

MENDELIAN INHERITANCE IN MAN-FAMILY STUDY

Mendel's Postulates

In the postulates listed (Klug, Cummings, Spencer, and Palladino, 2009), the Mendelian insight is in italics while the modern interpretation of his insight is discussed below it.

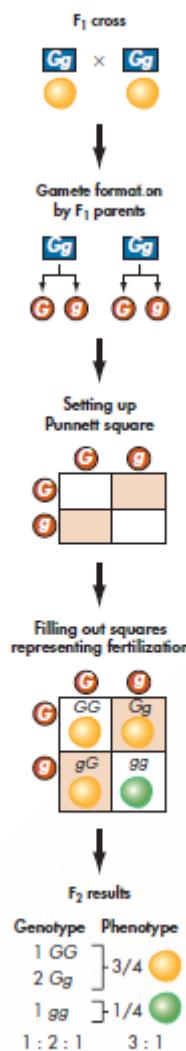


FIGURE 4.6 The Punnett square demonstrates how the F₂ ratio arises from an F₁ × F₁ cross.

1. Hereditary characteristics are controlled by particulate unit factors that exist in pairs in individual organisms.

The unit factors are genes, and they exist in pairs because in diploid organisms, chromosomes come in pairs. Each individual receives one copy of each chromosome from each parent: thus, he or she receives one of his or her pair of unit factors from each parent. Different versions of the unit factors (alleles) may exist. An individual may have two that are the same (homozygous) or two that are different (heterozygous).

2. When an individual has two different unit factors responsible for a characteristic, only one is expressed and is said to be dominant to the other, which is said to be recessive.

In heterozygous individuals, those who have different versions of a gene on each chromosome, the allele that is expressed is dominant to the allele that is not expressed. Thus, in Mendel's experiments, round seed form was dominant to wrinkled seed form, yellow seed colour was dominant to green, and so on.

Mendel did not examine a codominant character, such as AB in the ABO blood type system.

3. During the formation of gametes, the paired unit factors separate, or segregate, randomly so that each sex cell receives one or the other with equal likelihood.

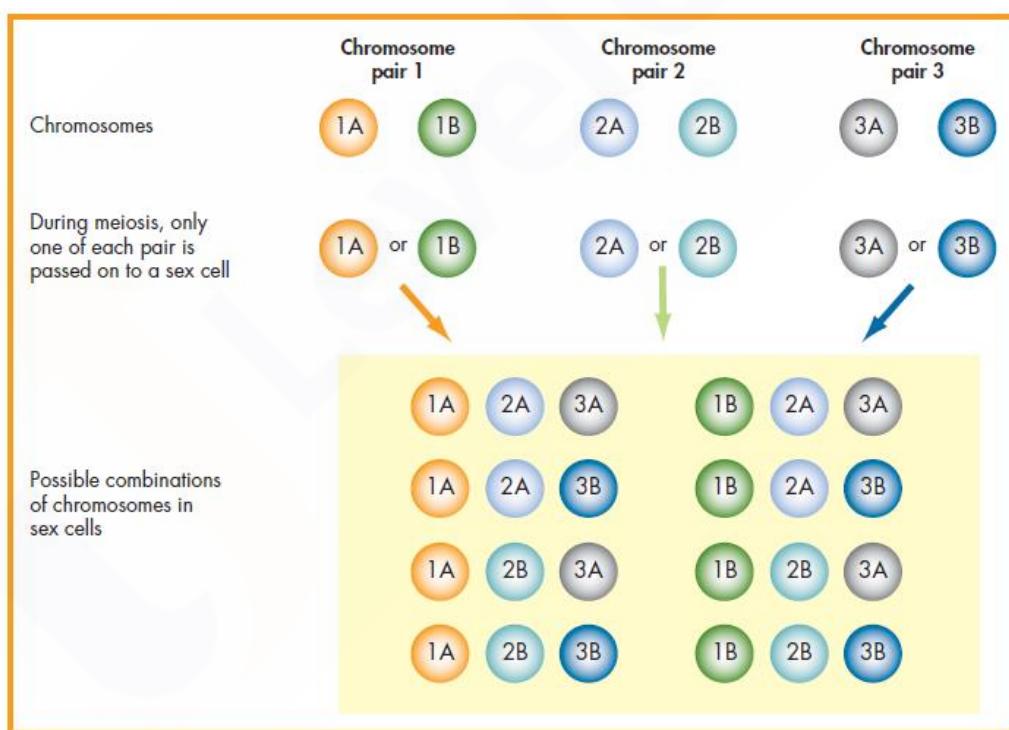
This is known as **Mendel's law of segregation**, and it reflects the fact that in diploid organisms, the chromosomes in a pair segregate randomly into sex cells during meiosis. Mendel formulated this law based on his interpretation of the phenotypes expressed in the F₁ (100 percent of which had the dominant phenotype) and F₂ generations (dominant: recessive phenotype ratio of 3:1).

4. During gamete formation, segregating pairs of unit factors assort independently of each other.

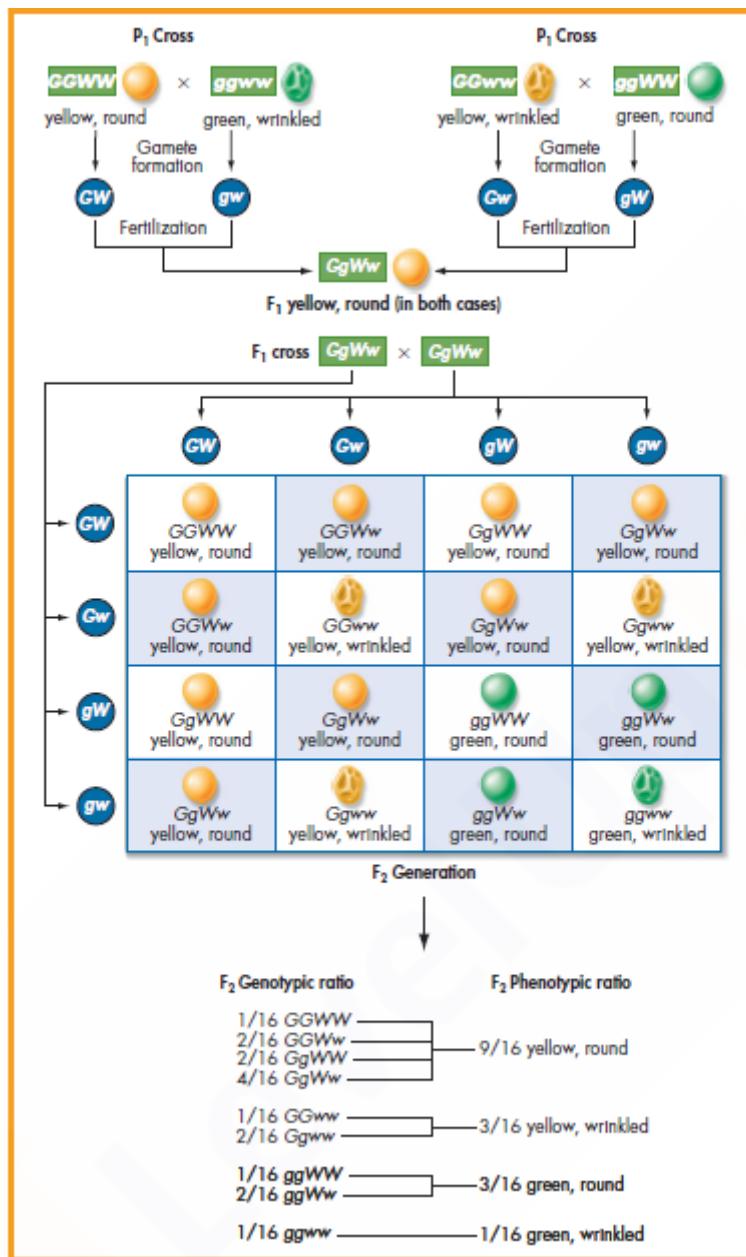
This is known as **Mendel's law of independent assortment**. Mendel did a series of more complex pea-breeding experiments known as *dihybrid crosses* that looked at the simultaneous transmission of two of the seven genetic characters of peas.

For example, Mendel looked at how both seed colour and seed shape might be transmitted across generations. What he found was that the unit factors (alleles) for different characters were transmitted independently of each other. In other words, the segregation of one pair of chromosomes into two sex cells does not influence the segregation of another pair of chromosomes into the same sex cells.

Mendel explored the transmission of seed colour (yellow dominant to green) and seed shape (round dominant to wrinkled) in a dihybrid cross experiment. He started by crossing yellow-round with green-wrinkled and yellow-wrinkled with green-round. In both crosses, he obtained peas that expressed the dominant characters of both traits (yellow and round) but were heterozygous for both as well. So the genotype of these plants (the F₁ generation) was GgWw. He then crossed the F₁ generation (GgWw * GgWw) with itself. There are sixteen possible genotypes resulting from this cross, with four possible phenotypes (yellow-round, yellow-wrinkled, green-round, and green-wrinkled). Mendel found that approximately 9/16 were yellow-round, 3/16 yellow-wrinkled, 3/16 green-round, and 1/16 green wrinkled. This 9:3:3:1 ratio is what would be expected if the two characters are transmitted independently of each other. Hence, we can say that they are independently (and randomly) assorted during meiosis.



Mendel's law of independent assortment. Each sex cell receives one chromosome (either A or B) from each of the three paired chromosomes. The assortment of one pair of chromosomes is not influenced by either of the other chromosome pairs, hence "independent assortment." There are eight possible combinations of chromosomes in the resulting sex cells.



Mendelian Inheritance in Humans

Mendelian traits, also called *discrete traits*, are controlled by alleles at only one genetic locus (or, in some cases, two or more very closely linked loci). The most comprehensive listing of Mendelian traits in humans is available on the Internet as *Online Mendelian Inheritance in Man* (OMIM) at: www.ncbi.nlm.nih.gov/omim/. Currently this listing includes more than 20,000 human characteristics that are inherited according to Mendelian principles.

Although some Mendelian characteristics have readily visible phenotypic expressions (such as polydactyly), most don't. The majority of Mendelian traits are biochemical in nature, and many genetic disorders result from harmful alleles inherited in Mendelian fashion. So if it seems like textbooks overly emphasize genetic disease in discussions of Mendelian traits, it's because so many Mendelian characteristics are the results of harmful alleles.

Blood groups, such as the ABO system, provide one of the best examples of Mendelian traits in humans. The ABO system is governed by three alleles, *A*, *B*, and *O*, found at the ABO locus on the ninth chromosome. These alleles determine a person's ABO blood type by coding for the production of molecules called antigens on the surface of red blood cells. If only antigen *A* is present, the blood type (phenotype) is *A*; if only *B* is present, the blood type is *B*; if both are present, the blood type is *AB*; and when neither is present, the blood type is *O*.

The *O* allele is recessive to both *A* and *B*; therefore, if a person has type *O* blood, he or she must have two copies of the *O* allele. However, since both *A* and *B* are dominant to *O*, an individual with blood type *A* can have one of two genotypes: *AA* or *AO*. The same is true of type *B*, which results from the genotypes *BB* and *BO*.

However, type *AB* presents a slightly different situation called codominance, where two different alleles are present, and both are expressed. Therefore, when both *A* and *B* alleles are present, both *A* and *B* antigens occur on the surface of red blood cells because neither allele is dominant to the other.

Exceptions to Mendelian Inheritance:

- a) Codominance and Incomplete dominance
- b) Polygenic or Multi factor Inheritance
- c) Genetic Linkage
- d) Multiple Allele or Genetic Polymorphism
- e) Pleiotropy

Dominant Traits Condition	Manifestations	Recessive Traits Condition	Manifestations
Achondroplasia	Dwarfism due to growth defects involving the long bones of the arms and legs; trunk and head size usually normal.	Cystic fibrosis	Among the most common genetic (Mendelian) disorders among European Americans; abnormal secretions of the exocrine glands, with pronounced involvement of the pancreas; most patients develop obstructive lung disease. Until the recent development of new treatments, only about half of all patients survived to early adulthood.
Brachydactyly	Shortened fingers and toes.	Tay-Sachs disease	Most common among Ashkenazi Jews; degeneration of the nervous system beginning at about 6 months of age; lethal by age 2 or 3 years.
Familial hypercholesterolemia	Elevated cholesterol levels and cholesterol plaque deposition; a leading cause of heart disease, with death frequently occurring by middle age.	Phenylketonuria (PKU)	Inability to metabolize the amino acid phenylalanine; results in mental impairment if left untreated during childhood; treatment involves strict dietary management and some supplementation.
Neurofibromatosis	Symptoms range from the appearance of abnormal skin pigmentation to large tumors resulting in severe deformities; can, in extreme cases, lead to paralysis, blindness, and death.	Albinism	Inability to produce normal amounts of the pigment melanin; results in very fair, untanable skin, light blond hair, and light eyes; may also be associated with vision problems. (There is more than one form of albinism.)
Marfan syndrome	The eyes and cardiovascular and skeletal systems are affected; symptoms include greater than average height, long arms and legs, eye problems, and enlargement of the aorta; death due to rupture of the aorta is common. Abraham Lincoln may have had Marfan syndrome.	Sickle-cell anemia	Abnormal form of hemoglobin (Hb^S) that results in collapsed red blood cells, blockage of capillaries, reduced blood flow to organs, and, without treatment, death.
Huntington disease	Progressive degeneration of the nervous system accompanied by dementia and seizures; age of onset variable but commonly between 30 and 40 years.	Thalassemia	A group of disorders characterized by reduced or absent alpha or beta chains in the hemoglobin molecule; results in severe anemia and, in some forms, death.
Camptodactyly	Malformation of the hands whereby the fingers, usually the little finger, is permanently contracted.	Absence of permanent dentition	Failure of the permanent dentition to erupt. The primary dentition is not affected.
Hypodontia of upper lateral incisors	Upper lateral incisors are absent or only partially formed (peg-shaped). Pegged incisors are a partial expression of the allele.		
Cleft chin	Dimple or depression in the middle of the chin; less prominent in females than in males.		
PTC tasting	The ability to taste the bitter substance phenylthiocarbamide (PTC). Tasting thresholds vary, suggesting that alleles at another locus may also exert an influence.		

DOMINANCE, CODOMINANCE AND INCOMPLETE DOMINANCE

Between two alleles if there is relationship of dominance, the dominant allele is able to completely suppress the recessive allele. Because of this expression of F1 hybrid is same as the expression of dominant parent gene.

According to this, Mendel formulated law of dominance which states that in crossing pure homozygous organism for contrasting character of a pair only one character of parents appear in first generation.

Eg:- Anonychia is transmitted as dominant trait in which some or all of nails of fingers and toes are absent or rudimentary.

Chin Fissure is a longitudinal fissure in middle of chin. This is due to an autosomal dominant allele.

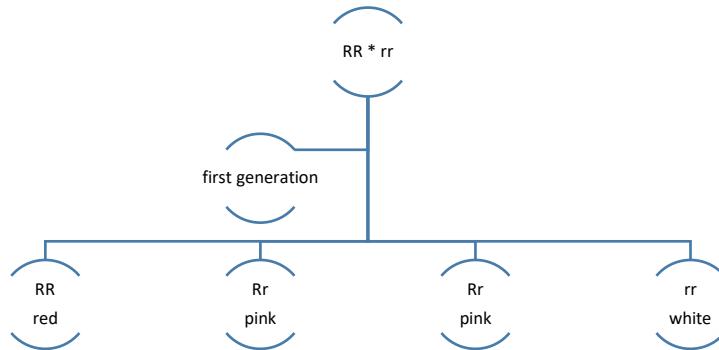
Mid digital hair presence of hair on the middle of the finger is supposed to be caused due to an autosomal dominant allele.

Dimple is also an autosomal dominant trait.

