a characteristic and reproducible pattern of light and dark bands (www.scribd.com).

Q (Quinacrine) banding: This gives a banding pattern similar to that obtained with Giemsa and requires examination of the chromosome with an ultraviolet fluorescent microscope (www.bogari.net).

R (Reverse) banding: In this technique, the chromosomes are heat denatured before staining with Giemsa, yielding light and dark bands patterns which are reverse of those obtained using conventional G banding (www.bogari.net).

C (Centromeric heterochromatin) banding: In C banding the chromosomes are pretreated with acid prior to G banding, the centromeres and other heterochromatic regions containing highly repetitive DNA are preferentially stained (Muller and young. 2001).

2.6 DNA AND RECOMBINANT TECHNOLOGY

The recombinant DNA technology also called as genetic engineering, involves artificial modification of genetic constitution of a living cell by introduction of foreign DNA through experimental techniques. The tools which are required in recombinant DNA include vectors, restriction enzymes, ligases and host organism.

Applications

- For the production of recombinant human peptide hormones:-These include highly publicized family of products of recombinant DNA technology. These include Insulin, Human growth hormone (HGH), Follicle stimulating hormone (FSH), Luteinizing hormone(LH), epidermal growth factors, gastrin, relaxin, neuropeptides (calcitonin) and secretin
 - **Insulin:** Insulin is secreted by the β cells of the pancreas. It is required for the cellular uptake of glucose for use in energy metabolism. When produced in insufficient amount it causes diabetes mellitus. It is made of 51 amino acids, consisting of two interconnecting chains: chain A and chain B. Chain A is made of 31 amino acids and chain B of 20 amino acids. In the formation of recombinant insulin, the two chains are synthesized in separate bacteria. In one vector the gene for chain A is inserted and in other vector the gene for chain B is inserted and then these two chains are joined in vitro with the help of disulphide bonds. Humulin (human insulin) was the first recombinant DNA product to be approved by food and drug administration insulin in 1986 (Gupta. 2003).

- Human growth hormone (HGH): This hormone stimulates growth and cell reproduction. It is secreted by the somatotroph cells of anterior pituitary gland. When present in insufficient amount it causes retarded growth, body fat at the waist and dwarfism. It is made of 191 amino acids. For the formation of recombinant human growth hormone the gene for HGH is inserted into plasmid and then introduced to a host for large production. It also consists of the 26 amino acid signal peptides which are removed from the HGH molecule with the help of *EcoRI* restriction enzyme.
- In production of recombinant vaccines: The recombinant technology is responsible for the production of vaccines for various diseases such as Hepatitis B, AIDS, Influenza, cholera and leishmaniasis.
 - AIDS vaccine: In this vaccine, genes of the two glycoproteins gp120 and gp41 are introduced into a suitable vector. When vector containing glycoproteins is injected into the patient, they stimulate antibody production, that neutralise the gp120 and gp41 binding sites and thus prevents its binding to the host T-lymphocytes.
 - DNA vaccine: It consists of plasmids containing a protein encoding gene, promoter site, cloning site for the gene, origin of replication, selectable marker and a poly A tail termination sequence. These vaccines are not infectious or replicative, so are safer for use. They elicit high immune response and are used to protect against influenza, HIV infection, several cancers (colon, renal, T cell lymphoma) and herpes simplex virus (Yang *et al.* 2002).
- In anti sense therapy
 Antisense therapy, it is possible to synthesize a strand of nucleic acid (DNA, RNA or a chemical analogue) that will bind to the messenger RNA (mRNA) produced by that gene and inactivate it and effectively turning that gene “off”. This synthesized nucleic acid is termed an “anti sense” oligonucleotide because its base sequence is complementary to the gene’s messenger RNA (mRNA), which is called the “sense” sequence. Antisense drugs are being researched to treat cancers, diabetes and diseases such as asthma and arthritis with an inflammatory component. One antisense drug, fomivirsen (marketed as Vitravene), has been approved by the US Food and Drug Administration (FDA) as a treatment for cytomegalovirus retinitis (Biroccio *et al.* 2003).

2.7 BIOCHEMICAL METHODS

Protein purification: Protein purification is a series of processes used to isolate a specific type of protein from a complex mixture. Protein purification is important for the characterization of the function, structure and interactions of the protein of interest. The various steps in the purification process may include the isolation of the protein from a matrix, separate the protein and non-protein parts of the mixture, and finally separate the desired protein from all other proteins. Separation of the proteins depends on protein size, physio-chemical properties, binding affinity and biological activity (Burgess. 2008).

- Ion-exchange chromatography separates proteins based on charge. Columns can either be prepared for anion exchange or cation exchange. Elution of the target proteins is done by changing the pH in the column, which results in a change or neutralisation of the charged functional groups of each protein (www.biotech.about.com).
- Size-exclusion chromatography (gel filtration) separates larger proteins from small ones, since the larger molecules travel faster through the cross-linked polymer in the chromatography column. The large proteins do not fit into the pores of the polymer whereas smaller proteins do, and take longer to travel through the chromatography column, via their less direct route.
- Affinity chromatography is a very useful technique for completing the protein purification process. Beads in the chromatography column are cross-linked to ligands that bind specifically to the target protein. The protein is then removed from the column by rinsing with a solution containing free ligands. This method generally gives the purest results and highest specific activity compared to other techniques (Wilson and Walker. 2006).

Blotting: is a method of transferring proteins, DNA or RNA, onto a carrier (for example, a nitrocellulose, polyvinylidene fluoride (PVDF) or nylon membrane.

Electrophoresis

Electrophoresis is the main biochemical technique for molecular separation. Electrophoresis can be one dimensional or two dimensional. One dimensional electrophoresis is used for most routine protein and nucleic acid separations. Two dimensional separation of proteins is used for finger printing , and when properly constructed can be extremely accurate in resolving all of the proteins present within a cell (greater than 1,500).When the detergent SDS (sodium dodecyl sulfate) is used with proteins, C all of the proteins become negatively charged by their attachment to the SDS anions. When separated on a polyacrylamide gel, the procedure is known as SDS—PAGE (Sodium Dodecyl Sulfate- PolyAcrylamide Gel Electrophoresis). The technique has become a standard means for molecular weight determination (Lodish *et al.* 2004).

2.8 PATERNITY TESTING

Blood Types and DNA

Occasionally, situations arise in which people require concrete, scientific evidence of parentage, whether it be their own or that of someone else. In most instances, maternity is easy to determine. The woman who gave birth to a child is obviously that child's gestational, genetic, and legal mother if she is not the surrogate mother (www.nature.com).

Unfortunately, questions of paternity aren't so easy to answer. In order to make a determination of fatherhood, scientists work backwards from the child to the potential parent to ascertain the actual nature of the relationship. In the past, this involved identifying specific phenotypes (in particular, specific blood types) in the child and using this information to either "rule in" or "rule out" possible fathers. However, this system presented a number of problems, one of which

was that it often yielded inconclusive results. Thus, since 1990s, the more common approach has been to consider the presence of particular genotypic markers when attempting to establish fatherhood (and, in a handful of cases, motherhood) (www.docstoc.com).

- a) **By using blood-typing:** The best-known blood-typing system is ABO typing, which involves the presence of antigens on red blood cells that are encoded by the ABO locus on human chromosome 9. In the ABO system, the A allele and the B allele are co-dominant, and the O allele is recessive. Thus, if a person's ABO blood type is O, he or she has two O alleles. If, however, a person's blood type is A, he or she has either two A alleles or one A allele and one O allele. Similarly, if a person has type B blood, this indicates the presence of either two B alleles or one B allele and one O allele. Finally, some people have type AB blood, which means they inherited both an A allele and a B allele (www.nature.com).

In cases when paternity is questioned, ABO blood-typing can be used to exclude a man from being a child's father. For example, a man who has type AB blood could not father a child with type O blood, because he would pass on either the A or the B allele to all of his offspring (www.docstoc.com).

- b) **DNA Markers and Electrophoresis:** In the 1970s and 1980s, electrophoresis of various biochemical markers became available. With this process, proteins from a person's blood or other tissue were placed onto a gel, such as potato starch, agarose, or polyacrylamide. An electric current was then run through the gel, and different forms or isozymes of the proteins were separated by their electrical charge and/or size. Differences in isozymes relate to differences in the alleles that code for these proteins. Thus, the presence of certain identical isozymes in samples from both a child and his or her potential father could be used to reveal the existence of a genetic relationship between the two individuals. Interestingly, improvements in paternity testing over the past several decades have not only led to an increase in the accuracy of test results, but also to expanded application of various testing methods. For example, as DNA technology has gotten more precise, it has become possible to determine paternity using DNA from grandparents, cousins, or even saliva left on a discarded coffee cup. Such DNA testing is clearly an important part of criminal investigations, including forensic analysis, but it is also useful in civil courts when the paternity of a child is in question (Adams. 2008).

2.9 TWIN STUDIES

Establishing twin registers have an enormous potential for research on the genetics of complex traits. Some of them have existed for decades and have carefully collected longitudinal data on behavioural traits, diseases and environmental risk factors in large samples of twins and their families. By making comparisons between monozygotic (MZ) and dizygotic (DZ) twins, twin registers represent some of the best resources for evaluating the importance of genetic variation in susceptibility to disease. They are an excellent source for studying the significance of the genotype-environment interaction and of the contribution of specific

polymorphisms to the total genetic variance. Recent advances in statistical modeling allow simultaneous analysis of many variables in relatives such as MZ and DZ twins.

Classical twin studies.: The classical twin study compares phenotypic resemblances of MZ and DZ twins. MZ twins derive from a single fertilized egg and therefore inherit identical genetic material. Comparing the resemblance of phenotypic characters of MZ twins for a trait or disease with DZ twins offers the first estimate of the extent to which genetic variation determines phenotypic variation of that trait. If MZ twins resemble each other more than DZ twins, then the heritability (h^2) of the phenotype can be estimated from twice the difference between MZ and DZ correlations.

Types of twin study and their applications

❖ **Classical MZ–DZ comparison:** These studies estimate the contributions of genetic and environmental effects to phenotypic variance, and test, for example, for age, cohort and sex differences in gene expression.

❖ **Multivariate analyses:** simultaneous analysis of correlated trait

This type of analysis involves:

- direction of phenotypic causality;
- causes of co-morbidity of two or more traits: multivariate modelling of environmental and genetic correlations between traits;
- multivariate modeling to obtain genotypic (or environmental) values for individuals;
- analysis of longitudinal data to study causes of phenotypic stability and tracking over time; and
- testing of Genotype $\times$ Environment using measured environmental indices.

❖ **Co-twin control study:** Case–control studies of MZ twins who are perfectly matched for genes and family background; such studies can also be used to study gene expression in discordant twins

Extended Twin Study: Studies of Twins and Their Families

- Parents of twins can be included to study cultural transmission and $G \times E$ covariance,
- Parents of twins can be studied in a quasi-longitudinal design to determine genetic and environmental stability,
- Assortative mating can be studied if spouses of twins are included; social interactions and special twin effects, such as prenatal hormone transition, the ‘private language’ of twins and shared prenatal environment, can be studied if siblings of twins are included, and
- Maternal effects, Genotype $\times$ Environment correlation and imprinting can be studied if offspring of MZ twins are included.

Twin studies are very helpful to understand the role of genes and environment for multifactorial traits (such as body height and weight, neuroticism and blood lipid levels) and complex diseases (such as obesity, depression and cardiovascular

disease). Lifestyle risk factors such as smoking, exercise, diet etc. are important for the development of complex diseases are often considered to be 'environmental', they might themselves be influenced by genes (Blickstein et al, 2005).

2.10 IMMUNOLOGICAL METHODS

Immunological techniques are important to detect emerging infectious agents like dengue fever, West Nile fever, and Rift Valley fever and biological weapons like *Bacillus anthracis* (anthrax) and variola major virus (smallpox), botulinum neurotoxins, *Yersinia pestis*, and *Francisella tularensis* which are great threat to public health. Following are the immunological methods are based mainly upon antigen antibody reactions.

- 1) Agglutination Tests
- 2) Coomb's Test (Antiglobulin Test)
- 3) Precipitation tests
- 4) Immunoelectrophoresis

2.11 SUMMARY

Modern techniques like Cytogenetic methods identify the underlying genetic causes of various diseases/disorders. Immunological methods help to identify the various infectious agents that aid in the manifestation of the diseases and thus help in the cure. Methods like DNA fingerprinting are very important to solve the paternity disputes and also help in forensics to identify the right culprit. DNA recombinant technology brings hope and opportunity to cure the genetic disorders that are otherwise incurable. Thus understanding and application of the genetic methods is very important for better disease control and good public health.

