GENETICS DISORDER

Pedigree Analysis And Genetics Disorder

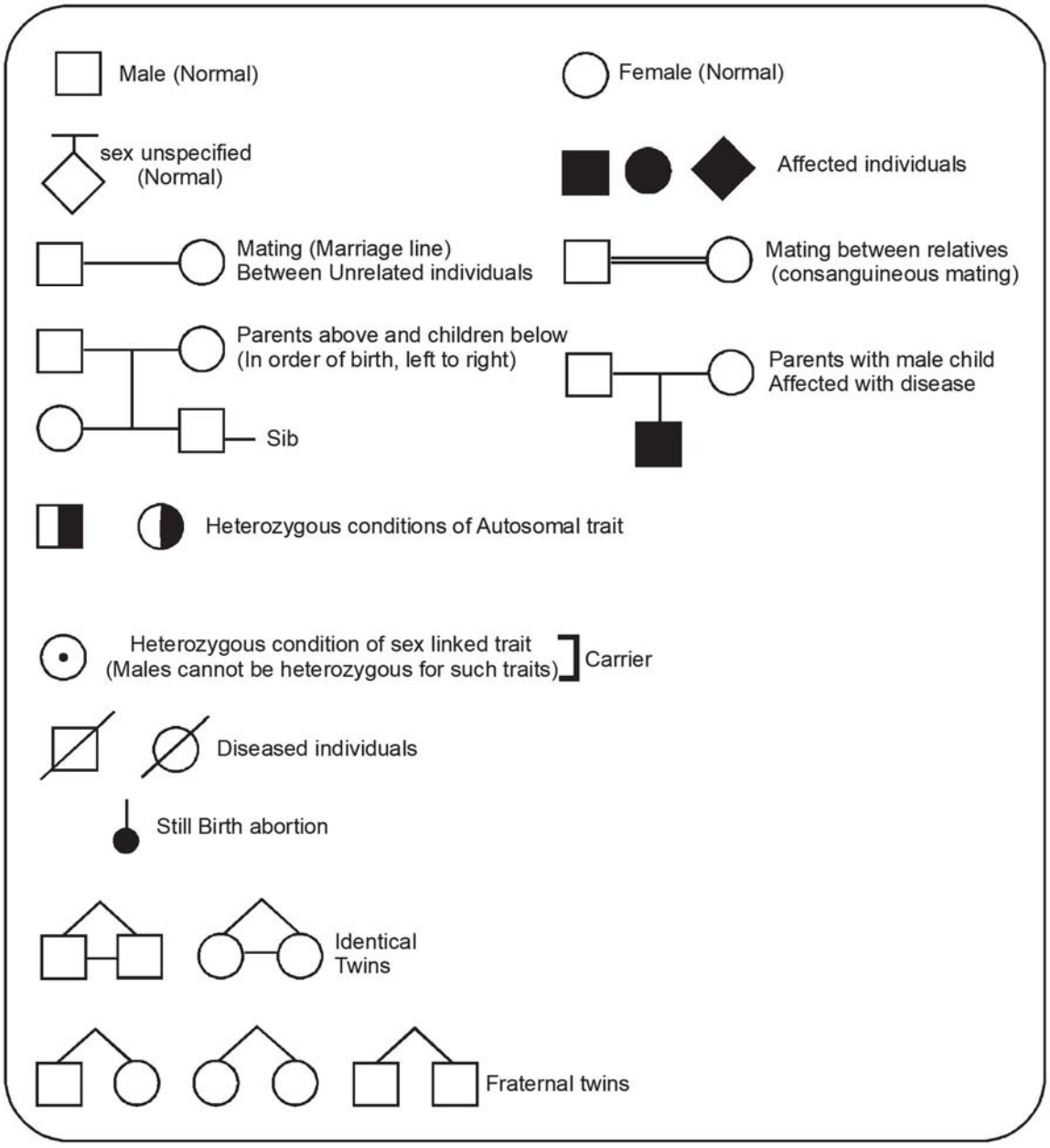
(Mendelian Disorders)

Devices Used In Human Genetical Studies :

People investigate and understand human genetics using various methods, including pedigree analysis, statistical analysis in population genetics, and human karyotyping. In this explanation, we'll focus on two crucial methods: pedigree analysis and human karyotype.