Incomplete Dominance

Though there is a dominance and recessive relation between alleles, the dominant allele is not completely dominant over the recessive allele. In the case of **incomplete dominance**, heterozygotes exhibit both alleles simultaneously, blended together. This is unlike **codominance**, where the traits are independently expressed together. Therefore, heterozygotes express entirely new **phenotypes** (physical expressions) that are not like the parent organisms. Incomplete dominance, while not the most common form of expression, is seen in many organisms, including plants, animals, and humans.

Because of this expression of first generation is intermediate between expression of both the parents. Have you ever seen pink roses? Pink roses are often the result of incomplete dominance. When red roses, which contain the dominant red allele, are mated with white roses, which is recessive, the offspring will be heterozygotes and will express a pink phenotype. Rather than express red or white, which is the parent phenotypes, the new phenotype is a blending of these two.



Sickle cell anaemia is a disease that affects the formation of red blood cells in humans. The allele for sickled cells is recessive, and the allele for normal cells is dominant. Therefore, heterozygotes are called carriers and do not have the actual disease. However, they do produce some sickled cells and therefore, their blood phenotypes show both normal and affected red blood cells. This is an example of incomplete dominance in humans, as the normal blood type and sickled cell blood type are expressed simultaneously.

If one of the child's parent has curly hair and the other has straight hair, the chances of the child having wavy hair -- the intermediate between curly and straight, are the most.

Codominance

In co dominance there is no dominance and recessiveness relationship between 2 alleles and both are equally expressed. Codominance is a form of dominance wherein the alleles of a gene pair in a heterozygote are fully expressed. This results in offspring with a phenotype that is neither dominant nor recessive.

A typical example showing codominance is the ABO blood group system. For instance, a person having A allele and B allele will have a blood type AB because both the A and B alleles are codominant with each other.

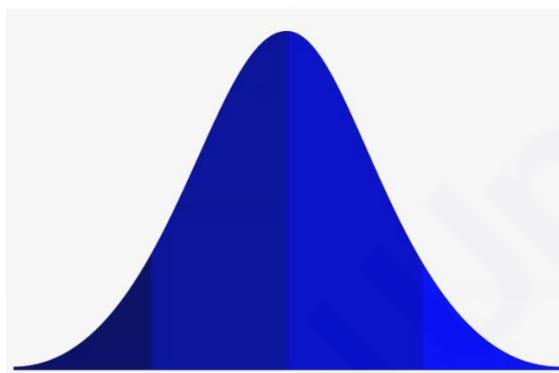
Codominance is different from incomplete dominance in a way that the former has both alleles manifesting the phenotypes whereas the latter produces an intermediate phenotype.

Genes	Blood Type
AA	A
AO	A
BB	B
BO	B
AB	AB
OO	O

POLYGENIC OR MULTI FACTOR INHERITANCE

Polygenic inheritance describes the inheritance of traits that are determined by more than one gene. These genes, called **polygenes**, produce specific traits when they are expressed together. Polygenic inheritance differs from Mendelian inheritance patterns, where traits are determined by a single gene. Polygenic traits have many possible phenotypes (physical characteristics) that are determined by interactions among several alleles. Examples of polygenic inheritance in humans include traits such as skin colour, eye colour, hair colour, body shape, height, and weight.

Polygenic Traits Distribution



In polygenic inheritance, the genes contributing to a trait have equal influence and the alleles for the gene have an additive effect. Polygenic traits do not exhibit complete dominance as do Mendelian traits but exhibit incomplete dominance. In **incomplete dominance**, one allele does not completely dominate or mask another. The phenotype is a mixture of the phenotypes inherited from the parent alleles. Environmental factors can also influence polygenic traits.

Polygenic traits tend to have a **bell-shaped distribution** in a population. Most individuals inherit various combinations of dominant and recessive alleles. These individuals fall in the middle range of the curve, which represents the average range for a particular trait. Individuals at the ends of the curve represent those who either inherit all dominant alleles (on one end) or those who inherit all recessive alleles (on the opposite end). Using height as an example, most people in a population fall in the middle of the curve and are average height. Those on one end of the curve are tall individuals and those on the opposite end are short individuals.

Eye Colour

Eye colour is an example of polygenic inheritance. This trait is thought to be influenced by up to 16 different genes. Eye colour inheritance is complicated. It is determined by the amount of the brown colour pigment melanin that a person has in the front part of the iris. Black and

dark brown eyes have more melanin than hazel or green eyes. Blue eyes have no melanin in the iris. Two of the genes that influence eye colour have been identified on **chromosome 15 (OCA2 and HERC2)**. Several other genes that determine eye colour also influence skin colour and hair colour.

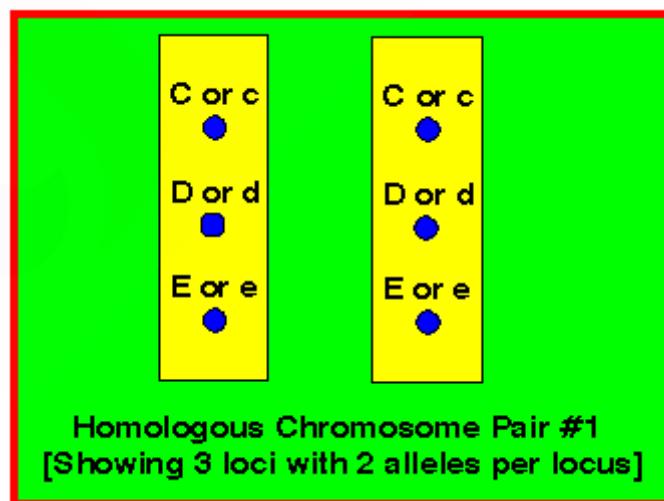
Skin Colour

Like eye colour, skin colour is an example of polygenic inheritance. This trait is determined by at least three genes and other genes are also thought to influence skin colour. Skin colour is determined by the amount of the dark colour pigment melanin in the skin. The genes that determine skin colour have two alleles each and are found on different chromosomes.

Rh blood group

Rh blood group system, system for classifying blood groups according to the presence or absence of the Rh antigen, often called the Rh factor, on the cell membranes of the red blood cells (erythrocytes). The designation Rh is derived from the use of the blood of rhesus monkeys in the basic test for determining the presence of the Rh antigen in human blood. The Rh blood group system was discovered in 1940 by **Karl Landsteiner and A.S. Weiner**. Since that time a number of distinct Rh antigens have been identified, but the first and most common one, called RhD, causes the most severe immune reaction and is the primary determinant of the Rh trait.

Unlike the A-B-O blood types where all the alleles occur on one pair of loci on chromosome pair #9, the Rh factor involves three different pairs of alleles located on three different loci on chromosome pair #1. In the following diagram, 3 pairs of Rh alleles (C & c, D & d, E & e) occur at 3 different loci on homologous chromosome pair #1. Possible genotypes will have one C or c, one D or d, and one E or e from each chromosome. For example: CDE/cde; CdE/cDe; cde/cde; CDe/CdE; etc.



Although the three pairs of genes are linked to one homologous pair of chromosomes, there are a total of eight different possible gametes for each parent: **CDE, CDe, CdE, Cde, cDE, cDe, cdE, and cde**. This number of gametes is based on all the total possible ways these genes can be inherited on each chromosome of homologous pair #1. [It is not based on the random assortment of these genes during meiosis in the parents because all three genes are closely linked together on the same chromosome; therefore, all three genes tend to appear together in the same two gametes: CDE and cde.

| Gametes | CDE |
|---------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| CDE | CDE/
CDE |
| CDe | CDe/
CDE |
| CdE | CdE/
CDE |
| Cde | Cde/
CDE |
| cDE | cDE/
CDE |
| cDe | cDe/
CDE |
| cdE | cdE/
CDE |
| cde | cde/
CDE |

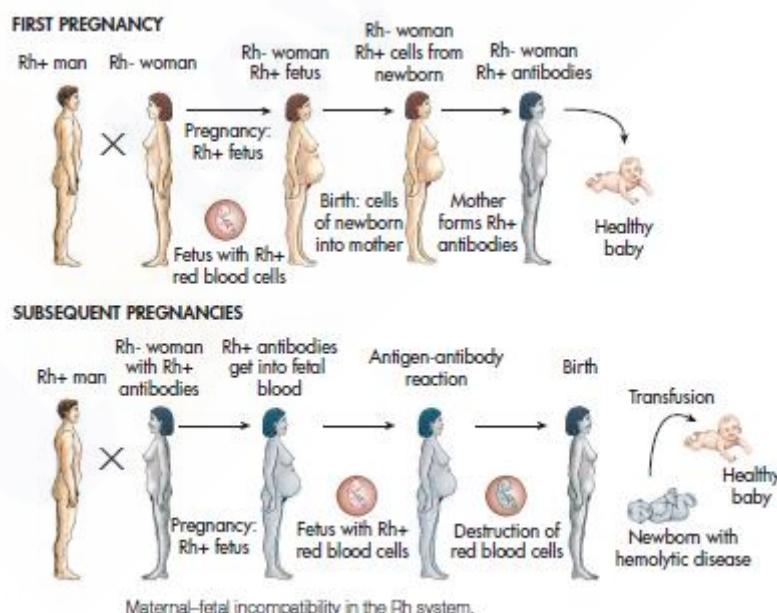
Every genotypic combination with DD or Dd is classified as Rh Positive. This is about 85% of the U.S. population because the D gene is more common than the C and E genes. Every genotypic combination with dd is classified as Rh Negative. Although the Rh-negative trait is rare in most parts of the world, it occurs in about 15 percent of Caucasians in Europe, Canada, and the United States. The trait's highest incidence is among the Basques of the Pyrenees (25–35 percent) and the Imazighen (Berbers) of Africa and the Bedouins of the Sinai Peninsula (18–30 percent).

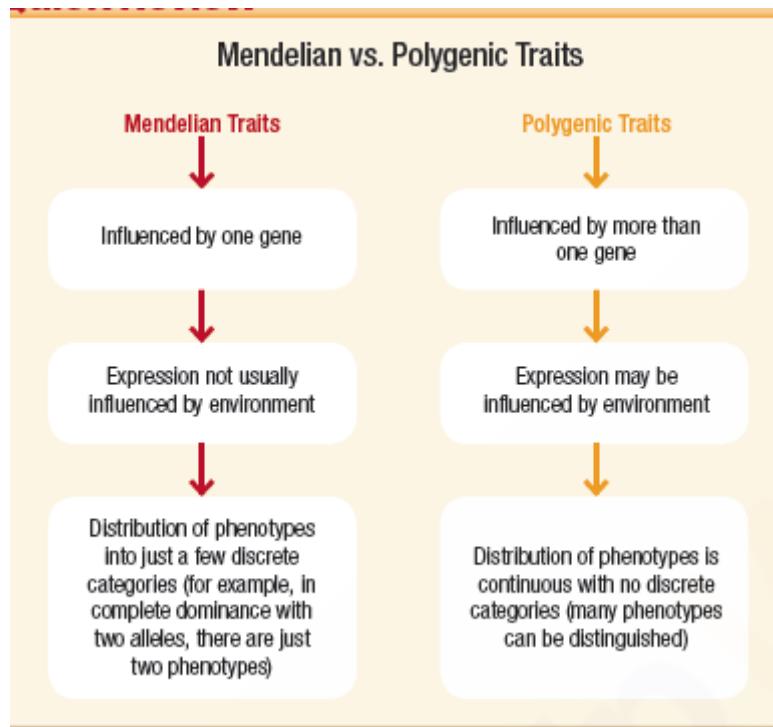
The Rh antigen poses a danger for the Rh-negative person, who lacks the antigen, if Rh-positive blood is given in transfusion. Adverse effects may not occur the first time Rh-incompatible blood is given, but the immune system responds to the foreign Rh antigen by producing anti-Rh antibodies. If Rh-positive blood is given again after the antibodies form, they will attack the foreign red blood cells, causing them to clump together, or agglutinate.

The resulting haemolysis, or destruction of the red blood cells, causes serious illness and sometimes death.

A similar hazard exists during pregnancy for the Rh-positive offspring of Rh-incompatible parents, when the mother is Rh-negative and the father is Rh-positive. The first child of such parents is usually in no danger unless the mother has acquired anti-Rh antibodies by virtue of incompatible blood transfusion. During labour, however, a small amount of the foetus's blood may enter the mother's bloodstream. The mother will then produce anti-Rh antibodies, which will attack any Rh-incompatible foetus in subsequent pregnancies. This process produces **erythroblastosis foetalis, or haemolytic disease of the newborn**, which can be fatal to the foetus or to the infant shortly after birth. Treatment of erythroblastosis foetalis usually entails one or more exchange transfusions. The disease **can be avoided by vaccinating the mother with Rh immunoglobulin** after delivery of her firstborn if there is Rh-incompatibility. The Rh vaccine destroys any foetal blood cells before the mother's immune system can develop antibodies.

Maternal-fetal incompatibility in both the ABO and Rh systems influences the distribution of their alleles in populations. For example, in the Rh system, only heterozygous offspring of an Rh-negative mother and an Rh-positive father are at risk of developing anaemia. In a traditional culture, these infants would be at great risk of dying without reproducing. Simple genetic models indicate that in a population that has a D allele frequency of 50 percent or more, the d allele eventually will be lost. The opposite case is also true if the d allele frequency reaches 50 percent (assuming that no selection or other evolutionary factors are at play).





PLEIOTROPY

Pleiotropy (from Greek *pleion*, "more", and *tropos*, "way") occurs when one gene influences two or more seemingly unrelated phenotypic traits. Such a gene that exhibits multiple phenotypic expression is called a pleiotropic gene. Therefore, mutation in a pleiotropic gene may have an effect on several traits simultaneously due to the gene coding for a product used by a myriad of cells or different targets that have the same signalling function.

An example of pleiotropy is phenylketonuria, an inherited disorder that affects the level of phenylalanine in the human body. Phenylalanine is an amino acid that can be obtained from food. Phenylketonuria causes this amino acid to increase in amount in the body, which can be very dangerous. The disease is caused by a defect in a single gene on chromosome 12 that codes for enzyme phenylalanine hydroxylase, that affects multiple systems, such as the nervous and integumentary system.

Genes affected in human genetic disorders are often pleiotropic. For example, people with a hereditary disorder called Marfan syndrome may have a set of seemingly unrelated symptoms, including the following:

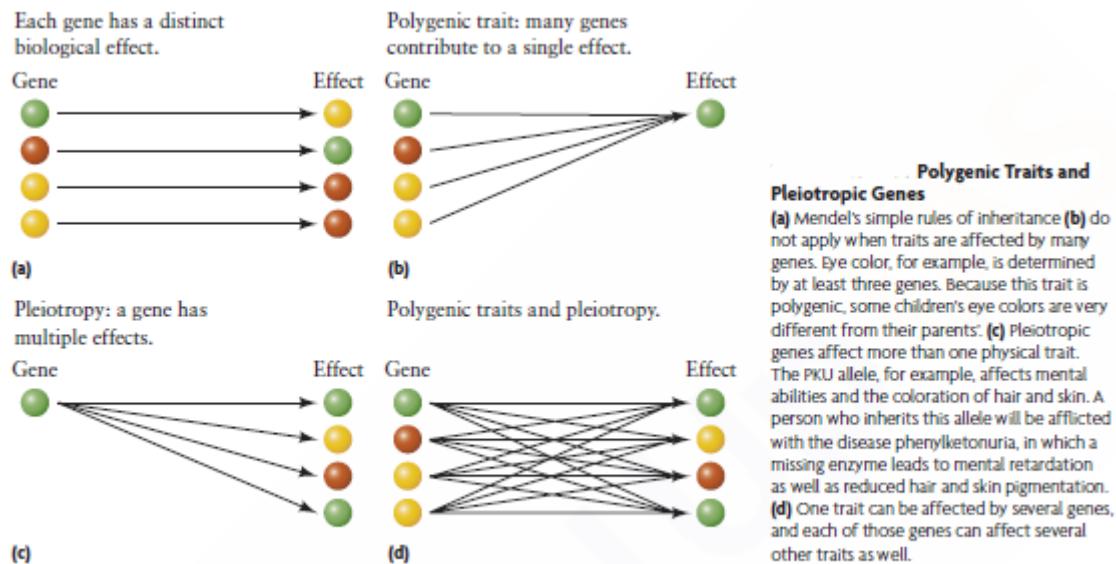
Unusually tall height

Thin fingers and toes

Dislocation of the lens of the eye

Heart problems (in which the aorta, the large blood vessel carrying blood away from the heart, bulges, or ruptures).