References

- Adams, J. 2008. *Paternity Testing: Blood Types and DNA*. Nature education 1(1).
- Biroccio, A., Leonetti, C. and Zupi, G. 2003. *The Future of Antisense Therapy: Combination with Anticancer Treatments*. *Oncogene* 22:6579–6588.
- Boomsa, D., Busjahn, A. and Peltonen, L. 2002 *Classical Twin Studies and Beyond*. Nature publishing group 3.
- Burgess, R.R. 2008. Protein Purification. In: H. G. Nothwang and S. E. Pfeiffer (Eds.), *Proteomics of the Nervous System*, Chapter 1, pp. 1-18. Weinheim; WILEY-VCH Verlag GmbH & Co.
- Comai, L. 2005 *The Advantages and Disadvantages of Being Polyploid*. *Nature Reviews, Genetics*. 6:836-46.
- Fenech, M. 2002. *Micronutrients and Genomic Stability: A New Paradigm for Recommended Dietary Allowances (RDAs)*. *Food Chem Toxicol* 40: 1113–1117.
- Graff J.C. 2006. *Community Nursing: Medical Care for Children and Adults with Developmental Disabilities*. 2nd edition.

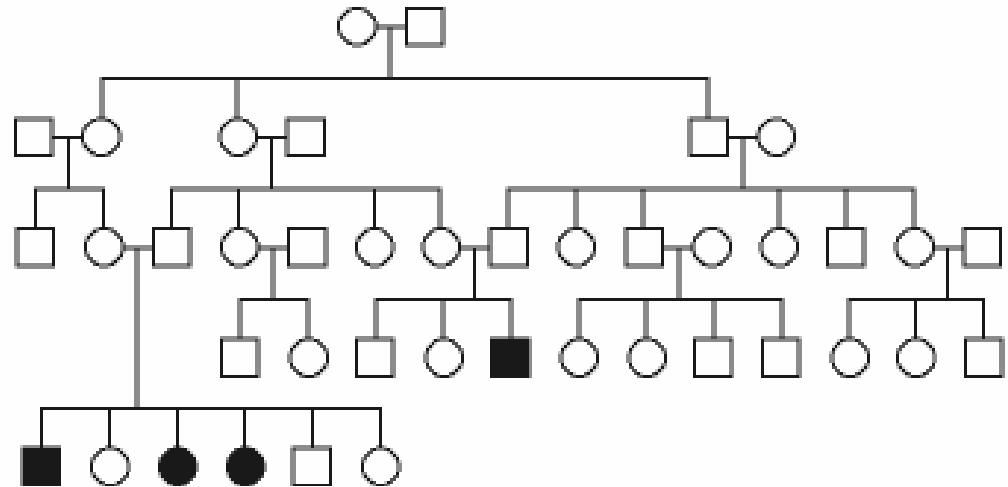
- Gupta, V. 2005. *Recombinant DNA Therapy in Medicine*. Keio J Med 54 (2): 85–94.
- Mayer, G. 2006. *Immunology* - Chapter Seven Immunoglobulins- Antigen-Antibody reactions and selected tests.: 67-74.
- Muller, R.F. and Young I.D. 2001. *Emery's Elements of Medical Genetics* (11th edition). Edinburgh; Churchill. Livingstone. Rooney DE .
- Peruski, A., and Peruski, F. 2003 *Immunological Methods for Detection and Identification of Infectious Disease and Biological Warfare Agents*. Clinical and Diagnostic Laboratory Immunology. 10: 506–513.
- Rowley, J. 2001. *Chromosome Translocations*. Nature Reviews Cancer 1: 246.
- Strachan, T. and Read, A.P. 1999. *Human Molecular Genetics* (2nd edition). New York; Wiley-Liss.
- Tseng, C.C. 1995. Human Chromosome Analysis. *Proceedings of the 16th Workshop of the Association for Biology Laboratory Education* 16: 33-36.
- www.biotech.about.com accessed on November 18, 2010
- www.bogari.net accessed on January 17, 2011
- www.bookrags.com accessed on November 18, 2010
- www.docstoc.com accessed on November 18, 2010
- www.doctorsmedicalopinion.com accessed on April 29, 2011
- www.dramarabiochem.blogspot.com accessed on March 10, 2010
- www.genetics.emory.edu accessed on March 10, 2011
- www.genetics.emory.edu accessed on March 11, 2011
- www.nature.com. accessed on March 10, 2011
- www.pathmicro.med.sc.edu accessed on April 10, 2011
- www.science.jrank.org accessed on March 10, 2011
- www.scientific-web.com accessed on March 10, 2011
- www.scribd.com accessed on April 29, 2011
- Yang, L., Li, S., Hatch, H., Ahrens, K., Cornelius, J.G., Petersen, B.E. and Peck, A. 2002. *In vitro Trans-Differentiation of Adult Hepatic Stem cells into Pancreatic Endocrine Hormone Producing Cells*. Proc Natl 99: 8078–8083.

Suggested Reading

- Gardner, E. J., Simmons, M.J. and Snustad, D.P. 1991. *Principles of Genetics*. New York, John Willey & Sons.
- Lewis, R. 2003. *Human Genetics: Concepts and Applications 5th edition*. Boston, WCB McGraw Hill.
- Mange, E. J. and Mange, A. P. 1994. *Basic Human Genetics*. Sunderland; MA. Sinauer Associates.
- Stern, C. 1960. *Principles of Human Genetics*. San Francisco and London; Freeman and Company.
- Strickberger, M. W. 2003. *Genetics 3rd edition*. New Delhi, Prentice Hall.

Sample Questions

- 1) Identify the mode of inheritance in the given below pedigree?



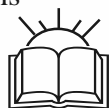
- 2) What do you mean by chromosome analysis and what is the difference between the numerical and structural abnormality?
- 3) To how many groups the chromosomes can be divided according to ISCN? How can chromosome analysis be used in prenatal diagnosis?
- 4) What are the main steps involved in karyotype analysis and why peripheral blood lymphocytes are considered to be ideal for karyotype analysis?
- 5) What are the different staining methods utilised to identify chromosomes? How SKY is different from FISH technique?

UNIT 3 POPULATION GENETICS

Contents

- 3.1 Introduction
- 3.2 Mendelian Population
- 3.3 Genetic Polymorphism
- 3.4 Hardy-Weinberg Law
- 3.5 Deviations from Hardy-Weinberg Law or Factors Affecting Gene Frequencies
- 3.6 Consanguineous and Non-consanguineous Mating
- 3.7 Genetic Load
- 3.8 Summary
- References
- Suggested Readings
- Sample Questions

Learning Objectives



Once you have studied this unit, you should be able to:

- know the importance of population genetics;
- understand what Mendelian population is and clearly differentiate breeding population and effective population;
- understand the concepts of genetic polymorphism;
- understand the significance of Hardy-Weinberg Law;
- explain how mutation, migration, selection, inbreeding, genetic drift, consanguineous and non-consanguineous mating disturb the genetic equilibrium and also clearly understand the process of evolution of populations; and
- know what genetic load is, and understand the effect of consanguineous marriages.

3.1 INTRODUCTION

Genetics, a discipline of biology, is the study of fundamental units of inheritance called genes, heredity, and variation in living organisms. This hereditary material (gene), whether as a unit of segregation, recombination, mutation, or function, is the unifying idea basic to the field of genetics. In 1866, Gregor Mendel put forward the mechanisms for heredity and variation. The Mendelian laws: the independent segregation and recombination of dominant and recessive characters constitute the cornerstone of the modern science of genetics. Mendel's monumental work (1866) on the principles of inheritance, that is, Mendel's Laws of inheritance, remained long ignored, and only received attention in 1900, sixteen years after his death (1884). It was not until 1900, when three botanists, de Vries, Correns, and Von Tschermak independently rediscovered the Mendelian Principles. Later Mendel's experiments were extended to many species of plants and animals including man.

Human genetics is a subject of special interest to us as students of anthropology. Human genetics itself is further subdivided into the areas of medical genetics, biochemical genetics, cytogenetics, somatic cell genetics, immunogenetics, formal or mathematical genetics, population genetics, and anthropological genetics. These subdivisions of human genetics are closely interrelated and interdependent. For example, the study of the distribution and evolution of the abnormal haemoglobins in human populations witnessed the union of medical genetics, biochemical genetics, formal genetics, and population genetics.

Population Genetics

Study of a whole population is, in fact, often superior to the collection of large pedigree, because pedigree has unusual characteristics and is of specific interest, and thus is not representative of a population. Within many populations an equilibrium of genotypes prevails. This was first pointed out in 1908 independently by the mathematician G. H. Hardy and the physician W. Weinberg whose several contributions laid the foundations of the genetic study of natural populations of man and wild animals. The foundations by Sewall Wright, R. A. Fisher and J. B. S. Haldane helped the formation of modern population genetics. The mathematical theory of population genetics was developed in the early twentieth century due largely to the work of Sewall Wright, Ronald Fisher, and J. B. S. Haldane. So the population genetics deals with the consequences of Mendelian laws on the composition of the population with special reference to the effects of mutation, selection, migration, and chance fluctuation of gene frequencies.

The population considered under Hardy-Weinberg law is a unique population. It does not change genetically and cannot and does not evolve. It is an *ideal population*, because it necessarily fulfilled certain “*ideal*” conditions and is a mathematical abstraction, because no real population fulfills the ideal conditions such as large size of the population with equal sexes, random mating and equal fertility among all couples and another stipulation that the population must be free from evolutionary forces.

3.2 MENDELIAN POPULATION

A population *isolate* is that group of persons within which individuals choose their partners. Such an isolate is also called a *Mendelian population*. Ideally the population isolate inhabits an island, a mountain valley, a peninsular region, a forested area, or even a large area covering several villages, where the marriage alliance is restricted within that endogamous group.

The general and simple definition of *population* is the number of people in an area at a given time. It may be used in reference to the number of people possessing a particular character or group of characteristics in an area at a given time. It is difficult to define a particular population strictly, for the actual boundaries around a specific human population are not always easy to find. A human population is usually found in a particular place, and it is a coherent entity largely because of geographical boundaries. Regardless of how they are circumscribed, the significance that populations have for evolutionary genetics lies in the web of genetic relationships within and between them—allele frequencies, consanguinity,

mating patterns, gene flow, natural selection, etc. The genetic approach uses the concept of the *Mendelian population*, which Dobzhonsky has defined as “a reproductive community of sexual and cross fertilizing individuals which share in a common gene pool”. If the isolate or the Mendelian population is not changed by natural selection, nor by mutation, nor by migration, and if the population size is large and if individuals are not mating assortatively (that is, random choice of partners), then the isolate is said to be in equilibrium. These assumptions are fundamental to population analysis and for maintaining an equilibrium of genotypes from generations to generations.

Although, all human gene pools are open to varying degree, it is evident that panmixis does not take place within the total species. The more important mechanisms maintaining genetic isolation of populations today are cultural rather than geographical.

Breeding Population

In addition to the problem introduced by the biological openness of human-population systems, accurate definition of a human Mendelian population is complicated by the fact that man clusters in social groupings which may or may not serve as biological breeding units. So the first problem of the population geneticist, therefore, is to identify and describe, as accurately as possible, the biological population before he can undertake an analysis of the gene pool and forces acting on it. Because direct analysis of a population's gene pool is impossible, all conclusions regarding its composition are necessarily inferential, and must be made on the basis of direct examination of the phenotypes of the reproducing individuals. To infer the composition of a gene pool at a single point in time the population geneticist must first enumerate and describe the actual progenitors, that is, the parents in a population. These progenitors constitute the breeding population.

3.3 GENETIC POLYMORPHISM

Genetic polymorphism is defined as the occurrence together in the same habitat at the same time of two or more distinct forms of a species in such proportions that the rarest of them cannot be maintained merely by recurrent mutation (Ford, 1940). Genetic polymorphism can also be defined as the occurrence in the same population of two or more alleles at one locus, each with appreciable frequency (Cavalli-Sforza and Bodmer, 1971). A formal definition, such as the above, based on the frequency of genes that are found in a population is likely to be the most satisfactory. At one time, polymorphism was defined in terms of the selective mechanisms responsible for maintaining relatively high gene frequencies of two or more alleles at a locus. Because it is difficult to determine these mechanisms or the nature of these forces and therefore can hardly be useful in a definition. This is the reason why it is difficult to accept unequivocally Ford's definition. However, it is likely that Ford's definition applies to many, if not most, instances of polymorphism (Ford, 1964).

Some knowledge of the theory of polymorphism is essential for a clear understanding of the blood groups and the kindred phenomena. It should be noted that the definition of polymorphism excludes the following forms of variation.