Pedigree Analysis

The examination of the ancestral history of humans and the transmission of genetic traits from one generation to the next is known as pedigree analysis. Traits such as dwarfism, albinism, color blindness, and hemophilia are examples of genetically inherited characteristics. To study and analyze these traits, pedigrees use genetic data and specific symbols.



In a family tree, it's common to put the males on the left side. If one parent isn't shown in the family tree, it means that person looked normal on the outside. Studying family trees helps us learn about the genes in humans. If there's a genetic illness in a family, studying the family tree can help parents know what to expect for their future children, like having extra fingers or toes in humans.

Human Karyotype

People have 23 pairs of chromosomes, making it a total of 46 chromosomes. In this approach, we organize chromosomes (which include autosomes and sex chromosomes) based on their size and structure. There are three kinds of chromosomes in humans – metacentric, submetacentric, and acrocentric – determined by where the centromere is and the length of the chromosome arms. Looking at a karyotype helps us understand the shapes (morphology) of chromosomes and identify them. It's also handy for studying abnormalities like Down syndrome.

Types Of Eugenics:

To make future generations better, we want more of the best individuals and fewer with less desirable traits. Eugenics has two main types:

Positive Eugenics:

Here, the goal is to increase the number of offspring with the best traits. This involves genetic counseling, carefully choosing mates (planned marriages), getting married at the right age, and having the freedom to make choices. Techniques like preserving high-quality eggs, artificial insemination, and keeping the best sperm using modern methods are also part of positive eugenics. Euphenics and gene engineering are used to promote the best hereditary traits in human society.

Negative Eugenics:

In negative eugenics, we prevent individuals with undesirable traits from having children. This is done through checks like controlling marriages, separating individuals, birth control, sterilization, and avoiding marriages between close relatives. For example, if a family tree shows the inheritance of albinism, a recessive disorder, and the fourth person is normal, we can figure out who might be a carrier of the trait.

1. Pedigree Analysis:

A pedigree is like a family tree that shows how certain genetic traits are passed down through two or more generations. It's a diagram where squares represent males, circles represent females, and symbols or words indicate specific traits. The parents are connected horizontally, and their offspring are linked vertically.

Studying pedigrees helps us understand how particular traits are transmitted. Genetic counselors use this information to guide couples on the likelihood of having children with conditions like hemophilia, colorblindness, and others.

Pedigree analysis uses two tools:

(i) figuring out the probability of traits being passed down, considering variations due to the small size of the family, and

(ii) narrowing down possibilities by eliminating alternatives.

2. Sudy of Twins:

When a woman gives birth to two babies at the same time, it's called having twins. There are different types of twins:

(i) Dizygotic Twins or Fraternal Twins:

These twins come from two separate fertilized eggs. They are known as dizygotic or fraternal twins.

(ii) Monozygotic Twins:

These twins develop from the same fertilized egg, which splits into two blastomeres. Also called identical twins, they are genetically similar except for occasional mutations.

(iii) Siamese Twins:

Sometimes, when the splitting of a young embryo is not complete, monozygotic twins can be joined in various regions. These are referred to as Siamese twins.

3. Population Genetics:

Population genetics is the study of how traits are spread out and how often genes show up in an entire population. This field relies on the principles of probability and statistical tools.

Hardy-Weinberg Law:

The Hardy-Weinberg law tells us that when individuals in a population randomly mate, the frequency of different genotypes depends on the gene frequencies. After just one generation of random mating, the population reaches equilibrium.

If we have a gene A (represented by p) and its alternative gene a (represented by q), their frequencies add up to 1.