These symptoms don't seem directly related, but as it turns out, they can all be traced back to the mutation of a single gene. This gene encodes a protein that assembles into chains, making elastic fibrils that give strength and flexibility to the body's connective tissues, end superscript. Mutations that cause Marfan syndrome reduce the amount of functional protein made by the body, resulting in fewer fibrils.



GENETIC LINKAGE

Genetic linkage is the tendency of DNA sequences that are close together on a chromosome to be inherited together during the meiosis phase of sexual reproduction.

Two genetic markers that are physically near to each other are unlikely to be separated onto different chromatids during chromosomal crossover and are therefore said to be more linked than markers that are far apart. In other words, the nearer two genes are on a chromosome, the lower the chance of recombination between them, and the more likely they are to be inherited together. Markers on different chromosomes are perfectly unlinked.

Genetic linkage is the most prominent exception to Gregor Mendel's Law of Independent Assortment. The first experiment to demonstrate linkage was carried out in 1905. At the time, the reason why certain traits tend to be inherited together was unknown. Later work revealed that genes are physical structures related by physical distance.

Linkage of the HLA Loci:

The region on the chromosome 6 that carries the major histocompatibility complex is now known as HLA. The different gene loci are designated as A, B, C, D and the specificities or alleles at each locus are identified by numbers 1, 2, 3 etc. The actual order of the loci is thought to be D, B, C, A and are situated close to each other and, therefore, the alleles at each of these four loci will nearly always be inherited together.

Types of Linkage of Genes:

Linkage is generally classified on the basis of three criteria, viz:

- (1) Presence or absence of crossing over,**
- (2) Genes involved, and**
- (3) The chromosome involved.**

These are briefly described below:

1. Based on Crossing Over:**(i) Complete Linkage:**

Linkage in which crossing over does not occur is known as complete linkage or absolute linkage. In other words, when only parental types are obtained from the test cross progeny, it refers to complete linkage. Good example of complete linkage is Drosophila male and female silk moth.

(ii) Incomplete Linkage:

If some frequency of crossing over also occurs between linked genes, it is known as incomplete linkage. To put in other way, when recombination's are also observed in the test cross progeny, besides parental combinations, it refers to incomplete linkage. Incomplete linkage has been observed in maize, pea, Drosophila female and several other organisms.

2. Based on Genes Involved:**(i) Coupling Linkage:**

It refers to linkage either between dominant genes or between recessive genes. Such linkage has been reported in pea, maize and several other crops.

(ii) Repulsion Linkage:

It refers to linkage of some dominant genes with some recessive genes. This type of linkage has also been observed in pea, maize and several other crops.

3. Based on Chromosome Involved:**(i) Autosomal Linkage:**

It refers to linkage of such genes which are located in other than sex chromosomes (autosomes).

(ii) X-Chromosomal Linkage:

It refers to the linkage of genes which are located in sex chromosomes.

GENETIC POLYMORPHISM/MULTIPLE ALLELES

Polymorphism is defined as occurrence of more than one morph or form (or gene loci or supergene) in a population in such a way that the rarest of them cannot be maintained by recurrent mutation. In order to be classified as genetic polymorphic trait a character must be present in a frequency greater than 1 percent. If it is present in a frequency below this, it is supposed that it is arising due to mutation and selection is not operating on it. If it is only above 1 percent in population we can be sure that some selection is involved in its maintenance in population.

Though mutation is source of all new genes in the population, a population is not dependent entirely on mutations for genetic polymorphism to develop. Mutation rate is slow and hence cannot maintain genetic polymorphism in population. The supply of genetic polymorphism upon which selection acts is provided by genetic combinations built up over many generations by the flow of genetic information from neighbouring population(migration) and production of mutation and selection.

Genetic Polymorphism at Cell Surface

Various types of cells are characterised by presence on their surfaces certain antigenic molecules. Human blood has antigen A, B, AB, O on the surface of their RBC. These antigens are glycoproteins in which certain sugars are linked with proteins.

Other tissues also possess significant of genetic polymorphism. In graft or transplantation, the graft is rejected by host organ. The reason is that tissue from different individuals possess different HLA. The system has extraordinary levels of polymorphism so that no 2 individuals, except identical twins, possess the same HLA system.

Genetic Polymorphism at Chromosomal Level (Functional)

Chromosomes undergo various rearrangements. These include insertional elements (IS elements), deletions, transposons, amplified and converted regions of transposons. Besides chromosomal aberrations such as inversions and translocations are often present in the chromosomes.

IS elements are stretch of nucleotides averaging more than 1000 base pairs that are removed from a chromosome and moved to another. Such a feature affect functions of genes present in both the chromosomes depending upon where the segments are removed from and where

attached to- making functional gene non-functional or vice versa. Deletion of functional part of chromosome may be detrimental but deletion of non functional part may be bring two functional part close together, thus modifying each other's functions.

Polymorphism at level of GENE PRODUCTS (Protein)

Two tools enable us to identify polymorphism at the level of gene product(proteins). These are electrophoresis and amino acid sequencing. We know that many proteins have large variation which can be seen from simple electrophoresis.

Several human proteins such as Haemoglobin have been sequenced. Hb sequencing has revealed hundreds of hidden variants. Some involve changes in amino acids, or duplication or deficiencies of sections of the protein. Occasionally different protein chains are fused together or there may be changes in time when the protein produced. Effect of such changes can be beneficial to neutral to harmful. The Hb-Hikari from a few families in Japan is neutral, Hb-Chesapeake is beneficial and Hb-M Boston, Hb- MHydepark is harmful.

Another protein which show polymorphism is isozymes or isoenzymes. These are similar but structurally different. One such enzyme is lactic dehydrogenase(LDH). The enzyme shows up 5 forms in a single individual.

BALANCED POLYMORPHISM/HETEROZYGOTE ADVANTAGE

Genetic polymorphisms may be '**transient**' or '**balanced**'. Genetic polymorphisms are called **balanced, if selection favours the heterozygotes**. When selection favours 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.

Balanced polymorphism is a situation in which two different versions of a gene are maintained in a population of organisms because individuals carrying both versions(heterozygotes) are better able to survive than those who have two copies of version alone. The evolutionary process that maintains the two versions over time is called balancing selection.

Genes are carried on chromosomes. Different versions of a gene are called alleles. The standard allele found in a population is referred to as the wild-type allele. Most plants and animals have at least two copies of each chromosome, one inherited from each parent. The copies of the genes found on these homologous chromosomes may be identical or different; that is, the organism may carry two copies of one allele, or one each of two different alleles. In the first case, the organism is called homozygous for that gene, and, in the second, it is called heterozygous.

Alleles differ from each other in their sequence of nucleotides, which may change the structure and function of the protein the gene codes for. Because of this, different alleles may have different effects on an organism's appearance or ability to survive. These effects can be helpful, harmful, or neutral.

An example of balanced polymorphism can be illustrated with the set of enzymes in the liver that act like an assembly line (or, more accurately, a disassembly line) to detoxify poisons and other chemicals. Different alleles for these enzymes can affect how well an organism can protect itself from exposure to harmful chemicals. An especially active form of a detoxifying enzyme, which is encoded by a specific allele, can cause accumulation of potentially harmful intermediates. If the other allele encodes an enzyme with low activity, the potential for this enzyme to cause harm is lessened, and the benefits of its activity will be felt by the organism. If an individual has two copies of the very active allele or two copies of the low-activity allele, it may not survive well. In the first case, too much enzyme activity will result in high levels of the harmful intermediate, and in the second case, too little enzyme activity will be present for detoxification. Therefore, the best situation for the organism is to have one copy of each allele. Because of this, both copies are maintained in the population.

The effects of alleles and whether they are maintained in a population can be influenced by the environment. A classic case of balanced polymorphism in humans that is influenced by the environment is the sickle-cell allele of the β -globin gene. This gene forms part of haemoglobin, which carries oxygen in red blood cells.

Individuals who have two copies of the β -globin sickle-cell allele develop sickle-cell disease and generally do not survive into adulthood without intensive medical care. Individuals with one copy of the β -globin sickle-cell allele and one β -globin wild-type allele have red blood cells that are functional and resistant to the organism that causes malaria. Because individuals with this combination of alleles tend to survive malaria better than those who carry only the wild-type allele, the combination is advantageous to those who live in areas where malaria is present. This is called "**heterozygote advantage**." As a result, the beta-globin sickle-cell allele will be maintained along with the wild-type allele in populations exposed to malaria—an example of balancing selection.

Resistance to hepatitis C virus infection

There is evidence that genetic heterozygosity in humans provides increased resistance to certain viral infections. A significantly lower proportion of **HLA-DRB1 heterozygosity** exists among HCV-infected cases than uninfected cases.

Mendelian Population

A population is a group of interbreeding individuals that share a common gene pool. As a rule, a population is the group within which individuals are most likely to find mates. In theory, this is a straightforward concept. In every generation, the genes (alleles) in a gene pool are mixed

by recombination and then reunited with their counterparts (located on paired chromosomes) through mating. What emerges in the next generation is a direct product of the genes going into the pool, which in turn is a product of who is mating with whom.

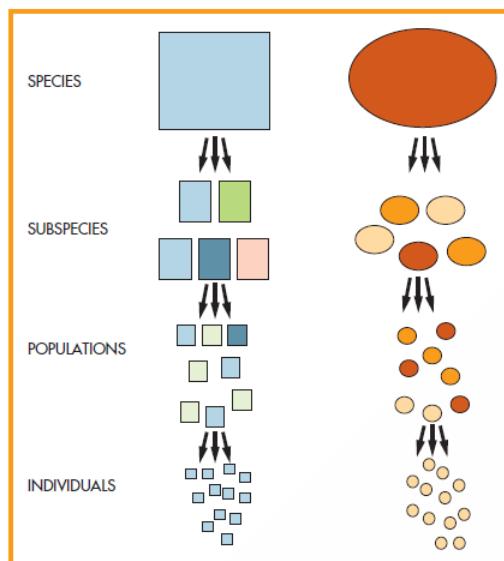
Factors that determine mate choice are geographical, ecological, and social. If people are isolated on a remote island in the middle of the Pacific, there isn't much chance they'll find a mate outside the immediate vicinity. Such breeding isolates are fairly easily defined and are a favourite subject of microevolutionary studies.

An isolate is a group of people which is totally separated from other groups and is reproductively unstratified so that all individuals share equally in the same gene pool. This isolation may be due to different factors geographical, cultural, biological etc. The net result being that the members of the group mate within the group. Due to this prolonged inbreeding, difference in gene frequencies between different population arise, and continue to grow as long as isolation continues.

Geography plays a dominant role in producing these isolates by strictly determining the range of available mates. But even within these limits, cultural rules can play a deciding role by prescribing who is most appropriate among those who are potentially available.

Most humans today aren't so clearly defined as members of particular populations as they would be if they belonged to breeding isolates. Inhabitants of large cities may appear to be members of a single population, but within the city, socioeconomic, ethnic, and religious boundaries crosscut in complex ways to form smaller population segments. In addition to being members of these smaller local populations, we're also members of overlapping gradations of larger populations: the immediate geographical region (a metropolitan area or perhaps a state), a section of the country, a nation, and ultimately the entire species.

Once specific human populations have been identified, the next step is to ascertain what evolutionary forces, if any, are operating on them. To determine whether evolution is taking place at a given locus, population geneticists measure allele frequencies for specific traits and compare these observed frequencies with a set predicted by a mathematical model called the Hardy-Weinberg equilibrium equation.



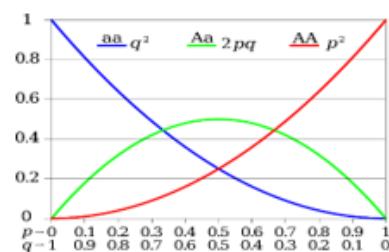
Species, subspecies, populations, and individuals. Species are reproductively isolated from one another, but all members of a species can interbreed.

HARDY-WEINBERG LAW

In 1908, **Godfrey Hardy** (1877–1947), an English mathematician, and **Wilhelm Weinberg** (1862–1937), a German obstetrician, independently recognized that some alleles are in a state of equilibrium. If no mutation or natural selection or gene flow occurs, if the population is large, if mating is random, and if all members of the population produce the same number of offspring, then genotype frequencies at a single gene locus will remain the same after one generation. Moreover, the equilibrium frequencies will be a function of the allele frequencies at the locus. This is called the **Hardy-Weinberg law of equilibrium**.

By determining the genotype frequencies for a population at different points in time, however, the Hardy-Weinberg equation establishes whether evolution is operating on a particular gene. If the genotype frequencies change from one generation to the next, the population is not in equilibrium—it is evolving. If the frequencies remain the same, the population is in equilibrium—the population is not evolving, at least with respect to the locus being studied.

		Punnett Square for Hardy-Weinberg Equilibrium	
		FEMALES	
		A (p)	a (q)
MALES	A (p)	AA (p^2)	Aa (pq)
	a (q)	Aa (pq)	aa (q^2)



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, all parents must be equally fertile, and **must be free from the forces of evolution; that is, mutation, natural selection, genetic drift, gene flow and inbreeding.**

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/ inbreeding
- Mutation
- Selection
- Genetic Drift (Sewal Wright effect)
- Small population size
- Gene flow (migration)

The gene pool

The total set of gene copies for all genes in a population is referred to as its gene pool. The gene pool gets its name from the idea that we are essentially taking all the gene copies—for all genes—in the individuals of a population and dumping them into one large, common pool.

By looking at all the copies of all the genes in a population, we can see globally how much genetic variation there is in the population. The more variation a population has, the better its ability to adapt to changes in its environment through natural selection. If there is more variation, the odds are better that there will be some alleles already present that allow organisms to survive and reproduce effectively under the new conditions.

Allele frequency

Allele frequency refers to how frequently a particular allele appears in a population. For instance, if all the alleles in a population of pea plants were purple alleles, W, the allele frequency of W would be 100%, or 1.0. However, if half the alleles were W and half were w, each allele would have an allele frequency of 50%, or 0.5.

In general we can define allele frequency as:

$$\text{Frequency of allele } A = \frac{\text{Number of copies of allele } A \text{ in population}}{\text{Total number of } A/a \text{ gene copies in population}}$$

Sometimes there are more than two alleles in a population (e.g., there might be A, a, and Ai alleles of a gene). In that case, you would want to add up all of the different alleles to get your denominator.

It's also possible to calculate genotype frequencies—the fraction of individuals with a given genotype—and phenotype frequencies—the fraction of individuals with a given phenotype. Keep in mind, though, that these are different concepts from allele frequency. We'll see an example of this difference next.

MUTATION: THE ONLY SOURCE OF NEW ALLELES

During cell reproduction, DNA almost always replicates itself exactly. Sometimes, however, the replication process produces an error or a collection of errors in the DNA code. If the problem is not at once detected and corrected by a set of enzymes that monitor DNA, a mutation results. The mutation can be any heritable change in the structure or amount of genetic material.