- ❖ Geographical races, White, Mongoloid and Negroid types of man. These are normally maintained by isolation from one another. It should be stressed here, that the occurrence of polymorphism in one district and its absence or different nature in another, may be an important attribute of distinct communities.
- ❖ 'Continuous variation' under multifactorial (or environmental) control, such as height, is brought about by cumulative effect of segregation taking place at many loci. This cannot be considered as polymorphic condition, as it is not maintained in the population by selection.
- ❖ The segregation of rare recessive, albinism for example or rare heterozygous conditions, such as Huntington's chorea, are eliminated by selection and maintained only by mutation. Hence they cannot give rise to polymorphism.

It must be noted that polymorphism cannot normally be maintained environmentally.

Genetic polymorphisms are very common phenomena in all human populations. Most of the polymorphisms encountered in human populations so far fall into two main categories: blood-cell antigens (blood groups) and blood proteins (serum proteins). The first category of polymorphisms, the kind detected by immunological techniques, is that of blood groups or blood cell antigens, of which the ABO blood groups are an outstanding example. The second category of polymorphisms, most of them detected by electrophoretic techniques, for which complications due to incompatibility are not known or are not likely to occur, comprises proteins found in the blood either in the free, liquid portion (serum or plasma) or in its cells (red or white). The modern techniques of biochemistry revealed how widely individual men and populations differ in the various enzymes and proteins systems of the body.

Polymorphism in Man

The human polymorphism may conveniently be introduced by two examples which reveal their essential qualities. Let us discuss about sickle-cell anaemia, which is genetically controlled by a gene which produces the disease when homozygous and is responsible merely for the sickling trait when heterozygous. This gene affects the formation of haemoglobin, but not for all, it only affects the structure of erythrocytes that assumes a sickle-like shape, that leads to haemolysis severe enough to cause an extreme and often fatal anaemia. Those who merely manifest the sickling trait appear on the other hand, to be perfectly healthy. Though their blood also contains the exceptional haemoglobin, but in smaller proportion, so the shape of the erythrocytes is normal when in circulation. It must be noted that the anaemia is recessive while the formation of the abnormal haemoglobin is not. In spite of the fact that the homozygotes suffer from this heavily lethal disease which usually eliminates them, the heterozygotes are quite common in certain regions of European population, as in some parts of Greece and Italy, and in African tribes. Evidently the heterozygotes must have an advantage which strongly counter-balances the destruction of the homozygotes in these areas. Allison (1954) discovered that the sickle-cell trait confers marked immunity against malaria especially, due to *Plasmodium falciparum*. The polymorphism is established only in those places where malaria is common.

Allison (1954) further observed polymorphism involving another genetically controlled disease, thalassaemia. Many homozygotes, and perhaps a few of the heterozygotes, die, yet the gene is present in 10 per cent of the population in

some of the districts of Greece and Italy where malaria is endemic. In India, particularly in parts of central India, such polymorphism exists where sickle-cell anaemia has been found to be prevalent in malaria endemic regions.

One of the oldest known such polymorphism is the ability to taste phenyl-thio-carbamide (PTC), or phenyl-thio-urea (PTU). For some people PTC has only a faint taste or no taste at all; for others it has a very bitter taste. More specifically there is a single dominant gene *T* (with incomplete penetrance) that determines a high sensitivity for the taste of PTC. Non-tasters are homozygous for the recessive allele *t*. When both parents are non-tasters, all their children are non-tasters. When one parent is taster and the other is not, either all or half of their children will be tasters, depending on whether or not the parent of the dominant (tasting) type is homozygote or heterozygote.

Genetic polymorphisms may be '*transient*' or '*balanced*'. Genetic polymorphisms are called balanced, if selection favors the heterozygotes. When selection favors the heterozygotes, a stable equilibrium may be achieved and substantial frequencies of both alleles may be maintained in one environment. The balanced or stable polymorphism is the result of natural selection operating as a *stabilizing* agent.

It is difficult to establish whether a polymorphism is stable or transient. However, direct evidence for at least one balanced polymorphism is available; the polymorphism for the group of haemoglobins, including haemoglobin S, in the presence of malaria.

3.4 HARDY-WEINBERG LAW

Definition

Mathematician Godfrey Hardy and physician Wilhelm Weinberg independently showed in 1908 that population gene frequencies remain constant from generation to generation under a system of random union of gametes in fertilization when the frequencies of the heterozygotes are equal to twice the product of the square roots of the two homozygotes: $p^2 AA + 2pq Aa + q^2 aa = 1$, where p and q are the frequencies of genes A and a ($p + q = 1$) in the population, which is ideally large, with non overlapping generations, sexes equally distributed and all parents are equally fertile, and where there are no changes in gene frequency due to mutation, gene flow, selection or genetic drift, or where mutation and selection rates are balanced so that there is no net change in gene frequencies.

This theory is considered as the cornerstone of population genetics because it mathematically describes the behaviour of genetic traits through time within a specific unit — the population. Actually, the population assumed under Hardy-Weinberg Law is a unique population. It does not change genetically, i.e., it cannot and does not evolve. It is a so-called ideal population, i.e., a hypothetical one, which means that within it certain 'ideal' conditions must necessarily be fulfilled. The ideal population is a mathematical abstraction, because no real population ever fulfills all of the necessary conditions, that is, the population must be large, the sexes must be equally distributed, mating must be random (panmictic¹), all parents must be equally fertile, and must be free from the four forces of evolution; that is, mutation, natural selection, genetic drift, and gene flow.

¹ A population undergoing random mating is often referred to as a panmictic population, or it is said to be in a state of panmixia.

The Hardy-Weinberg Law deals with the simplest genetic case, that of a single locus carrying only two alleles, p and q . The manner in which genetic stability is maintained under a two-allele system is best understood if the gene pool is visualized as divided into two component sexual units: one unit containing all the male gametes (spermatozoa), carrying the alleles p and q , the other unit containing all the female gametes (ova) in equal numbers. The relative proportions of p and q are identical between the two sex units. If all the male and female gametes mate randomly, the offspring will be distributed as shown in the box. Whether or not the gene pool is initially in equilibrium, after one generation of random mating, genetic equilibrium at a single locus is established and then perpetuated at the same gene frequencies through subsequent generations.

Male gametes →	P	q
↓ Female gametes		
P	P^2	pq
Q	pq	q^2

Genotype frequencies: $p^2+2pq+q^2$

Let us examine what would be expected under random mating in a simple and general case of an autosomal locus with two alleles A and a with frequencies, p and q and the corresponding genotypes AA , Aa and aa with the corresponding frequencies, $p^2:2pq:q^2$. The various mating types and the expected progeny are given in the following table.

Mating Type	Frequency of Mating	Expected Frequency		
		AA	Aa	aa
$AA \times AA$	P^4	P^4		
$AA \times Aa$	$2p^3q$	p^3q	p^3q	
$AA \times aa$	p^2q^2		p^2q^2	
$Aa \times AA$	$2p^3q$	p^3q	p^3q	
$Aa \times Aa$	$4p^2q^2$	p^2q^2	$2p^2q^2$	p^2q^2
$Aa \times aa$	$2pq^3$		pq^3	pq^3
$aa \times AA$	p^2q^2		p^2q^2	
$aa \times Aa$	$2pq^3$		pq^3	pq^3
$aa \times aa$	q^4			q^4
Total	*	$P^4+2p^3q+ p^2q^2$ = $p^2(p^2+2pq+q^2)$	$2p^3q+4p^2q^2+2pq^3$ = $2pq(p^2+2pq+q^2)$	$p^2q^2+2pq^3+ q^4$ = $q^2(p^2+2pq+q^2)$

$$*p^4+4p^3q+6p^2q^2+4pq^3+q^4 = p^2(p^2+2pq+q^2)+ 2pq(p^2+2pq+q^2)+ q^2(p^2+2pq+q^2) = p^2+2pq+q^2$$

The above table presents a formal demonstration or derivation that $p^2+2pq+q^2$ is an equilibrium.

Applications of Hardy-Weinberg Law

More precisely, Hardy-Weinberg equilibrium postulates a set of conditions where no evolution occurs. If all the conditions are satisfied, allele frequencies will not change (that is, no evolution will take place) and a permanent equilibrium will be maintained as long as these conditions prevail. However, it is obvious that the Hardy-Weinberg ideal population can never be found in the real sense in human populations. First, the formula provides a standard against which genetic change in a population may be measured and predicted. The formula serves as a basic theorem which can be expanded and elaborated by other mathematical models that deal with changes in populations (Jurmain et al 1998).

Secondly, the Hardy-Weinberg formula may be applied to large populations to provide an estimate of gene frequencies at a single point in time.

Population genetics is the study of allele frequencies in groups of organisms of the same species in the same geographic area.

The genes in a population comprise its gene pool.

Microevolution reflects changes in allele frequencies in populations. It is not occurring if allele frequencies stay constant over generations (Hardy-Weinberg equilibrium).

Five factors can change genotype frequencies - nonrandom mating, gene flow, genetic drift, mutation, and natural selection.

3.5 DEVIATIONS FROM HARDY-WEINBERG LAW OR FACTORS AFFECTING GENE FREQUENCIES

The discussion above relates to an 'ideal' population. By definition such a population is large and shows random mating with no new mutations, and no selection for or against any particular genotype. For some human characteristics, such as neutral genes for blood groups or enzyme variants, these criteria can be fulfilled. However, in genetic disorders, several factors can disturb the Hardy-Weinberg equilibrium by influencing either the distribution of genes in the population or by altering the gene frequencies. These factors include:

- Non-random mating
- Mutation
- Selection
- Small population size
- Gene flow (migration).
- **Non-random mating**

Random mating, or *panmixis*, refers to the selection of a partner regardless of that partner's genotype. *Non-random mating* can lead to an increase in the frequency of affected homozygotes by two mechanisms, either assortative mating or consanguinity.

Assortative mating

Assortative mating is the tendency for human beings to choose partners who share characteristics such as height, intelligence and racial origin for marriage.

Consanguinity

Consanguinity is the term used to describe marriages between blood relatives who have at least one common ancestor no more remote than a great-great grandparent. Widespread consanguinity in a community will lead to a relative increase in the frequency of affected homozygotes with a relative decrease in the frequency of heterozygotes.

- **Mutation**

The validity of the Hardy-Weinberg principle is based on the assumption that no new mutations occur. If a particular locus shows a high mutation rate then there will be a steady increase in the proportion of mutant alleles in a population. In that case the law will not be applicable.

- **Selection**

In the 'ideal' population there is no selection for or against any particular genotype. In reality for deleterious characteristics there is likely to be negative selection with affected individuals having reduced reproductive fitness in genetical sense, as the genes would not be transmitted in the next generation. In the absence of new mutations this reduction in fitness will lead to a gradual reduction in the frequency of the mutant gene and will cause disturbance of Hardy-Weinberg equilibrium.

Selection can act in the opposite direction by increasing fitness. For some autosomal recessive disorders there is evidence that heterozygotes show a slight increase in biological fitness as compared with unaffected homozygotes. This is referred to as heterozygote advantage. The best understood example is sickle-cell disease in which affected homozygotes have severe anemia and often show persistent ill-health. However, heterozygotes are relatively immune to infection with *Plasmodium falciparum* malaria because if their red blood cells are invaded by the parasite they undergo sickling and are rapidly destroyed. In areas in which this form of malaria is endemic, carriers of sickle-cell anemia, who are described as having sickle-cell trait, are at a biological advantage as compared with unaffected homozygotes. Therefore, in these communities, there will be a tendency for the proportion of heterozygotes to increase relative to the proportions of normal and affected homozygotes. Once again this will result in a disturbance of Hardy-Weinberg equilibrium.

We have earlier discussed about selection favouring heterozygotes as in sickle-cell anaemia, and thalassaemia. There is also the opposite situation, that is selection against heterozygotes, as we find in maternal-foetal incompatibility (Erythroblastosis fetalis) as is observed for the allele *R* (Rh blood group), and also for other blood group genes (Rh-ABO incompatibility).

Mutation alters genotype frequencies by introducing new alleles.

Heterozygotes and new mutations maintain the frequencies of deleterious alleles in populations.

Different alleles are more likely to confer a survival advantage in different environments. Cycles of infectious disease prevalence and virulence often reflect natural selection.

In balanced polymorphism, a disease-causing allele persists because heterozygotes resist a certain infectious illness or environmental condition.

Gene flow alters genotype frequencies by adding and removing alleles from populations.

Clines are gradual changes in allele frequencies between neighboring populations.

Geographical barriers and language differences often create great differences in allele frequencies.