This is expressed as $A + a = 1$ or $p + q = 1$. When we square this equation,

we get $(A + a)^2 = A^2 + 2Aa + a^2 = 1$.

Now, breaking it down further:

The frequency of A (p) gives us the frequency of individuals with the genotype AA (homozygous dominant), which is p^2.

The frequency of a (q) gives us the frequency of individuals with the genotype aa (homozygous recessive), which is q^2.

The frequency of Aa (2pq) gives us individuals with the genotype Aa (heterozygous).

Genetic Disorders

Genetic disorders happen when there are changes or irregularities in an organism's genetic material, called the genome. These disorders can stem from mutations in a single gene or multiple genes, as well as alterations in the structure or number of chromosomes.

Genes, the fundamental units of heredity, carry genetic information in the form of DNA. This information is crucial for creating proteins that perform essential life functions. Occasionally, genes experience mutations, altering the instructions for protein formation, leading to proteins that don't function properly. This results in what we call genetic disorders.

Some genetic disorders are present from birth, inherited from parents. Examples include cystic fibrosis, hemophilia, and sickle cell anemia. Others arise during a person's lifetime due to random mutations or exposure to specific substances like cigarette smoke or UV radiation, as seen in diseases like cancer.

Genetic disorders fall into two main categories: Mendelian Disorders, involving a single gene following Mendelian inheritance patterns, and Chromosomal Disorders, characterized by changes in chromosome structure or number. Chromosomes may be missing, duplicated, or parts may be translocated.

Exploring notes on genetic disorders helps us understand the different types and how they can affect individuals.

Types Of Genetic Disorders

Mendelian Disorder

Certain health problems happen because of changes in just one gene. You can find them out easily by looking at family history. These issues can be of different types, like being passed down from parent to child, and they might affect either boys or girls more.

Some of the most usual gene-related issues are:

- Cystic fibrosis (passed down from both parents)
- Haemophilia (more common in boys and passed down from moms)
- Albinism (passed down from both parents)
- Sickle cell anemia (passed down from both parents)

Chromosomal Disorder

Certain health problems occur when there are changes in the number or structure of chromosomes in the body. Sometimes, a person might have too many or too few chromosomes.

This kind of problem is often very serious and can affect many different genes in the body. Some of the big chromosome issues include:

- Down's syndrome - when there's an extra chromosome 21
- Turner's syndrome - when one of the X chromosomes is missing
- Klinefelter's syndrome - when there's an extra X chromosome

Multifactorial Genetic Inheritance

This is called polygenic inheritance, and it happens because of a mix of things like the environment and changes in our genes. Some examples of this kind of health issue are:

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

Mitochondrial Inheritance

This kind of genetic problem happens because of changes in a special type of DNA found in our cells, called mitochondrial DNA. We get this type of DNA from our moms. Some sicknesses caused by this kind of inheritance include:

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

Genetic Counselling

Genetic counseling is an amazing way to find out if a baby might have a genetic disease or if someone could develop a genetic disorder. Genetic counselors can assist with diagnosing and treating specific disorders.

Some genetic disorders have been treated with gene therapy, and new techniques are being tested for future use in medical science to cure genetic issues.

There are several reasons why someone might consider genetic counseling, such as:

- Family history of genetic diseases, heart defects, mental retardation, neural tube defects, short height, psychiatric disorders, cancer, etc.

- A parent has an autosomal dominant disease.
- The pregnant woman is 35 years or older.
- The mother has a disorder like depression, alcoholism, diabetes, thyroid issues, schizophrenia, etc.