Because so much of any person's DNA is noncoding, many mutations do not affect the individual's health, well-being, or survival. A new sequence of *coding* DNA that results from mutation may have profound consequences, positive or negative. For example, the mutation might code the DNA for a protein with an altered or different function than that performed by the protein coded for in the original parent strand of DNA, or the mutation might create a sequence that results in either no protein or an abnormal protein. Mutations occur at random, and they can occur in any cell, but the ones with consequences for future generations take place in gametes. Gametes may transfer mutations to offspring, depending on what happens during meiosis in the parents. Regardless of their causes or outcomes, *mutations are the only source of new genetic variation in a population.*

Mutations involving incorrect base pairing are called **point mutations**. A **synonymous point mutation** creates an altered triplet in the DNA, but the alteration carries with it the original amino acid. Because the amino acid is the same, the protein formed is the same. A **nonsynonymous point mutation** results in a matchup that brings along a different amino acid. Such a mutation can have dramatic results for the individual carrying it. For example, a mutation on human chromosome 11 converts a GAG codon into a GTG codon. The GAG codon is encoded to produce the amino acid valine, whereas the GTG codon is encoded to produce glutamic acid. This substitution leads to the abnormal haemoglobin that results in sickle-cell anaemia.

As a result of the shifting base pairs caused by base insertion, the reading frame of a gene is altered or stopped entirely. This **frameshift mutation** produces a protein having no function.

Such a mutation usually involves a small part of the DNA sequence, often just a base pair or a relatively limited number of base pairs.

Other kinds of mutations can affect far more of the genome. **Transposable elements** are genes that can copy themselves to entirely different places along the DNA sequence. If such a gene inserts itself into another gene, it can fundamentally alter the other gene, doing real damage. If, as is strongly likely, the gene transposes itself to a noncoding area of the DNA sequence, little or no significant alteration will occur.

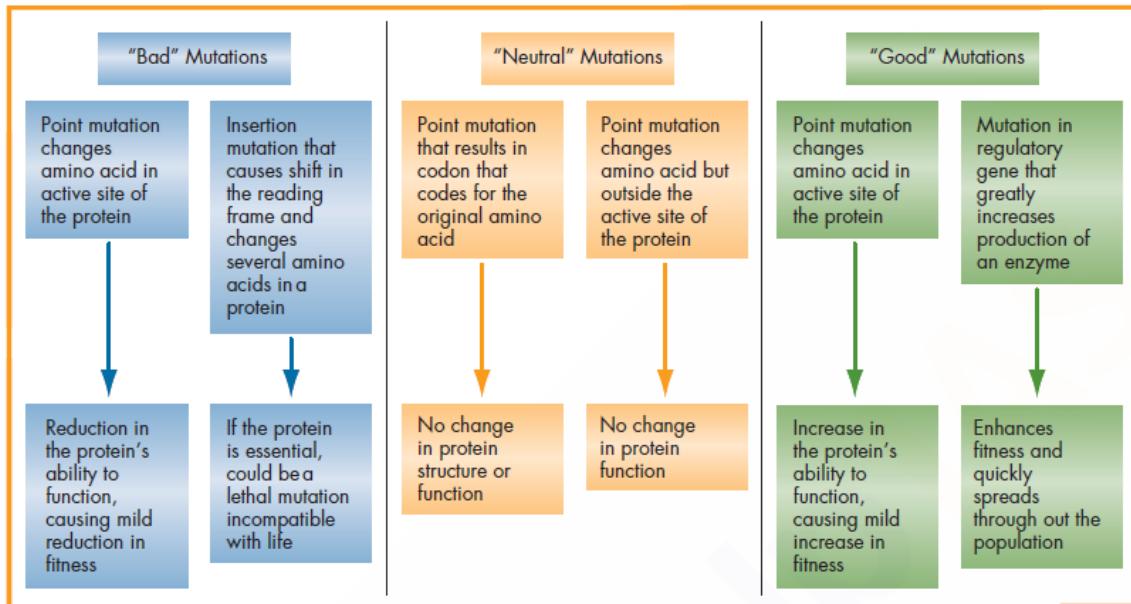
Large parts of DNA sequences or entire chromosomes can be affected by mutations. An entire piece of chromosome can be moved to another chromosome, can be placed differently on the same chromosome, or can be positioned in a chromosome backward. The impacts of these mutations are highly variable and depend on the mutations' loci. In the most extreme mutations, entire chromosomes can be duplicated (a trisomy) or lost altogether (a monosomy). Examples of trisomies are Down syndrome, with its extra twenty-first chromosome and **Klinefelter's syndrome**, a common sex chromosome variant that appears in about 1 of 500–1,000 births.

All mutations fall into either of two types: **spontaneous mutations** have no known cause; **induced mutations** are caused by specific environmental agents, usually associated with human activity. These agents, or **mutagens**, are increasingly becoming known. For example, ionizing radiation (X-rays) and various toxic chemicals have been linked to mutations in animals and humans. Most mutations are spontaneous, however, and are simply DNA copying errors. The human mutation rate is higher in male sex cells (sperm) than in female sex cells (eggs), but is generally on the order of one per million per nucleotide per generation.

The human genome includes about three billion base pairs, about 1.5% of which are protein coding, so the average mutation rate in humans is .45 mutations in protein-coding genes per generation, or about one new, potentially significant mutation in every other person born. For individuals, most mutations are relatively harmless, while a few may have profound consequences. For populations, mutations are inconsequential unless they offer selective adaptive advantages. A mutation can have such an advantage whether or not a biological characteristic related to it enhances survival and reproduction.

Can mutations be good? Absolutely. Mutations are the ultimate source of variation, and variation is the raw material on which natural selection acts. Without mutation, there could be no natural selection. Although chromosomal processes such as crossing over create new allele combinations and thereby increase phenotypic variability, mutation is the only source for new alleles that can be combined in novel ways. "Good" mutations—those that increase an organism's chance of surviving and reproducing—do not have to be common. The process

of natural selection makes their spread throughout a population possible. Once this happens, they are no longer considered to be mutations but are the normal or wild type.



"Bad," "neutral," and "good" mutations.

NATURAL SELECTION

In natural selection, those variations in the genotype that increase an organism's chances of survival and procreation are preserved and multiplied from generation to generation at the expense of less advantageous ones. Evolution often occurs as a consequence of this process. Natural selection may arise from differences in survival, in fertility, in rate of development, in mating success, or in any other aspect of the life cycle. All such differences result in natural selection to the extent that they affect the number of progeny an organism leaves.

Gene frequencies tend to remain constant from generation to generation when disturbing factors are not present. Factors that disturb the natural equilibrium of gene frequencies include mutation, migration (or gene flow), random genetic drift, and natural selection. A mutation is a spontaneous change in the gene frequency that takes place in a population and occurs at a low rate. Migration is a local change in gene frequency when an individual moves from one population to another and then interbreeds. Random genetic drift is a change that takes place from one generation to another by a process of pure chance. Mutation, migration, and genetic drift alter gene frequencies without regard to whether such changes increase or decrease the likelihood of an organism surviving and reproducing in its environment. They are all random processes.

Natural selection moderates the disorganizing effects of these processes because it multiplies the incidence of beneficial mutations over the generations and eliminates harmful ones, since their carriers leave few or no descendants. Natural selection enhances the preservation of a group of organisms that are best adjusted to the physical and biological conditions of their environment and may also result in their improvement in some cases. Some characteristics, such as the male peacock's tail, actually decrease the individual organism's chance of survival. To explain such anomalies, Darwin posed a theory of "sexual selection." In contrast to features that result from natural selection, a structure produced by sexual selection results in an advantage in the competition for mates.

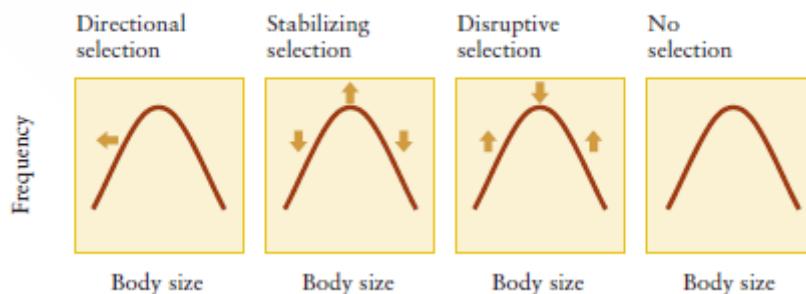
Stabilizing, Directional, and Diversifying Selection

Under **stabilizing selection**, extreme varieties from both ends of the frequency distribution are eliminated. The frequency distribution looks exactly as it did in the generation before. Probably this is the most common form of natural selection, and we often mistake it for no selection. A real-life example is that of birth weight of human babies

Under **directional selection**, individuals at one end of the distribution do especially well, and so the frequency distribution of the trait in the subsequent generation is shifted from where it was in the parental generation. This is what we usually think of as natural selection. Human evolution, for example, has clearly favoured larger brains. Industrial melanism is such an example.

The fossil lineage of the horse provides a remarkable demonstration of directional succession. Overall, though, the horse has evolved from a small-bodied ancestor built for moving through woodlands and thickets to its long-legged descendant built for speed on the open grassland. This evolution has involved well-documented changes in teeth, leg length, and toe structure.

Under **diversifying (disruptive) selection**, both extremes are favoured at the expense of intermediate varieties. This is uncommon, but of theoretical interest because it suggests a mechanism for species formation without geographic isolation. Given enough time, this pattern can result in a speciation event, as those in the middle fail to survive and reproduce and two new species arise at the extremes.



Natural Selection in Animals: The Case of the Peppered Moth and Industrial Melanism

Perhaps the best evidence ever documented of natural selection operating on a heritable trait concerns the peppered moth, *Biston betularia*, a species common throughout Great Britain. This moth is nocturnal, eating and breeding by night and attaching itself to trees, especially in the upper branches, during the day. Prior to the mid-1800s, all members of the species had a peppered appearance, their white colouring sprinkled with black. Trees throughout Great Britain were covered with lichen, and the moths' colouration provided excellent camouflage against the trees' variable-coloured surface and thus protected the moths from their major predator, birds. In 1848, a naturalist exploring the countryside near Manchester, England, spotted a completely black variety of the moth. A new species name, *Biston carbonaria*, distinguished this **melanic** (dark) form from the **nonmelanic** (light) form. The frequency of the melanic form remained relatively low for a couple of decades but climbed rapidly in the late nineteenth century. By the 1950s, 90% or more of peppered moths were melanic.

This rapid increase in melanic frequency was a case of evolution profoundly changing phenotype. Directional selection had favoured the melanic form over the nonmelanic form, and the melanic form exhibited a greater fitness. But what was this form's adaptive advantage? The selecting factor was the Industrial Revolution. With the rise of industry throughout England and elsewhere in the middle to late nineteenth century, mills, fuelled entirely by coal, spewed coal particles from smokestacks 50 tons per square mile per month, in some places—blackening the sky and covering the landscape. The trees survived this pollution onslaught, but the lichen covering the trees did not. The trees' surfaces went from light-coloured to black, greatly altering the peppered moth's habitat. This pollution crisis provided a huge selective advantage for the melanic moths, which were now perfectly camouflaged against blackened trees. Nonmelanic moths became easy prey.

Natural Selection in Humans: Abnormal Haemoglobins and Resistance to Malaria

The above case of industrial melanism is an example of **positive selection**, whereby an organism's biology is shaped by selection for beneficial traits. Natural selection for beneficial traits in humans is best understood by studying genes that control specific traits. Of the 90 or so different loci that are targets of natural selection, among the most compelling examples is the sickle-cell gene—the *Haemoglobin S* (or simply *S*) gene—which causes **sickle-cell anaemia**.

Millions of people suffer from such **haemolytic anaemias**, which involve the destruction of red blood cells. A low number of red blood cells can produce health problems because of the resultant lack of haemoglobin, the chemical in red blood cells that carries oxygen to all the body tissues. The *S* gene yields a specific kind of **abnormal haemoglobin**.

Sickle-cell anaemia has been known since the early 1900s, and the genetics behind it were documented in the 1950s. The *S* gene is a simple base-pair mutation. Genetically, people with normal haemoglobin have the alleles *AA*, the homozygous condition. People who carry the sickle-cell gene on one allele only are *AS*, and people who have the homozygous form of the disease are *SS*. *AS* individuals are for all practical purposes normal in their survival and reproduction rates. There is no cure for sickle-cell anaemia, and in the absence of modern medical treatment, some 80% of people who are *SS* die before the reproductive years, usually considerably earlier. The *SS* genotype results in many red blood cells' having a sickle shape caused by the abnormal haemoglobin, in sharp contrast to the round appearance of red blood cells in people with normal haemoglobin. The cells' abnormal shape prevents them from passing through the **capillaries**, the narrow blood vessels that form networks throughout tissues. When the clogging of capillaries cuts off the oxygen supply in vital tissues, severe anaemia and death can result.

THE GEOGRAPHY OF SICKLE-CELL ANAEMIA AND A POSSIBLE ASSOCIATION WITH MALARIA

Beginning in the mid-twentieth century, the medical community observed that many people living in equatorial Africa—as many as 20% to 30%—had the *S* gene. This finding represented a huge puzzle: since the gene was so bad for survival, why was its frequency so high? In other words, one would expect strong selection against this non beneficial gene. The solution to the puzzle began to emerge with the discovery that high heterozygous (*AS*) frequencies appear in regions of Africa where malaria is endemic. In other words, where malaria—a potentially lethal parasitic infection in which the parasite is introduced to a human host by a mosquito—is always present, there is a high frequency of carriers of the gene. Moreover, *AS* people (sickle-gene carriers) die of malaria in far fewer numbers than do *AA* people.

Anthony Allison discovered that in low-lying, wet areas of Kenya (where the number of mosquitoes was great and the rate of malaria was high), the frequency of the sickle-cell gene was considerably higher than in highland or arid areas. He developed the simple but elegant hypothesis that the infection and the genetic mutation were related. Individuals homozygous for normal haemoglobin (*AA*) were highly susceptible to dying from malaria; individuals homozygous for sickle-cell anaemia (*SS*) did not survive to reproduce; however, individuals heterozygous for normal haemoglobin and the sickle-cell mutation (*AS*) either did not contract malaria or suffered a less severe malarial infection. That these frequencies were being maintained indicated that the *AS* heterozygote was a **balanced polymorphism**. It was also a fitness trade-off: carriers could pass on the sickle-cell gene, but they received immunity from malaria.

THE HISTORY OF SICKLE-CELL ANAEMIA AND MALARIA

In the late 1950s, the American physical anthropologist **Frank B. Livingstone (1928–2005)** sought to

strengthen the case for natural selection by historically linking sickle-cell anaemia and malaria. Livingstone asked two important questions: *Where and when did the sickle-cell gene first appear in equatorial Africa?* and *What conditions led to the gene's being naturally selected?* He hypothesized that the Bantu, a group of peoples who speak Bantu languages, carried the mutation with them when they migrated south. Prior to the Bantu's arrival, the region was an unbroken forest. Bantu populations introduced agriculture there, clearing large swaths of the forest for cultivation. The peoples' iron-working technology made possible the creation of tools for cutting down large trees, ploughing fields, and planting crops—mostly yams and cassava.

Even under the best conditions, tropical forests are fragile ecosystems. Once their trees have been cleared and their fields have been planted, their relatively poor soil, which normally soaks up rainwater, becomes thin or disappears. As a result, pools of water collect and become stagnant, providing ideal conditions for the breeding of parasite-carrying mosquitoes. This picture became clear to Livingstone as he developed his research: the newly created ecological circumstances fostered mosquito reproduction and the spread of malaria, and the growing host of humans made possible by agriculture-fuelled population growth provided the food resources needed by the mosquitoes. The infectious disease gave those individuals with a very rare mutation—the sickle-cell allele—an adaptive advantage and the ability to survive and reproduce in these new environmental circumstances. Due to the advantage the heterozygous condition provides, the S allele was maintained and passed from generation to generation. For this reason, sickle-cell anaemia predominantly affects those whose descendants came from the malarial environments in large parts of equatorial Africa. Outside of such malarial environments, the S allele never became advantageous.