Genetic drift occurs when a subset of a population has different allele frequencies than the larger population.

The founder effect occurs when a few individuals leave a community to start a new settlement. The resulting population may, by chance, either lack some alleles from the original population or have high frequencies of others.

• Genetic drift

In a large population the numbers of children produced by individuals with different genotypes, assuming no alteration in fitness for any particular genotype will tend to balance out, so that gene frequencies will remain stable. However, in a small population it is possible that by random statistical fluctuation one allele could be transmitted to a high proportion of offspring by chance, resulting in marked changes in allele frequency from one generation to the next, so that Hardy-Weinberg equilibrium is disturbed. This phenomenon is referred to as random genetic drift. If one allele is lost altogether then it is said to be extinguished and the other allele is described as having become fixed ([www. faculty.ksu.edu](http://www.faculty.ksu.edu)).

• Gene flow (migration)

If new alleles are introduced into a population as a consequence of migration with subsequent intermarriage, this will lead to a change in the relevant allele frequencies. This slow diffusion of alleles across a racial or geographical boundary is known as gene flow. The most widely quoted example is the gradient shown by the incidence of the B blood group allele throughout the world. This allele is thought to have originated in Asia and spread slowly westward as a result of admixture through invasion.

3.6 CONSANGUINEOUS AND NON-CONSANGUINEOUS MATINGS

There are two general patterns of mating in human populations: random and non-random mating. Deviations from random mating can occur in two general directions. People who are related can either marry more frequently or less frequently than they would by chance. In the former case the mating system is one of inbreeding and in the latter one of outbreeding. Assortative mating is another important mating type which deviates from random mating. The assortative mating is either positive or negative. Inbreeding is defined as mating between close relatives. When the frequency of marriages between close relatives who have one or more common ancestors exceed the expected frequency under random mating in a population then it is called inbreeding and when it decreases the expected proportion then it is called outbreeding. Marriage between close relatives who have one or more common ancestors is called consanguineous marriage. Non-consanguineous marriages are between individuals of opposite sex who do not have a known common ancestor. Consanguinity refers to marriage type and inbreeding refers to the mating pattern of the population. Consanguinity is the term referred to describe the marriages between blood relatives who have one or more common ancestors and consanguinity is the name given to close

relationships (as distinct from relationships by marriage). In positive assortative mating, individuals tend to choose mates who resemble themselves (e.g., in native language, intelligence, stature, skin colour, musical talent, or athletic ability) more frequently than would be expected by chance. In negative assortative mating, the mating pairs are dissimilar in phenotype than would be expected by chance.

All societies have rules which forbid marriage between close blood relatives such as parent offspring and sibs (brother and sisters) called incest taboo. Though incest taboo is a universal feature of human society, it is complemented by a preference for marriage between certain other relatives. The most common form of consanguinity in the human population is cousin marriage. Marriage between children of siblings of the same sex (parallel cousins) is prohibited except in some Islamic societies of the Middle East where marriage between a man and his father’s brother’s daughter is common. There are in certain areas (South India, Japan, etc.) where marriages are commonly observed between the children of the siblings of opposite sexes (cross cousins). First cousin marriages make up almost 10 per cent. In southern part of India, especially in the state of Andhra Pradesh, among certain castes, uncle-niece unions also make up about 10 per cent of marriages. Less frequent marriage types also occur in this part of India such as the marriages between first cousins once removed, second cousins, double first cousins and aunt-nephew.

The possible types of mating between different relationships are shown in the following figure.

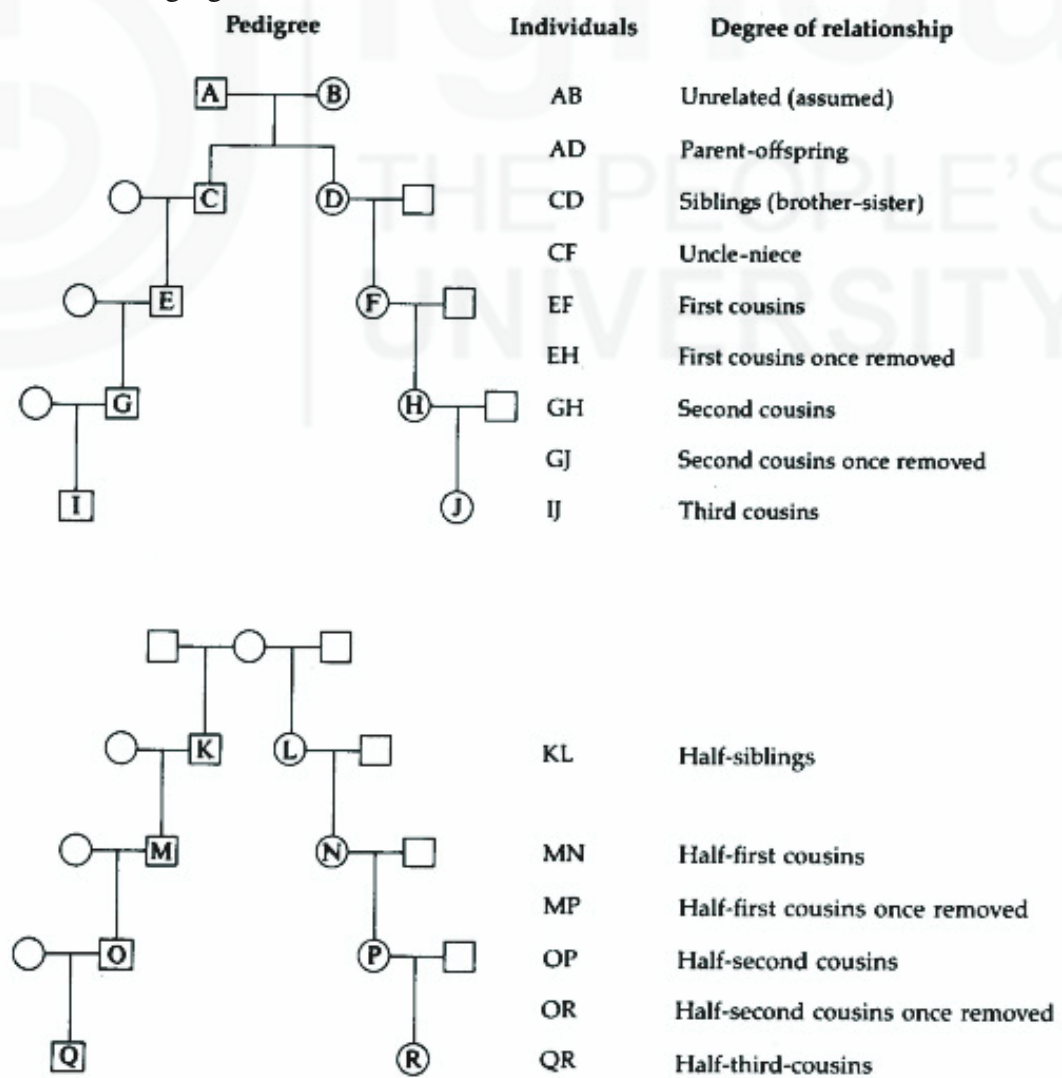


Fig. 4.1: The possible types of matings between different relationships

People choose partners for marriage, and they do not contribute the same numbers of children to the next generation. The marriage practices change allele frequencies in populations.

Traits lacking obvious phenotypes may be in Hardy-Weinberg equilibrium.

Consanguinity and endogamy increase the proportion of homozygotes in a population.

Effect of Consanguineous Marriages

The main genetic consequence of inbreeding is an increase in the proportion of homozygotes. Through inbreeding recessive genes are more easily brought to the fore.

Inbreeding Depression

Usually, inbreeding causes deterioration and outbreeding causes improvement of most of the characters. Animal breeders noticed that inbreeding particularly always lead to a deterioration in many important qualities; fertility for instance, tends to decrease and many an inbred stock, has lost because the fertility level became too low for the maintenance of the line in generations. In addition, some traits such as overall general size also decrease. This phenomenon of deterioration on inbreeding is known as *inbreeding depression*.

Heterosis

In contrast to inbreeding depression, if two independent pure lines are crossed, the hybrids between them (at least in the first generation) mostly show a considerable increase in size, fertility and many other desirable traits. This has been called *hybrid vigor* or *heterosis*, and clearly has a great potential for application in agriculture and animal husbandry. The first practical application of hybrid vigor as a technique for crop improvement was applied to corn and it led to a very significant increase in production. This practice is now being extended to other plants and animals. These inbreeding and outbreeding consequences are also seen in man. The genetic effects of inbreeding are similar to positive assortative mating. Both increase the frequency of homozygous genotypes at the expense of heterozygotes, relative to Hardy-Weinberg proportions. So it is clear that the inbreeding affects genotype frequencies and inbreeding along with selection modifies gene frequencies in a population.

It should be emphasised that the increasing homozygosity i.e., the general effect of inbreeding does not predict whether inbreeding is good or bad. It depends on the nature of the homozygotes. Many instances can be cited of talented persons whose parents were first cousins or otherwise closely related. Presumably consanguinity made it easier for 'good' genes to come together in these cases (example: Charles Darwin).

On the other hand, there is considerable evidence that homozygous recessives, albinism, alkaptonuria, etc., and the lethals are encountered with greater frequency in consanguineous marriages than in marriages of unrelated persons. Studies in Japan, where inbreeding is greater have shown increased rates of infant mortality and congenital abnormalities. Studies in France, Sweden, United States, and Japan have shown increased frequencies of certain physical diseases, and mental disorders among children of first cousin mating.

3.7 GENETIC LOAD

Among source of variability affecting Darwinian fitness (adaptive value) may lead to a genetic load. Crow (1970) proposed three definitions of genetic load of which mostly used one is that the (expressed) genetic load is the fraction by which the average population fitness is decreased in comparison with the genotype showing the highest fitness.

It appears that some polymorphisms exist because recurrent mutations replace genes lost to selection, whereas others exist because the heterozygote is adaptively superior and causes several alleles to persist even though many are lost due to selection against both homozygotes. The loss of individuals — often unseen individuals — under either situation because they carry certain genes, has been termed as genetic load of a species or population. So it is obvious that every human population carries a burden of deleterious mutations which impairs the fitness of the group. So the genetic load refers to the proportion by which fitness is reduced in the population due to the operations of a factor such as mutation.

So the genetic load of a species is a measure of the number of deleterious traits maintained in a population or of the damage to the population by the factors under study. It may be measured as decreased average fitness, or somewhat more specifically, as mortality, sterility, or morbidity due to specified causes, usually deleterious alleles. The genetic load of a species may be partially hidden and partially manifested. The genetic load depends on several variables — the occurrence of mutations, the number of detrimental mutations, the number of mutant recessive alleles, and the number of partially lethal mutant dominant alleles.

Genetic Radiation Hazard

In every generation numerous mutations, of every possible degree of harmfulness, will arise in human species; and in every generation, the carriers of some of these mutants — persons afflicted with hereditary diseases, malformations, or constitutional weaknesses — will die before they have children, or will remain unmarried, or will produce fewer children than they would have produced if they did not carry the mutant genes in question. The burden of genetic ill-health and abnormality in human populations is very great. And this is more so because of the genetic hazards of radiation. High-energy radiations cause two kinds of damage to living matter — physiological and genetic. Physiological damage consists of radiation burns, radiation sickness, and death, which occur soon after the irradiation (as had happened when an Atom Bomb was dropped on the twin cities of Japan by the Americans in 1945), and of various delayed effects, such as malignant growths. Genetic damage includes the mutations induced in the reproductive tissues and transmitted to the progeny. The genetic damage may inflict harm on the descendents of the exposed persons, and that too for many generations after the exposure.

3.8 SUMMARY

A population is a group of interbreeding members of the same species in a particular area. Their genes constitute the gene pool. Population genetics considers allele, genotype, and phenotype frequencies to reveal microevolution. Phenotypic

frequencies can be determined empirically. Genotype frequencies change if migration, nonrandom mating, genetic drift, mutations, or natural selection operate. In Hardy-Weinberg equilibrium, frequencies are not changing. Hardy and Weinberg proposed an algebraic equation to explain the consistency of allele frequencies. The Hardy-Weinberg equation is a binomial expansion used to represent genotypes in a population. According to Hardy-Weinberg equilibrium all individuals mate with the same frequency and choose mates without any consideration to phenotype. This seldom happens. We choose mates based on certain characteristics, and some people have many more children than others. Consanguinity increases the proportion of homozygotes in a population, which may lead to increased incidence of recessive illnesses or traits.