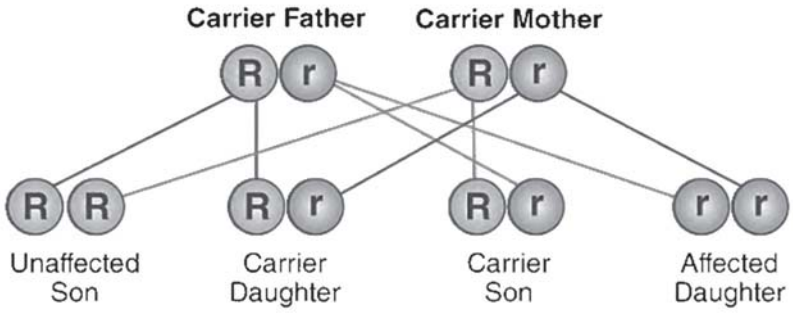
LIST OF GENETIC DISORDERS

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

i. Cystic fibrosis
ii. Thalassemia
iii. Huntington's disease
iv. Hemochromatosis
v. Turner's syndrome
vi. Kleinfelter's syndrome
vii. Leber's Hereditary Optic Atrophy
viii. Cancer
ix. High Blood Pressure
x. Obesit

Mendelian Disorder Definition

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



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

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

Types Of Mendelian Genetic Disorders

Mendel, a scientist, discovered laws about how traits are passed down, and there are different kinds of disorders based on these laws. Here are some types:

Autosomal dominant: Traits passed from parent to child through autosomes (non-sex chromosomes).

Autosomal recessive: Traits passed from parents through autosomes, but both parents need to carry the gene.

Sex-linked dominant: Traits linked to the sex chromosomes and dominant.

Sex-linked recessive: Traits linked to the sex chromosomes and recessive.

Mitochondrial: Traits passed through the mitochondria, the cell's energy producers.

We can figure out these disorders by looking at family trees, which is called pedigree analysis.

Here are some examples of these disorders in people:

- Sickle cell anemia
- Muscular dystrophy
- Cystic fibrosis
- Thalassemia
- Phenylketonuria
- Color blindness
- Skeletal dysplasia
- Hemophilia

Haemophilia

Haemophilia is a rare genetic disorder linked to the X chromosome, making it a type of recessive disorder.

Moms who are carriers can pass on the haemophilic genes to their sons, while it's less common in females unless the mom is a carrier or haemophilic and the dad is haemophilic.

This disorder affects blood clotting because the protein responsible for clotting is affected. People with haemophilia might experience excessive bleeding from cuts or injuries.

Since the affected gene is on the X chromosome, it's more common in males.

Sickle-Cell Anemia

Sickle-cell anemia is a genetic disorder inherited in a recessive way.

Following Mendelian genetics, it happens when both parents carry the gene.

The disorder occurs when a specific amino acid in the hemoglobin molecule changes, causing the molecule to take on a sickle shape. This alters the molecule's ability to bind with oxygen, leading to various health issues.

Phenylketonuria

Phenylketonuria is an autosomal recessive genetic disorder.

It's an inborn error related to the decreased metabolism of the amino acid phenylalanine.

People with this disorder lack an enzyme that converts phenylalanine to tyrosine. The resulting accumulation of phenylalanine in the body can lead to mental retardation.

Thalassemia

Thalassemia is a disorder where the body produces an abnormal amount of hemoglobin, leading to the destruction of many red blood cells and causing anemia.

It is inherited as an autosomal recessive trait.

Symptoms of thalassemia include facial bone deformities, abdominal swelling, and dark urine.

Types of thalassemia

(a) Alpha Thalassemia:

Alpha thalassemia involves genes HBA1 and HBA2, inherited in a Mendelian recessive manner. With two gene loci and four alleles, it's also linked to the deletion of the 16p chromosome. This deletion results in decreased alpha-globin production, leading to an excess of beta chains in adults and gamma chains in newborns. The surplus beta chains form unstable tetramers, known as Hemoglobin H or HbH, which have abnormal oxygen dissociation curves.

(b) Beta Thalassemia:

Beta thalassemia is caused by mutations in the HBB gene on chromosome 11, inherited in an autosomal-recessive manner. The severity depends on the mutation's nature. Mutations are classified as ß thalassemia major if they prevent any formation of beta chains (the most severe form), and ß thalassemia intermedia if some beta chain formation is allowed. In both cases, there's a relative excess of alpha chains. However, these do not form tetramers; instead, they bind to red blood cell membranes, causing membrane damage, and at high concentrations, they form toxic aggregates.