OTHER HAEMOGLOBIN AND ENZYME ABNORMALITIES

Sickle-cell anaemia turns out to be just one of a number of **haemoglobinopathies** and other genetic abnormalities in Africa, Asia, and Europe that provide a strong selective advantage in regions of endemic malaria. Heterozygous carriers of abnormal haemoglobins apparently make poor hosts for malarial parasites.

An association has long been recognized between deficiency of the enzyme **glucose-6-phosphate dehydrogenase (G6PD)** and malaria. A recessive hereditary mutation leads more males than females to lack the gene that is coded to produce this enzyme. Without the G6PD enzyme, a person who takes sulfa-based antibiotics or eats fava beans risks the destruction of red blood cells, severe anaemia, and occasionally death. Because of the connection with fava beans, this severe haemolytic disease is called favism. Its 130 genetic variants occur in high frequencies in some populations, the highest being 70% among Kurdish Jews. Heterozygote carriers have a strong selective advantage because they produce some of the enzyme but are protected from malaria (here again, the parasite cannot live in the abnormal red blood cells).

Analysis of genetic data by the anthropologist **Sara Tishkoff** indicates that the mutation for the disease arose between about 4,000 and 12,000 years ago, at the same time as the abnormal haemoglobins. Populations whose descendants did not encounter malaria do not have the *G6pd* mutation or abnormal haemoglobins. Today, for example, malaria appears throughout the tropical regions of the Americas, but Native Americans are 100% homozygous for normal alleles at the *G6pd* and haemoglobin loci. That these particular genes do not appear to have mutated in the New World strongly suggests that malaria was introduced to North and South America only after the Europeans' arrival. Indeed, the introduction of malaria and other Old World diseases—by either Spaniards or their African slaves—likely played an instrumental role in the precipitous decline in the native populations.

If malaria had been introduced in the Americas much earlier than the last few centuries—say thousands of years ago—and the mutations occurred, there might have been time for a natural selection to develop for the mutations. If the mutations did appear before the Europeans' arrival, however, they would have exhibited a clear selective disadvantage in the absence of malaria and been weeded out of the gene pool. Thus, red blood cell polymorphisms in the abnormal haemoglobin and *G6pd* loci reflect the fundamental interactions, among environment, genes, and culture, that have resulted in the modern human genome. The genes provide an important record about human evolution and the role of natural selection in shaping genetic variation.

CCR5-Δ32 Gene mutation and Disease Resistance

On a micro-evolutionary level, we can see the same thing when looking at variation of the CCR5-Δ32 mutation. The CCR5 gene (short for C-C chemokine receptor 5) is located on chromosome 3. This gene is responsible for the CCR5 protein, which functions in resistance to certain infectious diseases. A mutation of the CCR5 gene results in the deletion of a 32-bp section of the DNA sequence of CCR5, and is known as CCR5-Δ32 (delta 32) mutation. In European populations Δ32 mutation has a frequency of 0-14% but it is absent in rest of the world (Stephens et al. 1998). Statistical analysis of DNA sequences near this locus provides strong support that the distribution of this allele has been shaped by natural selection (Bamshad et al. 2002).

Heterozygotes with one CCR5-Δ32 allele show partial resistance to HIV, and homozygotes show almost complete resistance to AIDS (Galvani and Slatkin 2003). However, AIDS has been known only a short time in human history and therefore it could not have been responsible for the initial elevation of this mutant allele in some European populations. Most likely higher frequencies of CCR5- Δ32 arose because of selection related to some other disease such small pox.

Lactase Persistence and Human Diet

So far, the case studies presented above have focused on disease. Adaptation to disease through natural selection makes sense as disease directly affects one's probability of survival. However, let us consider a different sort of selection, evidence of adaptation to changing diet. Human infants are nourished through breastfeeding. Infant mammals produce the enzyme lactase, which allow lactose (milk sugar) to be broken down and digested. The typical pattern in mammals is to shut down the lactase production after the infant is weaned. After this, the mammal can no longer easily digest lactose. Today, many humans have developed lactose intolerance, that they cannot produce the lactase after about 5 years of age. The physical effect of lactose intolerance can vary and include flatulence, bloating, cramps, distention, and acute diarrhoea. The interesting fact is that although many people are lactose intolerant while others have no trouble in digesting lactose as they continue producing lactase enzyme throughout their lifetimes. The gene controlling lactase activity is present on the **chromosome 2**.

Lactase persistence has an interesting geographic distribution. It is found highest in northern Europe, and moderate in southern Europe and the Middle East. It is found very low in African and Asian populations on average.

The critical factor that explains global variation in lactose persistence is diet. Populations indulged in dairy farming tend to have higher frequencies of the lactase persistence allele. The fact can very well be explained by natural selection where lactase persistence was selected for the populations engaged in dairy farming because of the nutritional advantage among individuals who are able to digest the milk.

The evolution of skin color

Human skin colour (pigmentation) is a quantitative trait that shows an immense amount of variation between human groups around the world, ranging from very dark to extremely light. The wide range of skin colour is affected by natural selection, and the specific geographical distribution of skin color is another.

Skin color tends to be darker at or near the equator, and decrease with increasing distance from the equator, both north and south as the amount of ultraviolet (UV) varies with distance. UV radiation is strongest at the equator and diminishes with increasing distance. Skin color, levels of UV radiation, and distance from the equator are all highly correlated (Jablonski and Chaplin 2000). Pigmented skin acts as a protective barrier against UV radiation, therefore dark skin are preferable in areas at or near the equator

GENETIC DRIFT: GENETIC CHANGE DUE TO CHANCE

Genetic drift is random change in allele frequency over time. Provided that no allele confers a selective advantage over another, a random change can lead to a change in gene frequency, such as one allele being lost and the other becoming fixated—or fixed, the only allele of its kind, in the population. This force, this kind of change, makes possible the measuring of evolution as a statistical probability. A hurricane that wipes out 99 percent of the population of an island, leaving only a

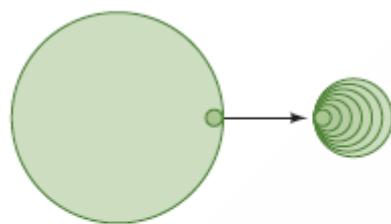
few individuals and their genotypes is a random event with respect to evolution. The odds that genetic drift will have great importance in changing the frequency of a trait are greatest in very small populations.

Among humans, for example, genetic drift might occur in a small group that is **endogamous**, discouraging reproduction outside the group. (An **exogamous** society extends reproduction outside its community.) Within such a group, the chances are great that the frequencies of genetic markers will differ from those of a larger population. When the **Dunkers**, a small religious sect that discourages outside marriage (and thus reproduction), first emigrated from Germany to Pennsylvania, in 1719, the group included just 28 members. Over the next few decades, several hundred more arrived in Pennsylvania; the breeding population remained quite small. Comparisons of contemporary blood type percentages among Dunkers, Germans, and Americans reflect significant changes in the Dunkers and a likely lack of change in the larger populations. That is, blood type frequencies among Germans and Americans remain basically the same as they were in the 1700s. The Dunkers' original frequencies were probably much like those of the Germans, but the small Dunker population meant a much greater chance for genetic drift. The frequencies diverged dramatically over time simply due to chance.

Founder Effect: A Special Kind of Genetic Drift

Founder effect, one form of genetic drift, occurs when a small group (fewer than several hundred members) of a large parent population migrates to a new region and is reproductively isolated. The new region is either unoccupied or occupied by species with which the small group cannot breed. Because the founding population is so small, there is a very good chance that its genetic composition is not representative of the parent population's. Thanks to the founder effect, as the founding population grows its gene pool diverges even further from the source. For example, around 12,000 yBP a very small number of individuals— perhaps just a few hundred—migrated from East Asia to North America. Today, Native Americans have very high frequencies of type O blood—in many places the frequency is 100% while East Asian populations have among the world's lowest frequencies of it. This discrepancy strongly suggests that the original East Asian immigrants, the founding “Native Americans,” had a higher frequency of type O blood than their parent population had.

Why had such a debilitating disease not been removed from the gene pool via natural selection? Since the effects of the gene are not expressed until later in life, people might not have known they had the disease until after they had passed on the detrimental allele to their offspring.

**Founder Effect**

The large circle on the left represents a parent population, from which a very small proportion is removed to begin a new population. Over time, the founding population grows, and its gene pool looks less and less like that of the parent population.

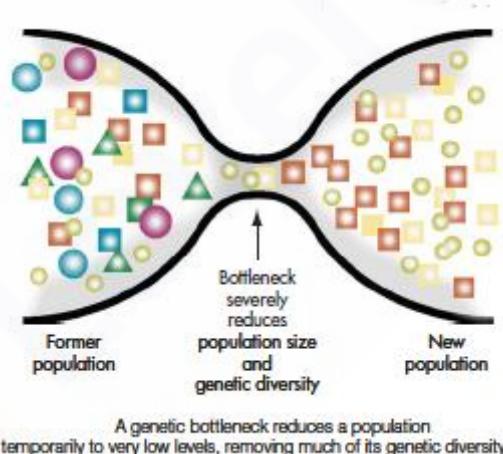
Some immigrant groups to the United States who have chosen to live in closed societies experience the effects of genetic drift. The Amish, a well-known religious sect, immigrated to the United States from Germany and the Netherlands in the 1800s. They practice farming with nineteenth-century technology, avoiding contact with the larger American culture around them; until recently very few Amish married outside the Amish community. As a consequence, some genetic diseases that were rare in the parent population in western Europe are common among the Amish in America. *Ellis-van Creveld (EVC) syndrome*, a genetic disease common among the Amish, is a form of dwarfism, and its victims always possess an extra finger on each hand and sometimes extra toes on the feet, a condition known as *polydactyly*. Not only is the EVC gene more common among the Amish than in the larger American gene pool, but it is restricted mainly to the Amish settlements in Lancaster County, Pennsylvania, and is extremely rare elsewhere. It appears that one or a few Amish individuals carried the gene with them from Europe to Lancaster County and, by virtue of their high reproductive rate (the Amish often have ten or more children), spread the gene rapidly through the very small founding population of other Amish (McKusick et al., 1964).

A **genetic bottleneck** is often associated with a founder effect and can bring about evolutionary change. A bottleneck occurs when a large, genetically diverse population undergoes a rapid reduction in size and then increases again. When the population size declines, a large percentage of the alleles present may be lost, and after the bottleneck, only the accumulation of mutations will rebuild genetic diversity. For example, Native Americans, Russians, and then Americans hunted the southern elephant seal, a minivan-sized marine mammal, nearly to extinction from the eighteenth to twentieth centuries. By the time complete protection was enacted, there were only a few dozen southern elephant seals left

in the wild. But elephant seals breed rapidly, and over the past several decades their numbers have grown exponentially. They are returning to former breeding beaches up and down the California coast (including a few bathing beaches, to the shock of human sunbathers). However, the new elephant seal population has a potential problem. It possesses only the genetic diversity present in the new post-bottleneck population. Should a disease strike the seals, it could well be that a gene for disease resistance that existed in the population before the bottleneck is gone, and the disease could devastate the remaining seals. Hundreds of generations will have to pass before mutations can begin to restore this diversity.

An extreme example is seen among the Pingelapese people of the eastern Caroline Islands in Micronesia. Four to 10 percent are born with “Pingelapese blindness,” an autosomal recessive combination of colorblindness, near-sightedness, and cataracts also called achromatopsia. Elsewhere, only 1 in 20,000 to 50,000 people inherits the condition. Nearly 30 percent of the Pingelapese are carriers. The prevalence of the blindness among the Pingelapese stems from a typhoon in 1780 that killed all but nine males and ten females who founded the present population. This severe population bottleneck, plus geographic and cultural isolation, increased the frequency of the blindness gene as the population resurged.

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GENE FLOW: SPREAD OF GENES ACROSS POPULATION BOUNDARIES

Another force of evolution, gene flow is the transfer of genes across population boundaries. Gene flow is the exchange of genes between populations. The term **migration** is also sometimes used; but strictly speaking, migration refers to the movement of people. In contrast, gene flow only occurs when the migrants interbreed. Also, even if individuals move temporarily and have offspring in the new population (thus leaving a genetic contribution), they don't necessarily stay there. For example, the children of U.S. soldiers and Vietnamese women represent gene flow. Even though the fathers returned to the United States after the Vietnam War, some of their genes remained behind, although not in sufficient numbers to appreciably change allele frequencies.

The key determinant for the amount of gene flow is accessibility to mates—the less the physical distance between populations, the greater the chance of gene flow. While mutation increases genetic variation between two populations over time, gene flow decreases such variation. Anthropologists and geneticists have found that for many kinds of biological traits, ranging from cranial shapes to blood types to microsatellite DNA markers, similarity increases the closer one population is to another population. Migration does not necessarily bring about gene flow. For example, when East Asians first migrated to North America (see “Founder Effect” above), they reached a continental land mass where no humans had ever lived. Written records suggest that Vikings first travelled from Greenland to Newfoundland around AD 1000, but there is no evidence that they interbred with the native people.

The first significant gene flow involving Native Americans and Europeans seems to have occurred when or soon after Christopher Columbus and his crew arrived in the New World, in 1492. From that point on, gene flow has been extensive. Gene flow and genetic variation are also highly influenced by social structure. Endogamous societies—for example, Australian aborigines—have relatively little genetic diversity because few individuals migrate into the community and thus little new genetic material is introduced. Exogamous societies have relatively high genetic diversity because proportionately more genetic material is brought into the gene pool. Gene flow has always affected human evolution, but its effects have increased greatly over time.

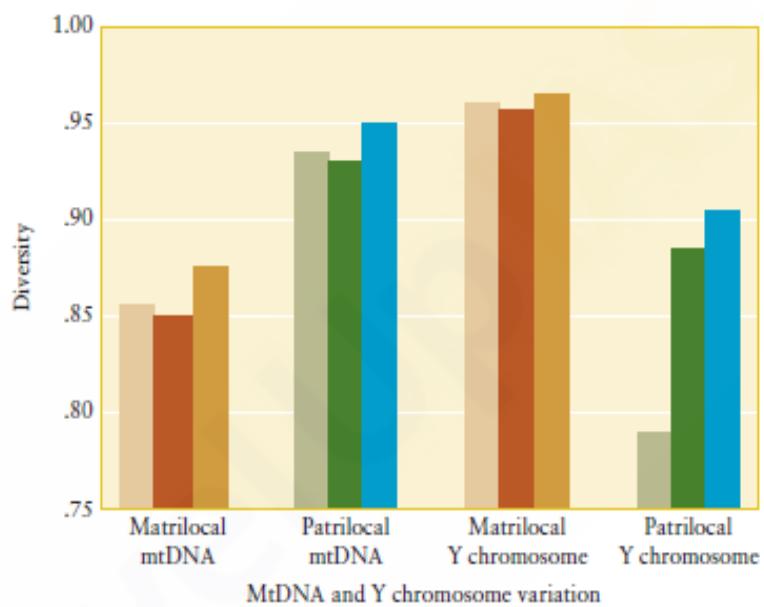
Originally, human populations tended to be small and isolated. Only during the last 10,000 years, with the development of agriculture and with major population increases, have humans had widespread interaction. Specific genetic markers in living populations, such as the ABO blood group system, provide evidence of gene flow across large regions. For example, the frequencies of type B blood change gradually from East Asia to far western Europe. This cline—that is, sloping—trend was first noted, in the early 1940s, by the American geneticist Pompeo Candela (1906–1956), who made the case that the gradient from east to west reflects significant gene flow that occurred as Mongol populations migrated westward from AD 500 to 1500. That is, if Mongols had higher frequencies of the B allele, they might have passed on that allele as they interbred with local populations.