Clines are changes in allele frequencies from one area to another. Clines may reflect geographical barriers or linguistic differences and may be either abrupt or gradual. Genetic drift occurs when a small population separates from a larger one, or its members breed only among themselves, perpetuating allele frequencies not characteristic of the larger population due to chance sampling. A founder effect occurs when a few individuals found a settlement and their alleles form a new gene pool, amplifying their alleles and eliminating others. Mutation continually introduces new alleles into populations. Mutation does not have as great an influence on disrupting Hardy-Weinberg equilibrium as the other factors. The genetic load is the collection of deleterious alleles in a population. Environmental conditions influence allele frequencies via natural selection. Alleles that do not enable an individual to reproduce in a particular environment are selected against and diminish in the population, unless conditions change. Beneficial alleles are retained. In balanced polymorphism, the frequencies of some deleterious alleles are maintained when heterozygotes have a reproductive advantage under certain conditions.

Reference

Jurmain, R., Kilgore, L. and Trevathan, W. 1998. *Essentials of Physical Anthropology*. Belmont California; Wadsworth.

www.faculty.ksu.edu accessed on February 19, 2011

Suggested Reading

Cavalli-Sforza, L. L. and Bodmer, W. L. 1971. *The Genetics of Human Populations*. San Francisco; W. H. Freeman and Company.

Ford, E. B. 1967. *Genetics for Medical Students*. Sixth edition. London; Methuen & Co. Ltd.

Hartl, D. L. and Clark, A. G. 2006. *Principles of Population Genetics*. 4th Ed. Sunderland; MA. Sinauer Associates.

Mange, E. J. and Mange, A. P. 1994. *Basic Human Genetics*. Sunderland; MA. Sinauer Associates.

Mueller, R. F. and Young, I. D. 1998. *Emery's Elements of Medical Genetics*. New York; Churchill Livingstone.

Stern, C. 1960. *Principles of Human Genetics*. San Francisco and London; Freeman and Company.

Sample Questions

- 1) What is a population? List three populations.
- 2) Explain the differences among an allele frequency, a phenotypic frequency, and a genotypic frequency.
- 3) What does Hardy-Weinberg equilibrium mean?
- 4) What are the conditions under which Hardy-Weinberg equilibrium cannot be met?
- 5) Why is knowing the incidence of a homozygous recessive condition in a population important in deriving allele frequencies?



UNIT 4 CHROMOSOMAL ABERRATIONS IN MAN

Contents

- 4.1 Introduction
- 4.2 Changes in Chromosome Number
- 4.3 Specific Autosomal Abnormalities
- 4.4 Sex Chromosomal Abnormalities
- 4.5 Mosaicism
- 4.6 Structural Abnormalities or Chromosome Rearrangements
- 4.7 Summary

Suggested Reading

Sample Questions



Learning Objectives

Once you have studied this unit, you should be able to:

- define chromosome and chromosome abnormalities or syndromes;
- describe and distinguish different chromosomal aberrations in man with examples;
- understand the causes for chromosomal anomalies; and
- understand the consequences of chromosomal aberrations.

4.1 INTRODUCTION

Chromosomes and genes

A chromosome is an organised thread-like microscopic structure found in the cell nucleus of living organisms including man. Until 1956, it was thought that the number of chromosomes in man was 48, when it was established that it is 46. Each human cell, except for the gametes, i.e. ovum (egg) and the sperm cells, contains 23 pairs of chromosomes (22 pairs of autosomes and one pair of sex chromosome). Women possess two identical chromosomes called the X chromosomes while men possess one X chromosome and one Y chromosome. The ovum and sperm cells each contain 23 chromosomes (22 autosomes and one X or Y chromosome). The behaviour of chromosomes at somatic cell division in *mitosis* provides a mechanism that ensures the daughter cells to retain its own complete genetic component. Similarly their behaviour in the reproductive cells during gametes formation in *meiosis* enables each mature ovum and sperm to contain a unique single set of parental genes.

In earlier lectures we have discussed about gene mutations, where a change occurs from one allelic form to another, and such changes led to new inherited properties. However, there are other type of changes, namely, changes in the quantity of the chromosomal material and changes in its arrangement. The cellular and developmental functioning of an organism depends not only on the presence of the necessary alleles, but also on their harmonious interaction with each other.

Generally, the chromosomes remain unchanged but under certain natural or artificial adverse circumstances certain structural changes may occur in the

chromosomes which alter the positions of gene or loss of some genes or changes in chromosomal number. Any alteration in the number of chromosomes or changes in gross structure of chromosome that disrupts this genetic balance generally produces developmental abnormalities with profound phenotypic effects in the form of physical effects and sometimes accompanied by mental imbalances. These structural and numerical alterations which affect the phenotype of the organisms in various degrees are collectively called chromosomal aberrations or anomalies or abnormalities. These accumulated sets of abnormalities so produced are called *syndrome*. If several specific abnormal traits present in the same individual are transmitted to his offspring as a unit, as they often are, it can usually be assumed that they depend jointly on a single gene. In medicine such group of characters is called a *syndrome*. A well-known example of a syndrome is Marfan's syndrome, or Arachnodactyly (spider-fingeredness), so called because of the excessive length of the bones of fingers and toes. Though abnormal chromosomes account for at least 50 per cent of spontaneous abortions, only 0.65 per cent of newborns have abnormal chromosomes as most embryos and fetuses with abnormal chromosomes stop developing before birth.

Chromosomal Changes

Normally, every somatic cell contains a pair of each type of autosome, each pair of autosomes has numerous pairs of homologous loci, and at each of these loci is one of a pair of alleles. The harmonious genic action depends on the twofold presence of each locus. Occasionally, however, abnormalities in the division or the distribution of the chromosomes or of chromosomal sections may result in some loci existing in triplicate or singly instead of as a pair. The abnormal chromosomal types in many plants and animals have shown that development does not proceed normally. Such imbalance in the genetic content of the zygotes – two alleles of most loci but three, or one, of the loci of certain chromosome – may result in early death of the zygote. Sometime, however, full development of the zygote may occur but the individual will not be normal. One of the most remarkable and abnormal syndromes in man is that called Down's syndrome or Mongolism, first described as a clinical syndrome in 1866 by Langdon-Down of England. Affected individuals are characterised by physical abnormalities of the face, eyelids, tongue, and other parts of the body and are greatly retarded both physically and mentally. The incidence at birth is about 1/700 among Europeans. This is caused due to the presence of a very small 47th chromosome, and the small chromosome is present in triplicate, instead of duplicate, on chromosome number 21, suggesting the synonym *Trisomy 21*.



By 1959 a variety of chromosomal aberrations was demonstrated in man. Different types of abnormalities which can occur are divided into numerical, structural and a third category consisting of different chromosome constitutions in two or more cell lines. A chromosome anomaly or abnormality or aberration reflects an atypical number of chromosomes or a structural abnormality in one or more chromosomes. A karyotype is a full set of chromosomes arranged in an order of their size from an individual which can be compared to a “normal” karyotype for the species via genetic testing. Any anomaly in the chromosome may be detected or confirmed in this manner. Chromosome anomalies usually occur when there is a fault in cell division following meiosis or mitosis. These chromosome anomalies can be organised and summarized into two basic groups, numerical and structural anomalies (Table 4.1).

Table 4.1: Chromosomal abnormalities

<i>Numerical</i>	
Aneuploidy	– Monosomy – Trisomy – Tetrasomy
Polyploidy	– Triploidy – Tetraploidy
<i>Structural</i>	
Translocation	– Reciprocal – Robertsonian
Deletions	
Insertions	
Inversions	– Paracentric – Pericentric
Rings	
Isochromosomes	
<i>Different cell lines (Mixoploidy)</i>	
	– Mosaicism – Chimaerism

4.2 CHANGES IN CHROMOSOME NUMBER

The most obvious way of disrupting the balance of genes is by the variation in number of chromosomes. There are two distinct types of abnormalities in chromosome number. The first one involves the presence of extra entire sets of chromosomes and the second type involves individual chromosomes instead of entire sets of chromosomes. Human gametes are *haploid* (n) i.e. the gametes carry 23 chromosomes. The gametes carry one complete set of chromosomes consisting of 22 autosomes and 1 sex chromosome and whereas the somatic cells in contrast are *diploid* ($2n$) and carry two haploid sets of chromosomes – 46 altogether. Abnormally higher multiple of the basic haploid (n) set is known as *polyploid* ($3n$, $4n$, and so forth). Polyploidy (*euploidy*, which means a good set) in man is extremely rare. A *triploid* cell ($3n$) would contain 69 chromosomes and *tetraploid* ($4n$) 92. Such genetic imbalance is intolerable in man and animals, but quite common in plants. Triploidy in man is relatively rarely found in

spontaneous miscarriages and rarely survive beyond mid-pregnancy. Only eight live-borns have been recorded and all have died soon after birth. Polyploidy can arise from fertilization involving unreduced gametes (essentially complete non-disjunction) containing 46 instead of 23 chromosomes, through fertilization of an ovum with two sperms called *dispermy*, or by the failure of duplicated chromosomes to separate into two daughter cells during mitosis – the observed live-born mosaics. A few full triploids have been born prematurely, but none survived more than several hours.

Chromosomal abnormalities in the form of aneuploidy (extra or missing chromosomes) are very regular among humans. Roughly 8 per cent of all conceptions are aneuploidy, and it is projected that up to half of all miscarriages are due to some form of chromosome disorders. Sex chromosome disorders are the most commonly observed type of aneuploidy in humans. Four common categories of aneuploidy crop up in humans:

(i) Nullisomy – occurs when a chromosome is missing altogether (www.dummies.com). Generally, embryos that are nullisomic don't survive to birth; (ii) Monosomy – Occurs when one chromosome lacks its homolog; (iii) Trisomy – Occurs when one extra copy of a chromosome is present and (iv) Tetrasomy – Occurs when four total copies of a chromosome are present and tetrasomy are extremely rare. In humans, it is unusual to find individuals surviving with more than one extra or one missing chromosome. If there is one extra chromosome present, which means a particular chromosome is represented three times instead of the usual paired diploid arrangement and the condition is known as trisomy for that chromosome and is symbolized as $2n + 1 = 47$. When one chromosome is missing from the diploid complement, only one representative of a particular pair is present, producing a condition known as monosomy symbolized as $2n - 1 = 45$.

24 different trisomies and 24 different monosomies are expected to occur in man as there would be one trisomic and one monosomic for each of the 22 autosomes and an X and a Y of each type. Of the 48 theoretical possibilities, only eight aneuploids were observed in live-born children of whom six were trisomics and three were monosomics. The types of aneuploids generally observed in man are shown in table 4.2.

Table 4.2: Types of Aneuploids in live-born Children

Abnormal Chromosomal Constitution	Name of the Syndrome	Year of Discovery	Occurrence
Trisomies			
13, 13, 13 (47, + 13)	Patau's	1960	1 in 5,000 births
18, 18, 18 (47, + 18)	Edward's	1960	1 in 6,500 births
21, 21, 21 (47, + 21)	Down's	1959	1 in 800 births
X, X, X (47, XXX)	Trisomy X	1961	1 in 950 female births
X, X, Y (47, XXY)	Klinefelter's	1959	1 in 1,000 male births
X, Y, Y (47, XYY)	Jacob's (Double Y Syndrome)	1961	1 in 950 male births
Monosomies			
21, 0 (45, - 21)	Al-Aish's	1967	Very rare (about 3 known)
X, 0 (45, X)	Turner's	1959	1 in 5,000 female births

The meiotic error that causes aneuploidy is called *non-disjunction*. *Non-disjunction* is the failure of two members of homologous chromosome pair to separate during cell division so that both pass to the same daughter cell. It is not clear how non-disjunction is caused. But the factors implicated for the cause of nondisjunction are aging, radiation and delayed fertilization after ovulation. The principal cause of aneuploidy is an accident in *meiosis* that leads to an unequal distribution of chromosome pair (www.scribd.com).

In meiotic cell division there are two instances in which non-disjunction can occur – during first meiotic division or second meiotic division (see figure 4.1). In either case, the result is the production of one or more gametes that carry an extra chromosome and one or more gametes that lack a chromosome.