(c) Delta Thalassemia:

Similar to ß thalassemia, mutations can affect the gene's ability to produce delta chains. While alpha and delta chains are present in hemoglobin, about 3% of adult hemoglobin is made up of alpha and delta chains. In contrast to conditions like SCA where incorrectly functioning globin is synthesized, thalassemia results in too few globins being produced.

Cystic Fibrosis

- This disorder is inherited in a way where both parents need to carry the gene, making it autosomal recessive.
- The illness impacts both the lungs and the digestive system, causing the body to make thick and sticky mucus that blocks the lungs and pancreas.
- Unfortunately, individuals with this disorder usually have a very short life expectancy.

Chromosmal Disorders :

Sex Chromosomal Disorders : These are as follows.

(1) Klinefelter's Syndrome

This condition is found in men. Individuals with Klinefelter's Syndrome have 47 chromosomes, and their genetic makeup is 44 + XXY. These men are unable to have children as their testes don't fully develop. They may also have thin body hair, challenges with learning, and some female characteristics like breast development (gynecomastia). The presence of an extra X-chromosome causes this syndrome, and there's one barr body. About one in every 500 baby boys is born with Klinefelter's Syndrome.

(2) Turner's Syndrome

Turner's Syndrome is found in women. The affected individuals have 45 chromosomes instead of the usual 46, and their genotype is 44 + X 0. These women are sterile, with underdeveloped ovaries, a small uterus, and undeveloped breasts. They often have a shorter stature, abnormal intelligence, and a webbed neck. The menstrual cycle is either irregular or absent. Turner's Syndrome affects about one in every 3000 children, predominantly in females.

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

Supermales (Jacob's syndrome or criminal syndrome)

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

Superfemale :

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

Autosomal Disorders

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

This condition was discovered by Langdon Down. In Down Syndrome, there's a trisomy in the 21st pair of chromosomes, meaning there's an extra chromosome number 21.

The cause is a mistake called nondisjunction during anaphase, leading to a total of 47 chromosomes instead of the usual 46. In males, the genotype becomes 45 + XY, and in females, it's 45 + XX.

Symptoms of Down Syndrome include a broad forehead, a rounded face, a mouth that stays open with a tongue sticking out, a protruding lower lip, distinctive eye features with a fold, short and stubby fingers, a broad palm with a unique crease, a short neck, limited intellectual development, and underdeveloped gonads and genitalia.

(2) Edward's Syndrome :

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

(3) Patau's Syndrome :

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

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

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

(5) Myelogenous Leukemia :

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

Gene Related Disorders

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

Phenylketonuria (PKU)

It described by Folling (1934). It is an autosomal recessive metabolic disorder. Enzyme phenylalanine hydroxylase is absent due to abnormal autosomal recessive gene on chromosome 12 as a result phenylalanine (amino acid) is not converted into tyrosine (amino acid) in liver. It is called hyperphenylalaninemia. The latter is characterised by accumulation and excretion of phenylalanine,

phenylpyruvic acid and related compounds. Symptoms are mental retardation (IQ less than 20), decreased pigmentation of hair and skin and eczema.

(1) Alkaptonuria :

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

(2) Albinism :

Albinos lack dark pigment melanin in the skin, hair and iris. It is an autosomal, recessive genetic disorder. Synthesis of melanin pigment from dihydroxyphenyalanine is absent due to lack of enzyme tyrosinase. Only homozygous individual (aa) is affected by this. It is due to recessive allele of long arm of chromosome 11 but may also be caused by another recessive allele of P-gene on long arm of chromosome 15.

(3) Cystic Fibrosis :

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

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

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

(5) Sickle Cell Anaemia :

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

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

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