Several gene flow studies have been done in African American populations to assess the contribution of European alleles in the composition of their genetic structures. Although for much of U.S. history admixture between African and European Americans has been strongly proscribed, gene flow studies indicate that it was not an unusual occurrence. A classic genetic study using a **Duffy blood group** allele that is largely absent in Africa but common in European populations showed that European admixture in five African American populations ranged from 4 percent in Charleston, South Carolina, to 26 percent in Detroit (Reed, 1969). In a more recent study using autosomal DNA markers, mtDNA haplotypes, and Y-chromosome polymorphisms, Esteban Parra and colleagues (1998) confirmed these high rates of

admixture. Looking at nine communities, they found admixture rates ranging from 11.6 percent in Charleston to 22.5 percent in New Orleans. A sample from a Jamaican population showed a European proportion of only 6.8 percent, indicating a substantial difference between Afro-Caribbean and African American communities. The mtDNA (maternally inherited) and the Ychromosome (paternally inherited) data indicated that gene flow from European to African American populations was strongly sex-biased, with men making a substantially greater contribution than women. This comes as no surprise, given that sexual contacts between male slave owners and female slaves were not uncommon.

Social Structure in MtDNA and Y Chromosome Diversity

In patrilocal societies, generally speaking, males stay in the birthplace, females migrate out, and female mates come from elsewhere. In matrilocal societies, females stay in the birthplace, males migrate out, and male mates come from elsewhere. To test the hypothesis that the out-migration of females and the out-migration of males produce different patterns of genetic diversity, the geneticist Hiroki Oota and colleagues studied six groups in Thailand, three of them patrilocal and three matrilocal. They found predictable patterns in the diversity of mtDNA and of Y chromosomes. Since mtDNA is passed from mother to daughter, the patrilocal groups showed high mtDNA variation (brought about by females' movement into new villages), and the matrilocal groups showed low mtDNA variation (brought about by females' remaining in place). Since the Y chromosome is passed from father to son, the patrilocal societies showed low Y chromosome variation (from males' not migrating), and the matrilocal societies showed high Y chromosome variation (from males' moving to new villages and introducing new Y chromosomes).



INBREEDING OR NON-RANDOM MATING

One of the chief condition for realising H-W equilibrium is that population under consideration breeds randomly. But that is a rarity due to many obvious reasons. Inbreeding is production of offspring from mating or breeding of individuals or organism that are closely related genetically in contrast to random mating.

A defect of this procedure is that together with desirable alleles, many other non-desirable alleles also become homozygous. The total effects of such homozygosity is a weaker, less successful or less fit member of the species.

Inbreeding thus lowers the fitness or adaptive value of species. If suddenly called upon to cope with new set of circumstances, such an inbred stock would be unable to do so, since many of the genes that could have helped in this situation have been lost. This is called **inbreeding depression**. However, it has been argued that some amount of inbreeding is good,

because it allows the expression of recessive genes with positive effects. The levels of inbreeding in US has been estimated at about $F=0.0001$ which is approximately equal to each person mating with fifth cousin.

Reasons of Inbreeding

Studies have shown that in many societies consanguineous marriages predominate. In fact, in many large populations of Asia and Africa twenty to fifty percent of all unions are that of consanguineous marriages (Bittles 1991). There are several circumstances that would give a population a reason to practice inbreeding at a large scale. Some of these reasons for practicing inbreeding include royalty, religion and culture, casteism, socioeconomic class, geographic isolation and small population size.

Some classical examples of Inbreeding and its deleterious effect

European Royal Families Inbreeding was very common among the royal families of Europe, and it has been linked as the cause of the widespread number of cases of hemophilia in the families. The presence of haemophilia in the royalty of Europe started with Queen Victoria of England. Victoria is thought to be the original carrier for the recessive X-linked hemophilia gene, which lead to over twenty members of royal families inheriting the disease in just over 100 years.

Study on Japanese Children after WWII

Shortly after the United States dropped two atomic bombs on Japan in World War II there was an increase in the number of consanguineous marriages in the areas surrounding Hiroshima and Nagasaki. The most common union was seen to be inbreeding at the first-cousin level. The study was set up to study some of the possible effects of inbreeding.

In the study, it was seen that inbreeding did not have an adverse effect on the fertility of the marriages, but there were some significant increases seen on childhood mortality in the first year of life. Inbreeding also increased morbidity in the study. There were significant increases in levels of handicapped offspring associated with inbreeding (Schull 1965).

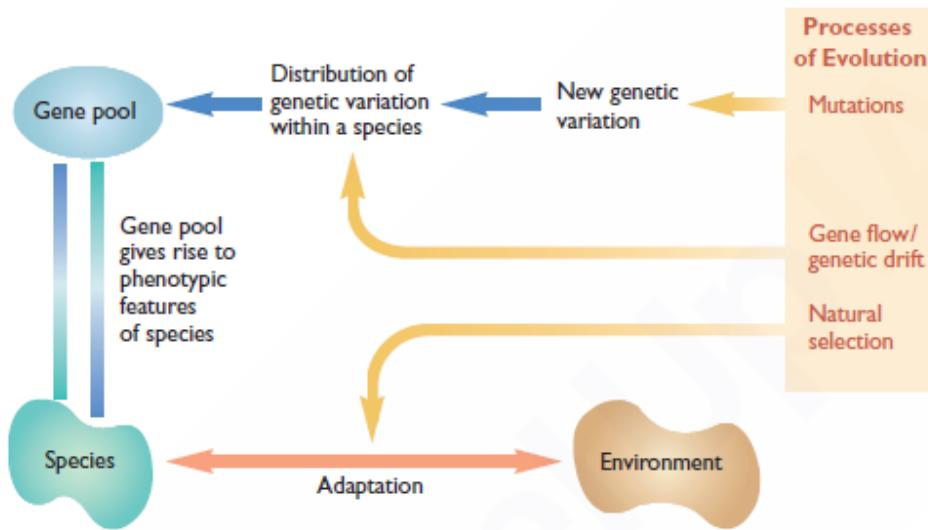
Inbreeding Avoidance and Incest Rules

All human cultures have rules and traditions that regulate sexual contact and reproductive relationships. **Incest** is any violation of such rules by members of a kin group. Incest rules are sometimes explicit (stated in legal or customary form) and sometimes implicit (followed but not overtly stated or codified). Definitions of kin vary from culture to culture and do not always closely follow biological patterns of relatedness. For example, in American culture, sexual contact between stepparents and stepchildren, or between relatives linked by adoption, is generally regarded as being incestuous, although from a biological standpoint a pregnancy that resulted from such a mating would not constitute inbreeding. Both cultural and biological scientists agree on the universality of cultural rules governing sexual relations between close kin—the *incest taboo*—but they differ on why it exists.

Non-random mating can lead to an increase in the frequency of affected homozygotes by two mechanisms, either assortative mating or consanguinity.

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.



Processes of evolution. A species is in an adaptive relationship with its environment. This relationship is maintained by natural selection. Environments, however, are constantly changing, so the adaptive characteristics of a species change through time. In addition, the gene pool of a species is always changing, altering the phenotypes on which selection acts. Processes that alter a species' gene pool are also, by definition, processes of evolution. Mutation provides new genetic variation by producing new alleles or otherwise altering the genetic code. Gene flow and genetic drift mix the genetic variation within a species, continually supplying new combinations of genetic variables.

CONSANGUINEOUS AND NON-CONSANGUINEOUS MATINGS- EFFECTS

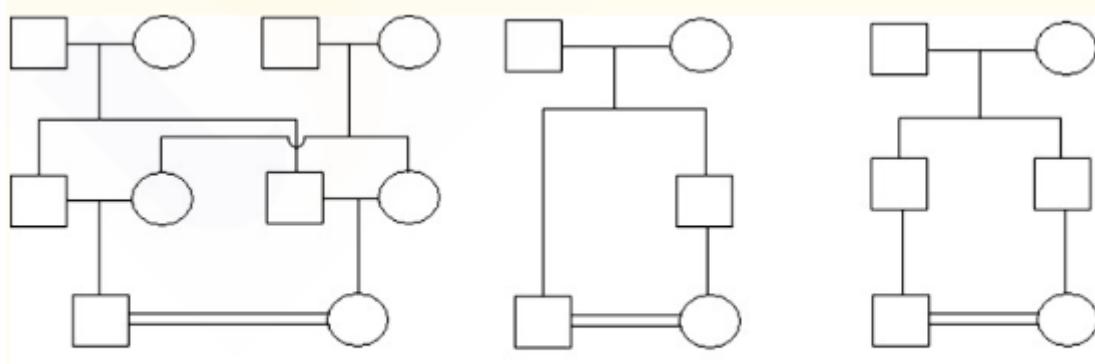
There are two general patterns of mating in human populations: **random and non-random mating**. Deviations from random mating can occur in two general directions. People who are related can either marry more frequently or less frequently than they would by chance. In the former case the mating system 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, second cousins, double first cousins and aunt-nephew.



Double First Cousins
 $F=0.125$

Uncle-niece
 $F=0.125$

First Cousins
 $F=0.0625$

Why are consanguineous marriages culturally favoured?

The actual reasons given for the preference of consanguineous marriages are primarily social. In communities with high consanguinity rates, sociological studies indicate that consanguineous marriage could enforce the couples' stability due to higher compatibility between husband and wife who share the same social relationships after marriage as before marriage, as well as the compatibility between the couple and other family members.

Consanguineous marriage may be more favourable for the women's status, including the wife's better relationship with her in-laws who could support her in time of need. There is a general belief that marrying within the family reduces the possibilities of hidden uncertainties in health and financial issues. It is believed that consanguinity strengthens family ties and enforces family solidarity, with cousin marriage providing excellent opportunities for the transmission of cultural values and cultural continuity (Sandridge et al. 2010). Premarital negotiations regarding financial matters of marriage are more easily conducted and sometimes less costly. Wife's parents prefer to have their daughter living near them and to enjoy the presence of their grandchildren. Moreover, wealthy landlords may prefer to keep their property within the family (Bittles 2001; Hamamy and Bittles 2008). Consanguineous marriages are also favoured where the group is endogamous with low population as was observed in population of inhabitants of Hiroshima and Nagasaki post world war II.

Consanguinity and health parameters

Health care providers and genetics specialists could consider both the negative impact of consanguineous marriage in terms of increased genetic risks to the offspring, as opposed to the potential social and economic benefits (Hamamy et al. 2011).

The reproductive health criteria related to consanguinity show that in first cousin marriages as opposed to non-consanguineous marriages, fertility rate is slightly higher, abortion rate is not different, stillbirths and infant mortality rates are slightly higher and birth defects frequency is estimated to be around 2–3% points more than the background rate among newborns in the general population (around 2–3%). Furthermore, consanguineous unions lead to increased expression of autosomal recessive disorders (Bittles et al. 1991; Bittles and Black 2010b; Hamamy et al. 2011; Tadmouri et al. 2009). The offspring of consanguineous unions may be at increased risk for recessive disorders because of the expression of autosomal recessive gene mutations inherited from a common ancestor. The closer the biological relationship between parents, the greater is the probability that their offspring will inherit identical copies of one or more detrimental recessive genes. For example, first cousins are predicted to share 12.5% (1/8) of their genes. Thus, on average, their progeny will be homozygous at 6.25% (1/16) of gene loci (Bennett et al. 2002).

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*.

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.

Preconception and premarital counselling for consanguinity

Preconception genetic counselling for consanguinity is considered one of the important pillars amongst the community genetic services in highly consanguineous populations. Premarital counselling is another increasingly demanded service in some countries and communities where consanguinity rates are still high and selective abortion of affected foetus is not feasible and/or not acceptable. Marriage in many such countries is regarded as a family decision and not just the couple's decision, although the frequency of "arranged marriages" may be declining in recent years due to the increasing number of females reaching university level education which gives them a broader choice of marriage partner. Many marriages, whether both interfamilial and intra-familial (consanguineous), are however still considered arranged marriages in some communities. The term "arranged marriage" does not mean that the marriage is planned against the will or acceptance of either partner, but it basically implies that a certain suitable couple is given the option of getting married under the family

supervision. Among marriages contracted from 1969 to 1979 in Jordan, 73.3% of 1983 marriages were arranged through parents' agreement first and then couples' consent, while in 18.6%, the marriage was through the couples' agreement first then the parents' consent (Khoury and Massad 1992).

In populations with high consanguinity rates and common inherited blood disorders, community programs for premarital screening to detect carriers of hemoglobinopathies such as thalassemia and sickle cell anaemia are in progress as for example in Jordan (Hamamy et al. 2007a), Saudi Arabia (Memish and Saeedi 2011), Iran (Fallah et al. 2009), Iraq (Al-Allawi and Al-Dousky 2010), Bahrain (Al-Arrayed 2005) and Turkey (Mendilcioglu et al. 2011). Carrier detection and genetic counselling programs have been very successful in reducing the birth prevalence of inherited disorders in some populations, such as in Iran (Khorasani et al. 2008; Samavat and Modell 2004). **These programs are most successful when they are sensitive to the cultural backgrounds of populations in which they are applied.**

In addition to their primary goals, premarital screening programs in some communities have helped in raising the public's awareness of genetic diseases in general, their prevention possibilities and the fear that consanguinity is a risk factor for expression of recessive disorders, which has led to an increase in numbers of couples seeking premarital and preconception counselling for consanguinity. In countries such as Tunisia, premarital genetic counselling is obligatory for all couples with a history of genetic complications and in cases of consanguinity.

METHODS FOR STUDY OF GENETIC PRINCIPLES IN MAN-FAMILY STUDY

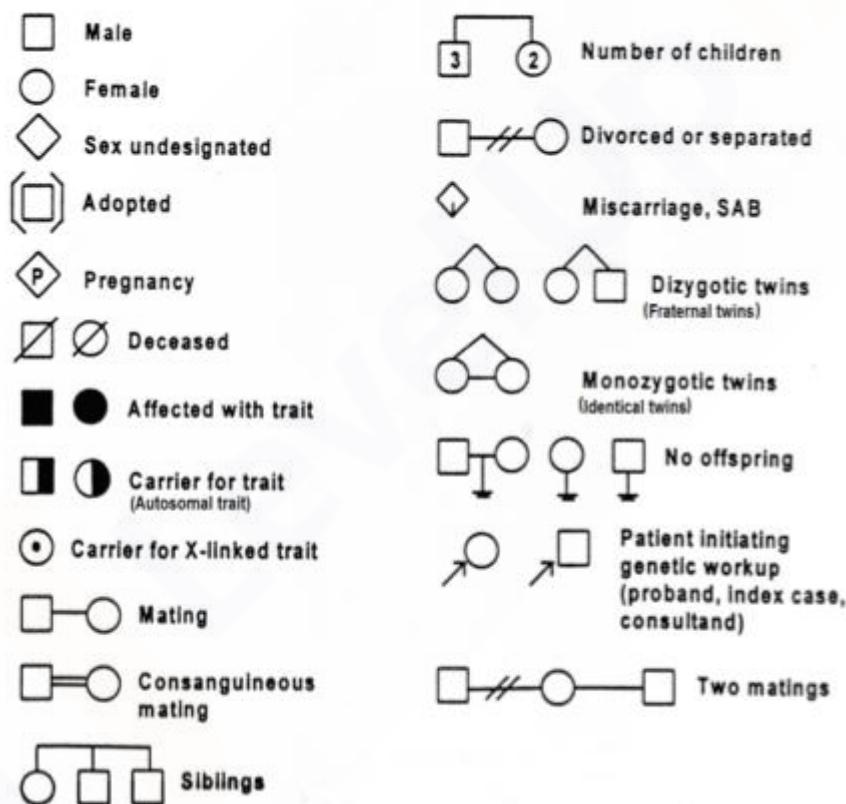
- a) Pedigree Analysis
- b) Twins Study
- c) Co-twin study
- d) Cytogenetic methods- Chromosomal Analysis and karyotype analysis (covered in previous notes)
- e) Bio-chemical methods
- f) Immunological methods
- g) DNA Technology and Recombinant Technologies

Pedigree Analysis

All of the conclusions regarding gene action (dominant/recessive; codominant) we have discussed so far have been obtained from analysing the results of controlled crosses. In some situations, we do not have the opportunity to perform controlled crosses. Rather we need to analyse an existing population. This is always the case when studying human genetics. Scientists have devised another approach, called **pedigree analysis**, to study the inheritance of genes in humans. Pedigree analysis is also useful when studying any population when progeny data from several generations is limited. Pedigree analysis is also useful when studying species with a long generation time.