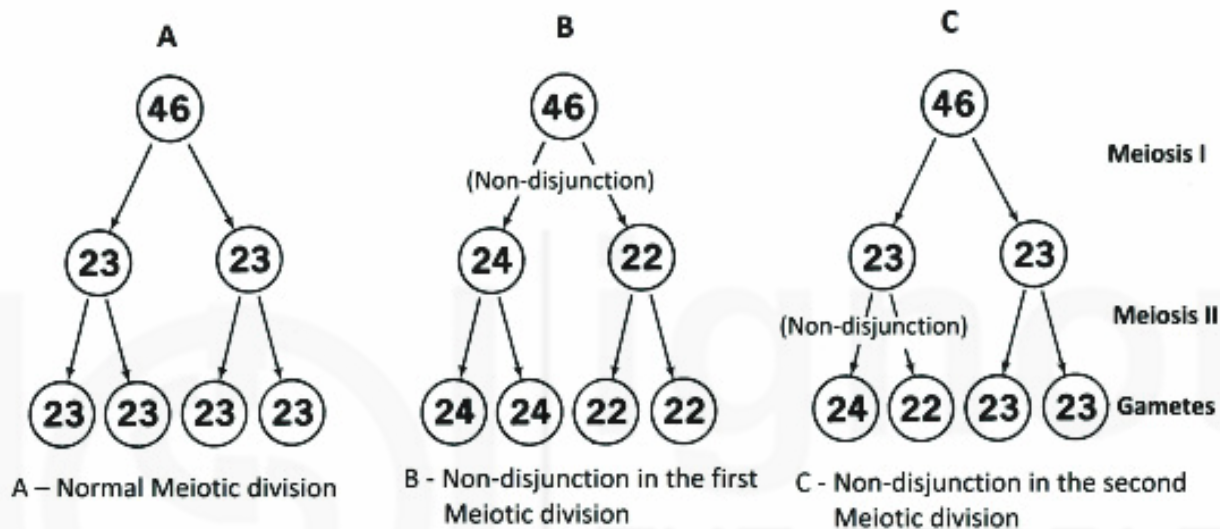


Fig.4.1: The effect of meiotic non-disjunction on gametic chromosome number

Source: Nagle, J.J. 1974 Heredity and Human Affairs. Saint Louis, The C.U. Mosby Company p. 256

4.3 SPECIFIC AUTOSOMAL ABNORMALITIES

Patau's Syndrome or 13-Trisomy: This syndrome occurs in about 1 in 5000 live births. Patau's syndrome also has a slightly increased incidence with maternal age. Generally they do not survive beyond three or four months after birth. The patients having a trisomy of the 13th chromosome, are characterised by multiple and severe body malformations, as well as profound mental deficiency.

Edward's Syndrome or 18-Trisomy: This syndrome is about eight times less frequent than the Down's syndrome and affects about 1 in 6500 live births. The children with Edward's syndrome have multiple congenital abnormalities, including severe mental and physical retardation. The head of such a patient is laterally flattened. The hands are short and show little development of the second phalanx. These children usually die before one year of age.

Down's syndrome (21-Trisomy): One of the most familiar human aneuploidy is trisomy 21. Originally studied by Langdon Down in 1866, it had been termed mongoloid idiocy or mongolism because of suggested resemblance to that ethnic feature. The condition is now referred to as Down's syndrome. The persons having

this syndrome are mentally retarded and have markedly defective development of the central nervous system. The face of such a patient has a moon-like appearance, with a skin fold (epicanthus) at the inner part of the eyes. The nose is flattened the ears are malformed; the mouth is constantly open; and the tongue protrudes. The heart, hands and feet too remain defective.

Al-Aish's Syndrome or 21-Monosomy: When one chromosome of the pair of chromosome 21 becomes completely deleted 21-monosomy occurs and it remains lethal to the patient. In 21-monomics, the nose remains prominent, the distance between eyes is shorter than normal, the ears are large and the muscles are contracted. Its incidence is very rare.

4.4 SEX CHROMOSOMAL ABNORMALITIES

Different kinds of sex chromosomal numerical aberrations have been detected in man. Most of them are caused either by meiotic non-disjunctions or mitotic non-disjunctions. They are expressed phenotypically in the following different kinds of syndromes:

Trisomy X or Triplo-X: Women with this syndrome have 47 chromosomes, including three X chromosomes. XXX females are physically normal but many are mentally retarded. Some are reported to have menstrual irregularities.

All kinds of syndromes are caused by meiotic non-disjunctions of sex chromosomes and all of them are expressed phenotypically in dwarfisms, mental retardation and various other physical abnormalities. Some of the triplo-X females menstruate.

Klinefelter's syndrome: This XXY condition (44 autosomes + XXY) occurs in about 1 in 1000 newborn males. The patients of this syndrome have some degree of mental retardation; growth and physical development are quite normal, but the affected males are tending to be tall for their age. Puberty does not occur normally and they remain sterile.

Turner's syndrome: The persons with the karyotype of 45 chromosomes (44 autosomes and one X chromosome) have the symptoms of disease called female gonadal dysgenesis. Such persons have female phenotype, but with rudimentary gonads and without menstruation cycle during puberty. Further, a patient of Turner's syndrome is characterised by short stature, and a pronounced webbing of the neck, and short fourth metacarpal (www.microbiologyprocedure.com).

4.5 MOSAICISM

Mosaicism

All forms of aneuploidy are not clear as discussed earlier as mixtures of aneuploidy and normal cell lines are possible to exist within the same person. These are called chromosomal mosaicism. Mosaicism is defined as the presence of two or more cell lines in an individual or in a tissue which differ in their genetic constitution and are derived from the same zygote (Fig.4.2). The degree of abnormality may range from severe to negligible. Mosaicism may occur in two ways. The most common one is the mitotic non-disjunction — that occurs at an

early stage of embryonic development and in this case one daughter cell will be trisomic for the chromosome in question and the other daughter cell will be monosomic. Thus the individual is a chromosomal *mosaic* – an individual with two or more chromosomally distinct cell lines.

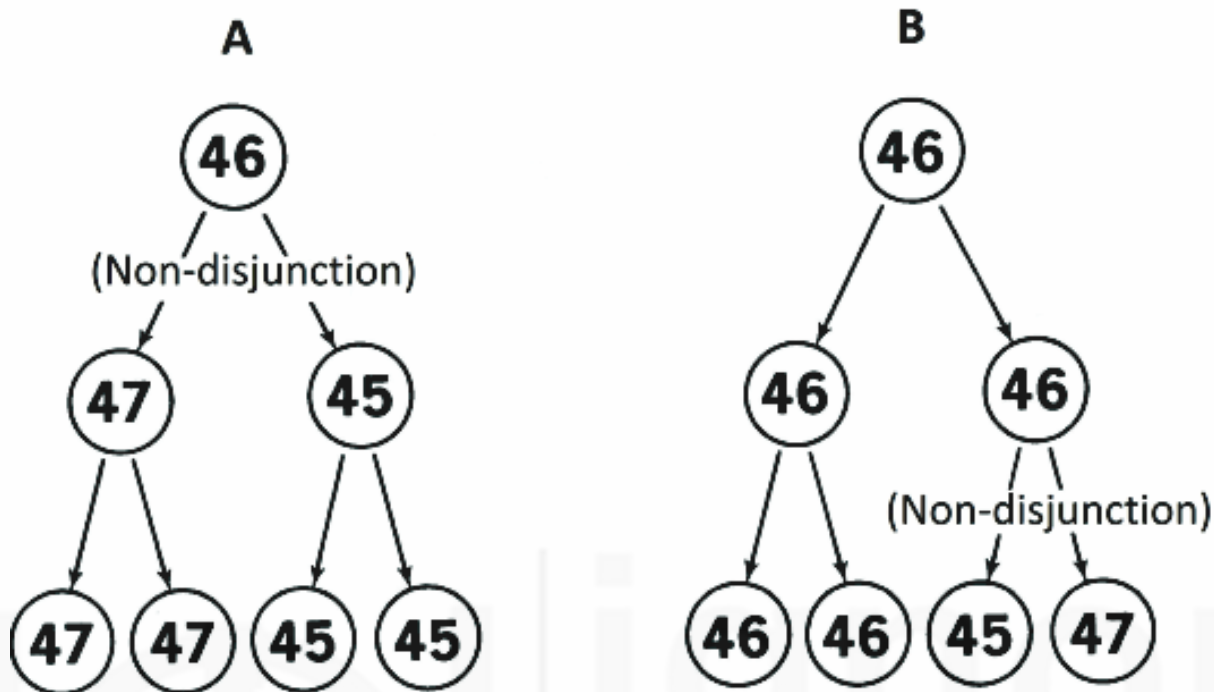


Fig. 4.2: Chromosomal mosaicism as a result of mitotic non-disjunction

Source: Nagle, J.J. 1974 Heredity and Human Affairs. Saint Louis, The C.U. Mosby Company p. 263

A – Zygotic non-disjunction, producing trisomic and monosomic cell lines and

B – Postzygotic non-disjunction, producing three different cell lines.

The second manner in which chromosomal mosaicism may be developed is by the loss of one chromosome as it moves towards the pole during mitosis. This is known as anaphase lag and results in one cell line with normal chromosome constitution and one with monosomy for the lost chromosome.

Chimaerism

It can be defined as the presence of two or more genetically distinct cell lines in an individual derived from more than one zygote. The word chimaera is derived from the mythological Greek monster which had the head of a lion, the body of a goat and the tail of a dragon. In humans these are of two kinds, dispermic and blood chimaeras (www.uqu.edu.sa). Chimeras are gynandromorphs like individuals which are mosaics for different cells having various abnormalities of sex chromosomal number. The occurrence of male and female cells in the animal body in a mosaic like pattern is called gynandromorphism. However, the different kinds of cells arise from different zygotes. The most common chimerism in man occurs with the passage of fetal cells into the maternal circulation, in which the immunization of ABO and Rh blood group takes place. This kind of chimerism is called post-zygotic chimerism. Chimerism can also be produced by double fertilization (zygotic chimerism) or by artificial means such as grafting and organ transplantation.

Polyploids have extra sets of chromosomes and do not survive for long.

Aneuploids have extra or missing chromosomes.

Nondisjunction during meiosis causes aneuploidy.

Trisomies are less severe than monosomies, and sex chromosome aneuploidy is less severe than autosomal aneuploidy.

Mitotic nondisjunction produces chromosomal mosaics.

Down syndrome (trisomy 21) is the most common autosomal aneuploid, followed by trisomies 18 and 13.

Sex chromosome aneuploid conditions include XO, triplo-X, XXY, XXYY, and XYY syndromes

4.6 STRUCTURAL ABNORMALITIES OR CHROMOSOME REARRANGEMENTS

Chromosomes are prone to accidents that break and alter their individual structure. Structural abnormalities are referred to the chromosomes having an abnormal structure with a missing portion or a portion represented twice. They range in size from those that are so small as to be almost undetected with the light microscope to those that are so large as to be striking and obvious. Large scale chromosome changes are called chromosomal rearrangements. A chromosome rearrangement is a structural change in a chromosome such as a deletion, translocation, inversion, or gene amplification. Chromosome rearrangements can contribute to the transformation of a normal cell into a cancerous cell and are therefore found in many cancer cells. The chromosomal aberrations may remain confined to a single chromosome or may extend to both of the member of the homologous pair. In considering chromosome rearrangements, it is important to note whether the rearranged chromosomes still carry all of the genes they should have in their proper dosage, although of course, in an incorrect arrangement, or whether the rearranged chromosomes have lost or gained genes. A chromosome rearrangement that retains all the genes in proper dosage is said to be a *balanced* rearrangement. One that has lost or gained genes is said to be an *unbalanced*. Four kinds of structural abnormalities of chromosomes are of great importance in human genetics.

- Deletions or deficiencies (large parts of the chromosome are lost),
- Duplications (large parts of the chromosome are copied more than once, making the chromosome substantially large),
- Inversions (a section of the chromosome gets turned around, reversing the sequence of genes) and
- Translocations (parts are exchanged between non-homologous chromosomes) (Fig.4.3).