Pedigrees are used to analyse the pattern of inheritance of a particular trait throughout a family. Pedigrees show the presence or absence of a trait as it relates to the relationship among parents, offspring, and siblings. These diagrams are used to determine the **mode of inheritance** of a particular disease or trait, and to predict the probability of its appearance among offspring. Pedigree analysis is therefore an important tool in both basic research and **genetic counselling**.

Defn: Pedigree analysis is a classical technique of medical genetics by which a thorough family tree is depicted, with symbols for persons affected with known genetic disease. Thus is rendered a broad summary of inheritance patterns through generations that serves to clarify mode of transmission even for traits that may have identical phenotypes



Autosomal Dominant Inheritance

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

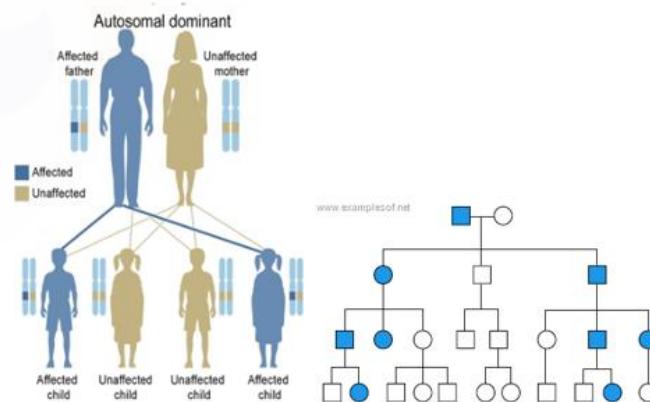
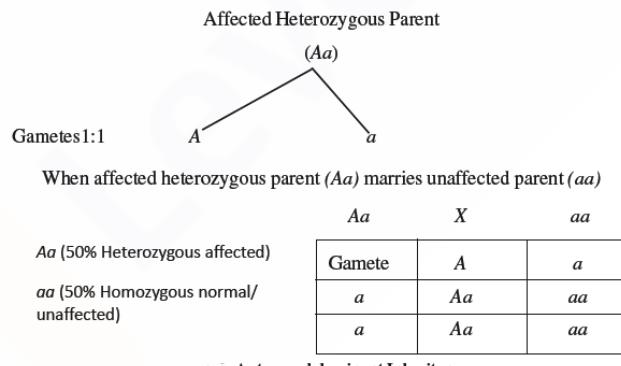
Trait	Characteristic features
Achondroplasia	Dwarfism with short limbs, normal size head and trunk.
Hypercholesterolemia	Very high serum cholesterol levels, heart disease.
Polydactyly	Extra fingers and/or toes.
Huntington disease	Progressive uncontrollable movements and personality changes, beginning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

Characteristic features of autosomal dominant inheritance are listed below:

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

Affected heterozygous parent (Aa)

A: Mutant gene a: Normal gene
 $Aa = 50\%$ (Heterozygous affected) $aa = 50\%$ (Homozygous normal)



Autosomal Recessive Inheritance

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

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

Following are the characteristic features of autosomal recessive inheritance

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

Aa X Aa

Mating between carrier parents

		Normal but carrier parent (<i>Aa</i>)	
		<i>A</i>	<i>a</i>
Normal but carrier parent (<i>Aa</i>)	<i>A</i>	<i>AA</i>	<i>Aa</i>
	<i>a</i>	<i>Aa</i>	<i>aa</i>

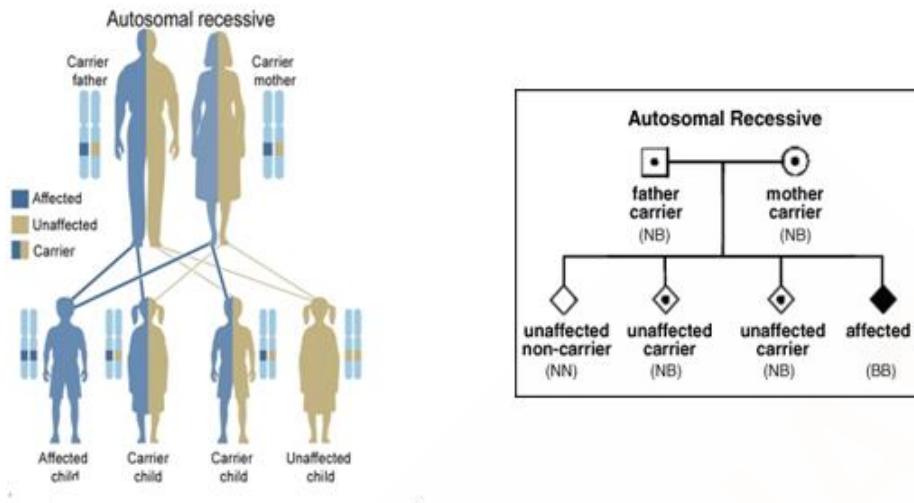
AA = 25% normal

Aa = 50% normal but carrier

aa = 25% affected

Genotypic ratio 1:2:1

Phenotypic ratio 3:1



Sex Linked Inheritance

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

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

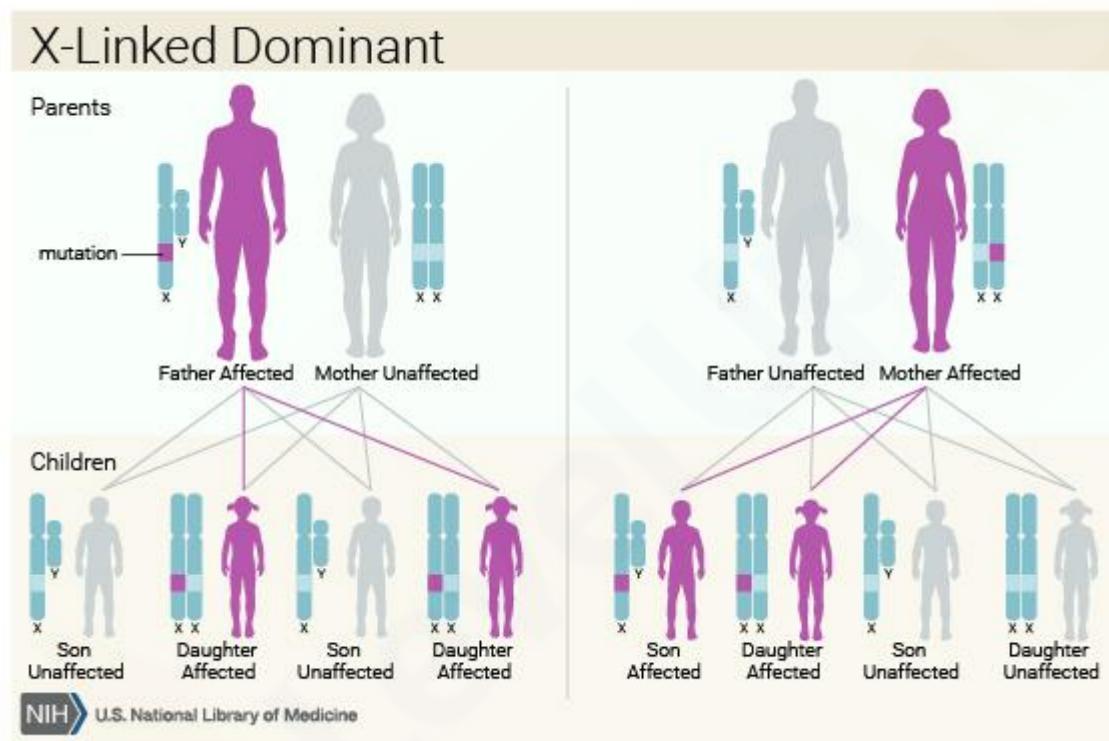
X-linked Inheritance may be dominant or recessive.

X-Linked Dominant Inheritance

This disorder is due to the presence of mutant gene on X chromosome. As the gene is dominant, it expresses in heterozygous females as well as in males. This type of inheritance resembles that of an autosomal dominant inheritance but can be distinguished owing to the fact that an affected male passes on this trait to all his daughters but to none of his sons. Therefore, to distinguish this character from autosomal inheritance one has to observe the offspring of affected males. Further, gene expression of X-linked dominant allele is different in two sexes. A female who inherits dominant X-linked allele has the associated trait or illness, but a male who inherits the allele is more severely affected because he is hemizygous for X chromosome and therefore has no other allele to offset the effect of the dominant allele.

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

Affected Heterozygous female ($X^R X$)	Oocytes	
	$X^R X$ (affected daughter)	$X^R X'$ (unaffected daughter)
	$X^R Y$ (affected son)	$X' Y$ (unaffected son)



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

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

X-Linked Recessive Inheritance

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

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

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

Some Mendelian Disorders Inherited as X-linked Recessive Traits in Humans

Condition	Manifestations
G-6-PD (glucose-6-phosphate) deficiency	Lack of an enzyme (G-6-PD) in red blood cells; produces severe, sometimes fatal anemia in the presence of certain foods (e.g., fava beans) and/or drugs (e.g., the antimalarial drug primaquine).
Muscular dystrophy	One form is X-linked; other forms can be inherited as autosomal recessives. Progressive weakness and atrophy of muscles beginning in early childhood; continues to progress throughout life; some female carriers may develop heart problems.
Red-green color blindness	Actually, there are two separate forms, one involving the perception of red and the other involving the perception of green. About 8 percent of European males have an impaired ability to distinguish green.
Lesch-Nyhan disease	Impaired motor development noticeable by 5 months; progressive motor impairment, diminished kidney function, self-mutilation, and early death.
Hemophilia	There are three forms; two (hemophilia A and B) are X-linked. In hemophilia A, a clotting factor is missing; hemophilia B is caused by a defective clotting factor. Both produce abnormal internal and external bleeding from minor injuries; severe pain is a frequent accompaniment; without treatment, death usually occurs before adulthood.
Ichthyosis	There are several forms; one is X-linked. A skin condition due to lack of an enzyme; characterized by scaly, brown lesions on the extremities and trunk. In the past, people with this condition were sometimes exhibited in circuses and sideshows as "the alligator man."

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

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

Carrier female (mother)

Normal male (father)	Gamete	X^H	X^h
	X^H	$X^H X^H$	$X^H X^h$
	Y	$X^H Y$	$X^h Y$

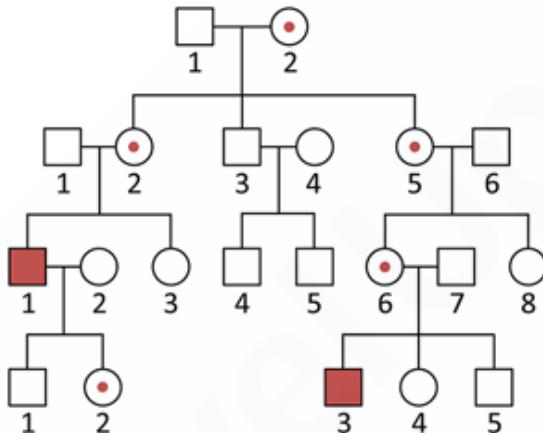
X^H = Normal gene, X^h = Abnormal gene

25% $X^H X^H$ Normal daughter

25% $X^H X^h$ Carrier daughter

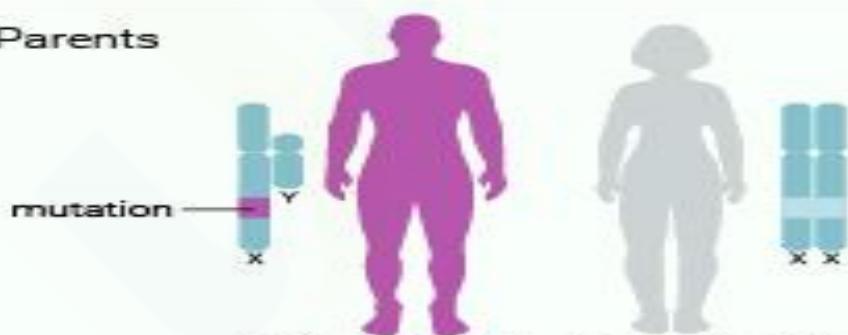
25% $X^H Y$ Normal son

25% $X^h Y$ Son with haemophilia



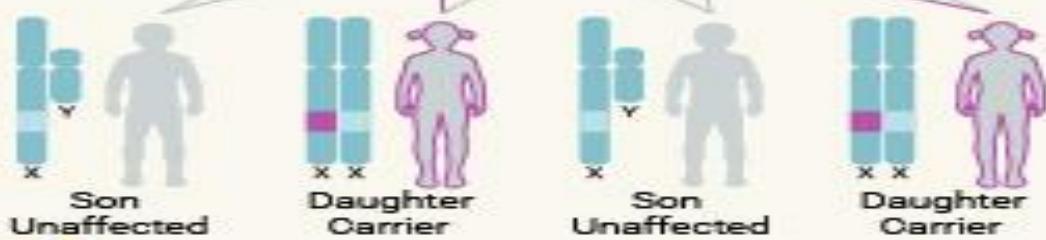
X-Linked Recessive

Parents



Father Affected Mother Unaffected

Children

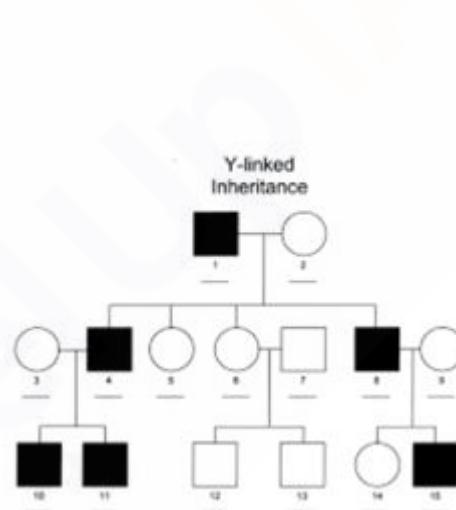
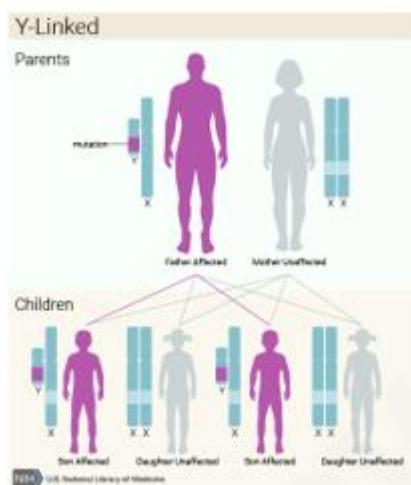


Y-Linked Inheritance

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

Characteristic features of Y-linked inheritance are listed below:

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



Summary

Pedigree characteristics of autosomal recessive, autosomal dominant, X-linked recessive, X-linked dominant, and Y-linked traits

Autosomal recessive trait

1. Appears in both sexes with equal frequency.
2. Trait tends to skip generations.
3. Affected offspring are usually born to unaffected parents.
4. When both parents are heterozygous, approximately 1/4 of the offspring will be affected.
5. Appears more frequently among the children of consanguine marriages.