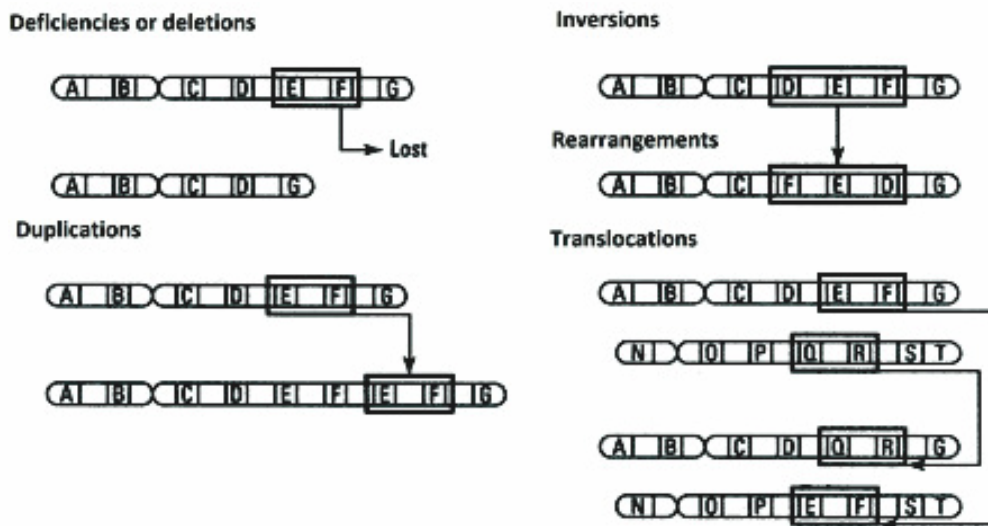


Fig.4.3: The Four Types of Chromosomal Abnormalities or Rearrangements

Source: Hartl, D.L., 1985. *Our uncertain heritage: Genetics and Human Diversity*.
New York, Harper and Row Publishers

Deletions (Deficiencies)

In deletion or deficiency type aberration, a chromosome lacks either in an interstitial or terminal chromosomal segment which may include only a single gene or part of a gene. If break occurs near the end of a chromosome a small piece of the terminal end is lost and thus, terminal deficiency occurs. Sometimes two breaks may occur at any two points, releasing an intercalary segment which may remain rod-shaped or may become ring-shaped, if its broken ends join and fuse, a ring-shaped chromosome called deletion ring is formed (www.microbiologyprocedure.com). The broken ends of original chromosome are fused and have intercalary or interstitial deficiency. A deletion is the loss of a portion of a chromosome and, in effect, represents *partial monosomy*. Breakage may occur by any of a number of agents such as irradiation, chemicals, drugs, and viral infections. Deletions occur in one of two ways:

- ✓ the chromosome breaks during interphase of the cell cycle and the broken piece is lost when the cell divides, and
- ✓ parts of chromosomes are lost due to unequal crossing-over during mitosis.

The syndromes caused by the deletion of either short arm or long arm are associated with mental and physical retardation. The physical abnormalities tend to be variable from patient to patient. However, children with partial deletion of the short arm of chromosome 18 sometimes have malformations in their ear and jaws and those with partial deletion of the long arm of 18 have severe eye and ear defects.

Duplications

Duplications are the chromosomes having an extra part and gene sequences. Traditionally, only large duplications could be visualized in karyotypes and, in general, the more genes involved, the more severe the associated syndrome. Small duplications tend to be less severe than deletions of small sizes. Small duplications involving only a few genes, called repeats can be tolerated. In fact, such duplications are thought to be an important evolutionary mechanism for the origin of "new genes". Duplications of large unwanted copies of portions of the chromosome most often arise from unequal crossing-over. Most disorders arising from duplications are considered partial trisomies because large portions of one chromosome are usually present in triplicate.

Inversions

An *inversion* (see Fig. 4.4) involves breaks (a) in one chromosome, followed by repair in the form of reversal of the broken segment (b), and restitution of the broken ends (c), resulting in an inverted chromosome (d). The normal order of genes of this chromosome is ABCD, but in the inverted chromosome the order of the genes is ACBD. Depending on whether or not the centromere is included within the inverted section, two kinds of inversions can be distinguished:

- ❖ *paracentric inversion* when the centromere is outside the inverted segment and
- ❖ *pericentric inversion* when the centromere is included in the inverted segment of the chromosome.

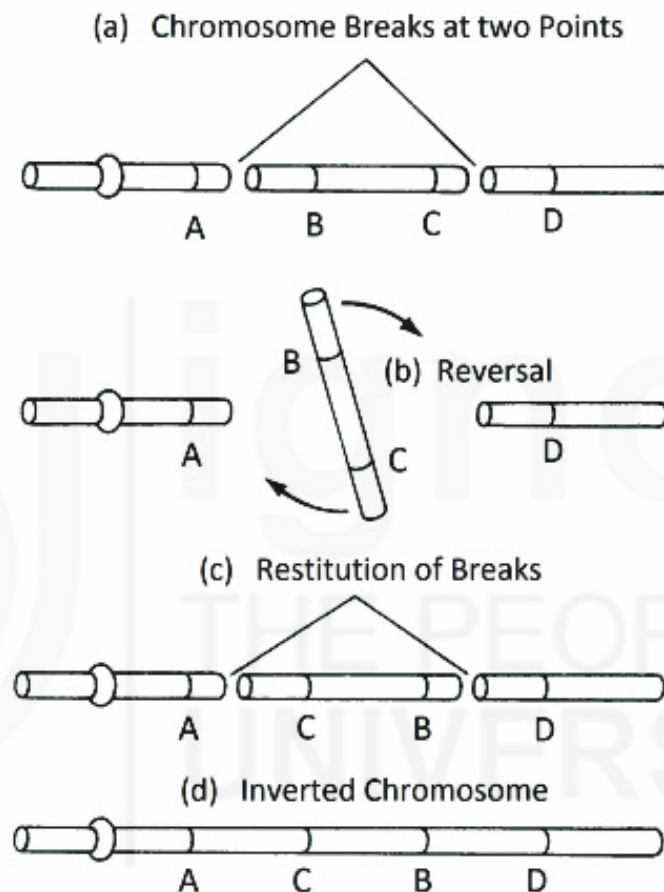


Fig. 4.4: Inversion in a chromosome

Source: Hartl, D.L, 1985. Our uncertain heritage: Genetics and Human Diversity. New York, Harper and Row Publishers, p- 185

The above example of inversion is called *paracentric inversion*. It is so called because the inverted segment does not include the centromere. The pericentric inversion is illustrated in Figure 4.5. When the breakpoints of a pericentric inversion are at appropriate distances from the centromere, the inversion can alter the physical appearance of the chromosome. In the illustrated figure a metacentric chromosome (a) after its inversion it is converted to a submetacentric one (b). Because of this kind of change the pericentric inversions can be microscopically detected as the relative position of the centromere changes. Inversions interfere with normal pairing during meiosis and may cause nondisjunction of the improperly paired chromosomes. They also suppress the effect of crossing over within the inverted section and retain groups of genes intact, producing what have been called supergenes that can evolve (be selected for or against) as units.

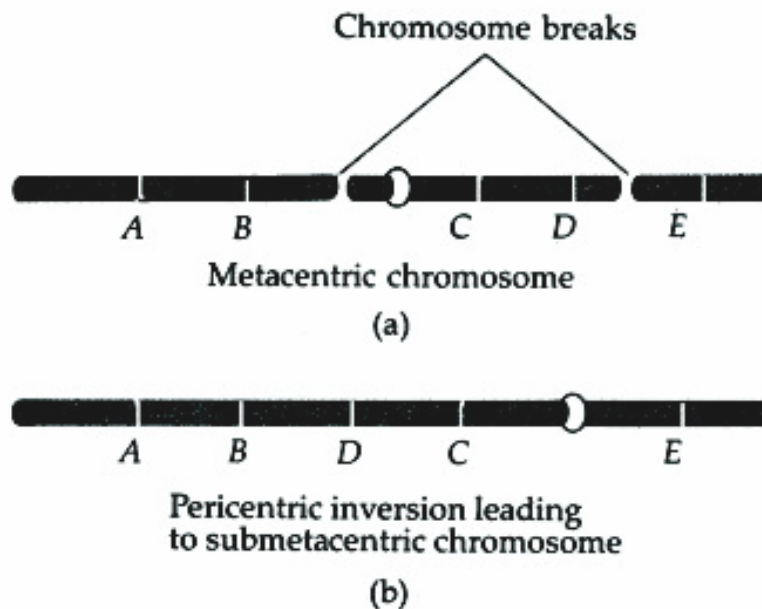


Fig. 4.5: Pericentric Inversion

Source: Hartl, D.L., 1985. Our uncertain heritage: Genetics and Human Diversity. New York, Harper and Row Publishers, p. 187

Heterozygous inversions can cause problem during meiosis. When synapsis occurs during prophase 1, all regions of the inverted chromosome try to pair gene for gene with the corresponding regions of the normal chromosome. To accomplish this, the inverted region in one of the chromosomes must form a loop (see Fig. 4.6); this loop will permit gene-for-gene pairing with homologue. Thus, except for a relatively small region around the breakpoints themselves, the normal and the inverted chromosomes can synapse all along lengths. The result is the formation of four gametes from the Anaphase I cell (see Fig.4.6), one will carry the normal chromosomes, one will carry the inverted chromosome, and two will have major abnormalities as a result of the crossover. In addition, among the phenotypically normal offspring (whether the inversion is large or small, and whether a crossover occurs or not), half will inherit the inverted chromosome and the other half will inherit its noninverted homologue.

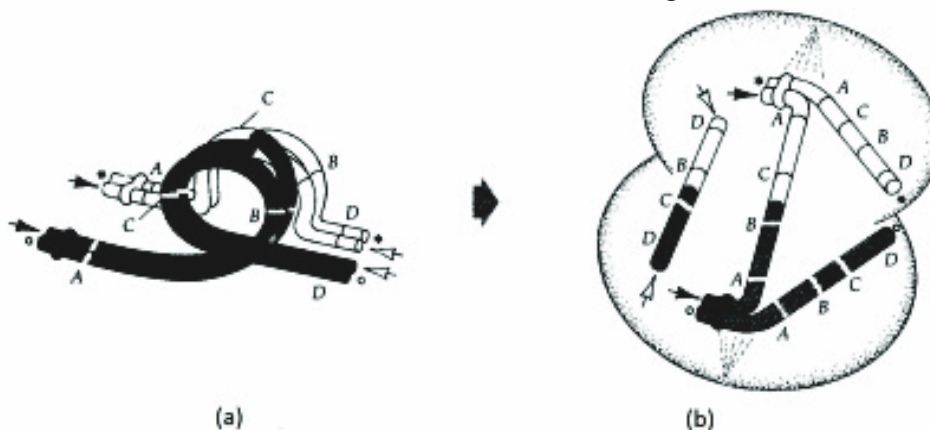


Fig. 4.6: (a) Synapsis in an individual who is heterozygous for a paracentric inversion showing a crossover within the inversion loop. (b) Anaphase I configuration resulting from the crossover in (a). One of the chromatids involved in the crossover is dicentric (solid arrows); the other is an acentric (open arrows)

Source: Hartl, D.L., 1985. Our uncertain heritage: Genetics and Human Diversity. New York, Harper and Row Publishers, p. 186

Similar to paracentric inversions, synapsis in meiosis produces an inversion loop and crossing-over within this loop resulting in abnormal chromatids in pericentric inversions also (Fig.4.7). The chromatids involved in a crossover within the inversion loop of a heterozygous pericentric inversion will carry duplications and deficiencies and will lead to offspring who have major chromosomal abnormalities. Among the phenotypically normal offspring of an individual who is heterozygous for a pericentric inversion, half will receive the inverted chromosome and the other half will receive its noninverted homologue.

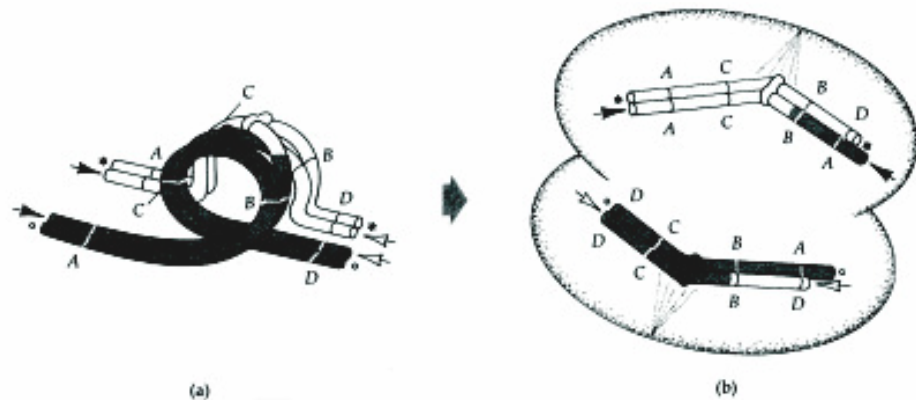


Fig. 4.7: (a) Synapsis in an individual who is heterozygous for a paracentric inversion showing a crossover within the inversion loop. (b) Anaphase I configuration resulting from the crossover in (a). One of the chromatids involved in the crossover has a duplication of A and a deficiency of D (solid arrows); the other chromatid has a deficiency of A and a duplication of D (open arrows)

Source: Hartl, D.L., 1985. Our uncertain heritage: Genetics and Human Diversity. New York, Harper and Row Publishers, p.185

The larger the segments in the duplication and deletion in the recombinant chromosome, the greater the degree of imbalance and the more likely miscarriage will result. Also the smaller the size of the inversion, the greater will be the degree of imbalance which will result in miscarriage of recombinant conceptions.

Translocations

Translocation is another class of structural abnormalities commonly found in man which involves the detachment of a segment of one chromosome and reattachment to another, usually nonhomologous, chromosome. The genetic significance of this structural rearrangement is that genes from one chromosome are transferred to another. These are of two types: (1) *Reciprocal translocation* and (2) *Nonreciprocal translocation*. The reciprocal translocation is referred to the structural rearrangement when segments of two nonhomologous chromosomes are interchanged without any net loss of genetic material (Fig. 4.8). A special type of nonreciprocal translocation is a *Robertsonian translocation*, in which the centromeric regions of two nonhomologous acrocentric chromosomes become fused to form a single centromere (Fig.4.9) (www.udl.es/usuaris).

In the reciprocal translocation as illustrated in Figure 4.8 no chromosomal material is gained or lost and also each chromosome is monocentric. An individual who carries the parts of reciprocal translocation (see (c) of Figure 4.8) would also carry the normal homologue of both chromosome (i.e., ABCDE and YZ). Such an individual is said to carry a *balanced translocation* because the individual carries all the normal genes in their proper dosage; only the order of genes has been changed. Individuals who carry only part of reciprocal translocation and thus have duplications and/or deficiencies are said to carry *unbalanced translocations*. When the interchanged parts of the reciprocal translocation are

large, the individuals with unbalanced translocations will have large duplications or deficiencies and would be expected to undergo spontaneous abortion.

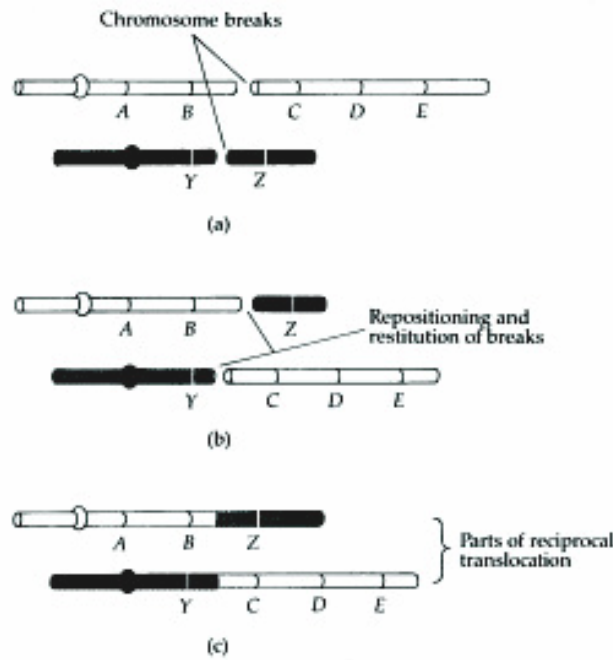


Fig. 4.8: Origin of a reciprocal translocation (c) from breaks in two nonhomologous chromosomes (a) followed by repositioning of broken ends and restitution of the breaks (b)

Source: Hartl, D.L., 1985. *Our uncertain heritage: Genetics and Human Diversity*
New York, Harper and Row Publishers, p.189

Robertsonian translocation as illustrated in Figure 4.9 involves the interchange of the long arm of one acrocentric chromosome with the short arm of a nonhomologous acrocentric chromosome (see (a) and (b) of Figure 4.9) leading to a tiny metacentric chromosome consisting of both short arms along with a large metacentric chromosome consisting of both long arms (see (c) of Figure 4.9). The tiny metacentric chromosome frequently undergoes mitotic or meiotic nondisjunction and is lost, but its loss has no detectable phenotypic effect owing to the small amount of chromosomal material in tiny metacentric chromosome. Robertsonian translocation is sometimes referred to as a chromosomal fusion or centric fusion as there is a fusion of the long arms of two acrocentrics.

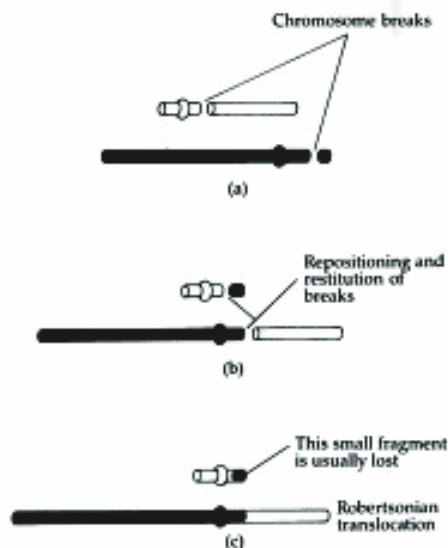


Fig. 4.9: Origin of Robertsonian translocation (c) from nonhomologous acrocentrics broken as shown in (a) with restitution as in (b). In most cases the tiny metacentric chromosome is lost

Source: Hartl, D.L., 1985. *Our uncertain heritage: Genetics and Human Diversity*.
New York, Harper and Row Publishers, p.192

Chromosomes can also be fused end-to-end to shape a structure with two centromeres. If one of these is inactivated, the chromosome fusion will be stable. Such a fusion clearly occurred in the evolution of our own species. Human chromosome 2, which is a metacentric, has arms that correspond to two different acrocentric chromosomes in the genomes of the great apes. Detailed cytological analysis has revealed that the ends of the short arms of these two chromosomes apparently fused to create human chromosome 2.

Isochromosomes

An isochromosome is a chromosome in which both arms are identical. Isochromosome is formed by the mirror image copy of a chromosome segment including the centromere. It is thought to arise when a centromere splits transversely in the wrong plane instead of along the normal longitudinal plane, yielding two daughter chromosomes (Fig. 4.10), each of which carries the information of one arm only but present twice. So these chromosomes show loss of one arm and duplication of the other. They are perfectly metacentric chromosomes. The isochromosomes are formed during mitosis and meiosis.

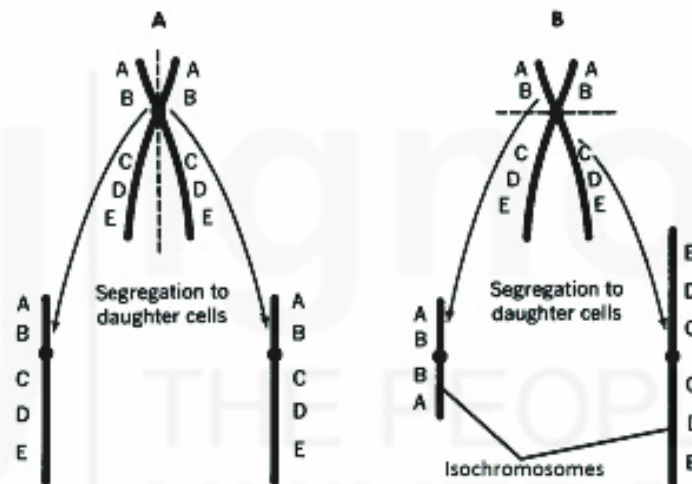


Fig. 4.10: Diagrammatic interpretation of the formation of isochromosomes. A) Normal longitudinal splitting of the centromere (dotted line). B) Abnormal transverse splitting of the centromere (dotted line) forming isochromosomes

Source: Nagle, J.J. 1974 Heredity and Human Affairs. Saint Louis, The C.U. Mosby Company, p.271

Isochromosomes have been observed for the X chromosome with some regularity, but they are virtually unknown in autosomes, except possibly for chromosome 21 in a few cases of Down's syndrome.

Ring Chromosomes

A portion of a chromosome gets broken off and forms a circle or ring. A *ring chromosome* is formed when a break occurs on each chromosome leaving two sticky ends on the central portion which reunites as a ring. This can happen with or without loss of genetic material. Ring chromosomes can be a centric or acentric event.

Chromosome rearrangements can cause deletions and duplications.

In a Robertsonian translocation, the long arms of two different acrocentric chromosomes join.

In a reciprocal translocation, chromosomes exchange parts.

If a translocation leads to a deletion or duplication, or disrupts a gene, symptoms may result.

Gene duplications and deletions can occur in isochromosomes and ring chromosomes, and when crossovers involve inversions.

An isochromosome has two identical arms, introducing duplications and deletions.

Ring chromosomes form when telomeres are missing.

4.7 SUMMARY

A Chromosome is a thread-like structure located in the cell nucleus of living organisms. Generally, the chromosomes remain unchanged but due to certain natural or adverse conditions the chromosomal number changes or certain structural alterations may occur in the chromosomes which modifies the positions of gene or loss of some genes. **Abnormal Chromosome Number:** A euploid somatic human cell has 22 pairs of autosomes and one pair of sex chromosomes. Polyploid cells have extra chromosome sets. Aneuploids have extra or missing chromosomes. Trisomies (an extra chromosome) are less harmful than monosomies (lack of a chromosome), and sex chromosome aneuploidy is less severe than autosomal aneuploidy. Nondisjunction is uneven distribution of chromosomes in meiosis. It causes aneuploidy. Most autosomal aneuploids cease developing as embryos.

There are two different types of abnormalities in chromosome number, (1) the presence of extra entire sets of chromosomes, and (2) involves individual chromosomes instead of entire sets of chromosomes. Monosomic and trisomic zygotes are usually the consequence of non-disjunction during meiotic cell division. Non-disjunction is the inability of two members of homologous chromosome pair to separate during cell division so that both pass to the same daughter cell and the result is the production of one or more gametes that carry an extra chromosome and one or more gametes lack a chromosome. There are three types of trisomies and one monosomy of sex chromosomes observed in man. Turner's syndrome is a monosomy (XO, 45,X) and Klinefelter's syndrome (XXY, 47,XXY), Trisomy X syndrome (XXX, 47,XXX), and Jacob's (Double Y) syndrome (XYY, 47,XYY) are the trisomics. Among the autosomes, only one monosomy is observed which is very rare. It is called Al-Aish's syndrome (21, 0 or 45, -21). There are three autosomal trisomics in man and they are Patau's syndrome (13, 13, 13 or 47, +13), Edward's syndrome (18, 18, 18 or 47, +18) and Down's syndrome (21, 21, 21 or 47, +21).

A mixture of aneuploidy and normal cell lines are possible to exist within the same person. These are called chromosomal mosaicism. The presence of two or more genetically distinct cell lines in an individual derived from more than one zygote is called chimerism. Chromosomes are prone to accidents that break and alter their individual structure. Deletions and/or duplications result from crossing over after pairing errors in synapsis. Crossing over in an inversion heterozygote can also generate deletions and duplications. A chromosome with a deletion (deficiency) has certain genes missing. Small duplications involving only a few genes, are thought to be an important evolutionary mechanism for the origin of "new genes". In a Robertsonian translocation, the short arms of two acrocentric

chromosomes break, leaving sticky ends on the long arms that join to form an unusual, large chromosome. In a reciprocal translocation, two nonhomologous chromosomes substitute parts. A translocation carrier may have an associated phenotype and generate some unbalanced gametes. Isochromosomes repeat one chromosome arm but delete the other. This happens when the centromere divides in the wrong plane during meiosis. Ring chromosomes form when telomeres are removed, leaving sticky ends that hold on.

Reference

www.dummies.com
 www.microbiologyprocedure.com
 www.udl.es
 www.scribd.com
 www.uqu.edu.sa

Suggested Reading

Borgaonkar, D. S. 1977. *Chromosomal Variation in Man*. New York, Alan R. Liss.

Gardner, R. J. M. and Sutherland, G. R. 2004. *Chromosome Abnormalities and Genetic Counseling*. London, Oxford University Press.

Stern, C. 1960. *Principles of Human Genetics*. San Francisco and London, W. H. Freeman and Company.

Therman, E. S. 1993. *Human Chromosomes: Structure, Behaviour and Effects*. New York. Springer-Verlag.

Whittinghill, M. 1965. *Human Genetics and Its Foundations*. Calcutta, New Delhi, Oxford and IBH Publishing Company.

Sample Questions

- 1) Distinguish among a euploid, aneuploid, and polyploid. State which of the following involve in aneuploid number of chromosomes: diploidy, duplication, haploidy, triplication, Trisomy 21, Turner's syndrome, XXYY.
- 2) Discuss classification of some structural mutants, and illustrate them diagrammatically.
- 3) How many chromosomes would a person have who has Klinefelter syndrome and also trisomy 21?
- 4) Describe an individual with each of the following chromosome constitutions. Mention the person's sex and possible phenotype.
 - a) 47, XXX; b). 45, X; c) (47, + 21) trisomy 21
- 5) List three types of chromosomal aberrations that can cause duplications and/or deletions, and explain how they do so. List three causes of Turner syndrome.