Autosomal dominant trait

1. Appears in both sexes with equal frequency.
2. Both sexes transmit the trait to their offspring.
3. Does not skip generations.
4. Affected offspring must have an affected parent, unless they possess a new mutation.

5. When one parent is affected (heterozygous) and the other parent is unaffected, approximately 1/2 of the offspring will be affected.
6. Unaffected parents do not transmit the trait.

X-linked recessive trait

1. More males than females are affected.
2. Affected sons are usually born to unaffected mothers; thus, the trait skips generations.
3. A carrier (heterozygous) mother produces approximately 1/2 affected sons.
4. Is never passed from father to son.
5. All daughters of affected fathers are carriers.

X-linked dominant trait

1. Both males and females are affected; often more females than males are affected.
2. Does not skip generations. Affected sons must have an affected mother; affected daughters must have either an affected mother or an affected father.
3. Affected fathers will pass the trait on to all their daughters.
4. Affected mothers (if heterozygous) will pass the trait on to 1/2 of their sons and 1/2 of their daughters.

Y-linked trait

1. Only males are affected.
2. Is passed from father to all sons.
3. Does not skip generations.

Twin Study

Twins are of 2 types: Dizygotic, two egg or fraternal twins result when two ova are produced at about same time and both are fertilized. Monozygotic, one-egg or identical twins result from splitting of zygote at an early stage. Monozygotic twins are, of course, genetically identical barring somatic mutation. Dizygotic twins are genetically no more similar than ordinary siblings. Monozygotic twins are either both male or female. Dizygotic twins can be of either sex.

Identical, or monozygotic (MZ), twins occur at a fairly stable frequency of 3 to 4 per 1,000 births all around the world. In contrast, the occurrence of fraternal, or dizygotic (DZ) twins (non-identical twins) varies wildly across different kinds of populations — only 6 per 1,000 in Asia but 40 per 1,000 in Africa. Older mothers are four times more likely to have non-identical twins than younger ones; taller, heavier women who smoke and have family history of twinning are also reportedly more prone to having fraternal twins. All of this lends to the long-held suspicion that there exist genetic factors that affect a woman's susceptibility to give birth to fraternal twins.

Two genes that affect a woman's likelihood of giving birth to twins have been identified in a new study published in American Journal of Human Genetics. This could have implications for fertility research and help predict how women will respond to treatments for infertility. Before they arrived at the two genes, the scientists combed through the entire genomes of 1,980 mothers of non-identical twins and 12,953 control subjects (mothers with no non-

identical twins). They found 30 spots that seemed to be linked with twinning and kept narrowing down. "Two genetic variants, one near FSHB gene and the second one in SMAD3 gene showed a statistically significant association".

Mothers who had one specific variant of the FSHB gene were more likely to have given birth to non-identical twins. This variant is linked to increased production of follicle stimulating hormone (FSH), leading to more than one egg maturing and consequently multiple ovulation. The second, SMAD3, likely affects how the ovaries respond to FSH. Mothers of non-identical twins were significantly more likely to carry a variant of SMAD3 which makes her ovaries more sensitive to the same amount of FSH.

Knowing one's predisposition to multiple births can be very useful in the light of risks like premature birth associated with twinning. Future studies into SMAD3, the totally new candidate for twinning, may offer a novel avenue for fertility treatments, particularly in women who poorly respond to ovarian stimulation and also help in prevention of premature ovarian ageing.

Twin studies are studies conducted on identical or fraternal twins. They aim to reveal the importance of environmental and genetic influences for traits, phenotypes, and disorders. Twins are a valuable source for observation because they allow the study of environmental influence and varying genetic makeup: "identical" or monozygotic (MZ) twins share nearly 100% of their genes, which means that most differences between the twins (such as height, susceptibility to boredom, intelligence, depression, etc.) are due to experiences that one twin has but not the other twin. "Fraternal" or dizygotic (DZ) twins share only about 50% of their genes, the same as any other sibling. Twins also share many aspects of their environment (e.g., uterine environment, parenting style, education, wealth, culture, community) because they are born into the same family. The presence of a given genetic trait in only one member of a pair of identical twins (called discordance) provides a powerful window into environmental effects.

The classical twin design compares the similarity of monozygotic (identical) and dizygotic (fraternal) twins. If identical twins are considerably more similar than fraternal twins (which is found for most traits), this implicates that genes play an important role in these traits. By comparing many hundreds of families with twins, researchers can then understand more about the roles of genetic effects, shared environment, and unique environment in shaping behaviour.

Like all behaviour genetic research, the classic twin study begins from assessing the variance of a behaviour (called a phenotype by geneticists) in a large group, and attempts to estimate how much of this is due to:

- genetic effects (heritability);
- shared environment – events that happen to both twins, affecting them in the same way;

- unshared, or unique, environment – events that occur to one twin but not the other, or events that affect either twin in a different way.

Typically, these three components are called **A** (additive genetics) **C** (common environment) and **E** (unique environment); hence the acronym **ACE**. The **ACE** model indicates what proportion of variance in a trait is heritable, versus the proportion due to shared environment or un-shared environment.

Monozygotic (identical – MZ) twins raised in a family share both 100% of their genes, and all of the shared environment. Any differences arising between them in these circumstances are random (unique). The correlation between identical twins provides an estimate of $A + C$. Dizygotic (DZ) twins also share C , but share on average 50% of their genes: so the correlation between fraternal twins is a direct estimate of $\frac{1}{2}A+C$. If r is correlation, then r_{mz} and r_{dz} are simply the correlations of the trait in identical and fraternal twins respectively. For any particular trait, then:

$$r_{mz} = A + C$$

$$r_{dz} = \frac{1}{2}A + C$$

A , therefore, is twice the difference between identical and fraternal twin correlations : the additive genetic effect (Falconer's formula). C is simply the MZ correlation minus this estimate of A . The random (unique) factor E is $1 - r_{mz}$: i.e., MZ twins differ due to unique environments only

As the identical correlation reflects the full effect of A and C , E can be estimated by subtracting this correlation from 1

$$E = 1 - r_{mz}$$

Finally, C can be derived:

$$C = r_{mz} - A$$

Twin studies yield heritability estimates. Heritability is the proportion of the differences among individuals on a particular trait that are due to genetic differences. For example, the heritability of childhood attention deficit hyperactivity disorder (ADHD) is around 80 percent. Thus, most of the differences among individuals on symptoms of ADHD are due to genetic differences. On the other hand, the heritability of childhood delinquency is approximately 20 percent to 40 percent, suggesting that both genes and environment account for individual differences in delinquency. There are several important limitations to the heritability statistic that are often misunderstood. Heritability describes the variance, or the differences among people, in a particular population at that time. It does not apply to the development of single individuals nor to differences between populations.

Advantages of twin studies

- Twin studies allow disentanglement of the shared genetic and environmental factors for the trait of interest.
- Researchers can estimate the proportion of variance in a trait attributable to genetic variation versus the proportion that is due to shared environment or unshared environment.
- The use of twins can improve the statistical power of a genetic study by reducing the amount of genetic and/or environmental variability.

Limitations of twin studies

- Results from twin studies cannot be directly generalized to the general population, due to lack of randomization; in addition, they are different with regard to their developmental environment, as two foetuses growing simultaneously.
- Findings from twin studies are often misunderstood, misinterpreted, and blown out of proportion, not just by the media, but even by serious scientists who get their work published.
- Many twin registries depend on the voluntary participation of twins. This leads to volunteer bias or recruitment bias, a special type of selection bias, which may lead to overinclusion of identical and female twins, resulting in overestimation of the heritability of the trait or condition under study.
- The use of twins does not allow the researcher to consider the effects of both shared-environment and gene/environment interaction simultaneously. This can be addressed by including additional siblings in the design.
- For many conditions studied even the monozygotic concordance rate is well below 50% indicating that environmental factors before birth are important in causing them.

Co-Twin Study

Twins are of 2 types: Dizygotic, two egg or fraternal twins result when two ova are produced at about same time and both are fertilized. Monozygotic, one-egg or identical twins result from splitting of zygote at an early stage. Monozygotic twins are, of course, genetically identical barring somatic mutation. Dizygotic twins are genetically no more similar than ordinary siblings. Monozygotic twins are either both male or female. Dizygotic twins can be of either sex.

In this study a twin receives treatment for a trait while other is studied as a control. For example, one may attend an after school program to enhance gymnastic ability and the other will not. Learning effects are examined by comparing twin's gymnastic abilities before and after the program.

In twin method it has been stated that if monozygotic twins reared apart then the differences caused among them is caused by environment. Such investigation when done under control condition is called co-twin control method. Dizygotic twins are also included in such experiments. After giving a psychological exercise of improving intelligence to one sibling, if the trained individuals performed well that is influence of environment. Whereas the concordance of schizophrenia is expressed same in monozygotic twins irrespective of environment.

Arnold Gesell was one of the first to use the twin method to study early development. He noticed that identical twins were very similar both physically and behaviourally and used the identical co-twin control method to examine the effects of training on physical development. He studied a pair of twins, neither of whom could climb stairs when they were forty-six weeks of age. One twin was given daily practice and encouragement to climb stairs, while the co-twin had no stairs in his environment. After six weeks of practice, the trained twin could climb the stairs and the co-twin could not. One week later, however, the co-twin could also climb the stairs. Replicating this result in several similar studies, Gesell demonstrated that physical training can cause physical skills to appear sooner but that identical co-twins who were trained later performed the same after a relatively shorter period of training. Gesell later became interested in individual differences and the individual's role in creating his or her own environment. At the beginning of the twenty-first century, this dynamic view of person-environment relationships was being studied with newer sophisticated statistical techniques.

Advantages of twin studies

- Twin studies allow disentanglement of the shared genetic and environmental factors for the trait of interest.
- Researchers can estimate the proportion of variance in a trait attributable to genetic variation versus the proportion that is due to shared environment or unshared environment.
- The use of twins can improve the statistical power of a genetic study by reducing the amount of genetic and/or environmental variability.

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- For many conditions studied even the monozygotic concordance rate is well below 50% indicating that environmental factors before birth are important in causing them.

FOSTER CHILD

Foster children method is complementary to twin studies on the nurture and nature aspects, particularly of mental traits. In this method various groups of children are selected at random and are placed in different homes classified as good, average and poor homes of intelligence as a factor of genetic component. Since group of children are selected, the genetic factor of the trait studied, say intelligence is equally distributed among them. After a lapse of time they are tested on different intelligent scales. If intelligence has an environmental component, children placed in good homes should score better than average and poor homes.

In practice the experiment is never free of biases and errors. Children selected for placement in different homes are generally not random, and as it generally happens, intelligent children from good families are placed in good families. However, in **Chicago studies** was greatly minimised. The study revealed that the mean IQ scores of the adopted children were related to the quality of the adoptive homes. According to **Minnesota graded home studies** in which children of managerial class were placed in labour class homes and vice-versa it was found that there is effect of environment on IQ, but at the same time it was also reported that children of managerial class had more IQ in labour class homes than children of labour class in their own homes. This indicates importance of heredity in determination of IQ.

Osborne in 1951 has given 4 requirements for using this technique

- a) Foster child must be placed in the adoptive home sufficiently early to be relatively uninfluenced by the environment of their original homes.
- b) There must be little or no selective placement of children.
- c) Adequate sample of adoptive children from various social levels must be included.
- d) Foster children must be from one population to eliminate variation due to ethnicity or race.

Study of Chromosomes: Cytogenetics

Cytogenetics can be defined as the study of chromosomes, the hereditary units. It has been an active field of research contributing to the understanding of organization of chromosomes and human genome. It is a discipline that matches phenotypes to detectable chromosomal abnormalities. In other words, you can correlate the abnormal changes occurring in the

number (numerical aberrations like, monosomy, trisomy, nullisomy, triploidy) or structure (structural aberrations like chromosomal deletions, duplications, translocations and inversions) of chromosomes in an individual with the clinical features and symptoms.

Barr body analysis

Barr body is the condensed, single X-chromosome, appearing as a densely staining mass, that is found in the nuclei of somatic cells of female mammals. It is named after its discoverer, Murray Barr, and is derived from one of the two X-chromosomes which becomes inactivated. The number of Barr bodies is thus one less than the number of X-chromosomes. Barr bodies are commonly referred to as sex chromatin. The human abnormalities called Kleinfelter's syndrome and Turner's syndrome both result from an unnatural presence or absence of a Barr body. In the case of the former, the male possesses a Barr body that it would normally not have, and in the latter case the Barr body is absent.

Most of the genes on the Barr body are inactive, meaning that they are not transcribed. The process of X-inactivation was discovered by the British geneticist Mary F. Lyon and is sometimes called Lyonization in her honour.

A woman has two X chromosomes, one from each parent. Which one will she inactivate? X-inactivation is a random process that happens separately in individual cells during embryonic development. One cell might shut down the paternal X, while its next-door neighbour might shut down the maternal X instead. All the cells descended from each of these original cells will maintain the same pattern of X-inactivation.

Interesting note: if you were a kangaroo, what I just said would not be true! In kangaroos and other marsupials, it is always the paternal X chromosome that undergoes X-inactivation.

X-inactivation example: Calico cat

A classic example of X-inactivation is seen in cats. If a female cat is heterozygous for black and tan alleles of a coat colour gene found on the X, she will inactivate her two Xs (and thus, the two alleles of the coat colour gene) at random in different cells during development.

The result of is a tortoiseshell coat pattern, made up of alternating patches of black and tan fur. The black patches come from groups of cells in which the X with the black allele is active, while the tan patches come from cells in which the X with the tan allele is active.

Barr body testing **was used in the 1968 Olympic games** in an effort to detect male athletes supposedly trying to "pass" as females to gain a competitive advantage. Teams from eastern Europe were particularly suspect. Such allegations had been made for many years, and a number of athletes were stripped of their medals as a result of ambiguous genital sex. Barr Body testing never detected deliberate fakery. It did however detect a cases of Androgen Insensitivity Syndrome (AIS, formerly called TFS), a genetic condition in which an XY zygote develops as a phenotypically female adult, due to failure of androgen receptors. Such

individuals would test negative for the presence of a Barr body. In most if not all cases, the athletes were themselves unaware of their condition.

Karyotype analysis and banding:

A karyotype is simply a picture of a person's chromosomes. In order to get this picture, the chromosomes are isolated, stained, and examined under the microscope. Most often, this is done using the chromosomes in the white blood cells. A picture of the chromosomes is taken through the microscope. Then, the picture of the chromosomes is cut up and rearranged by the chromosome's size and shape. The chromosomes are lined up from largest to smallest. A trained cytogeneticist can look for missing or extra pieces of chromosome.

Tijo and Levin were the first group of scientists who in 1956 demonstrated that each human cell contains 46 chromosomes and broke then prevailing belief that it is 48 chromosomes. The entire chromosome complement of an individual organism or cell as seen during mitotic metaphase is used to arrange the karyotype. Any tissue with living cells having a nucleus that can undergo cell division is suitable for studying human chromosomes. The commonest method is to use circulating lymphocytes from peripheral blood.

Chromosome Banding Techniques

Now there is an important step which is called as the staining step. Many different stains and methods are used to identify individual chromosomes, using:

i) G (Giemsa) banding is the most common method used. The chromosomes are treated with Trypsin. Trypsin denatures their protein content; following this, the cells are stained with a DNA binding dye known as Giemsa. On **staining with Giemsa** each chromosome takes up a characteristic pattern of light and dark bands. These light and dark bands can be reproduced in the same pattern for each chromosome. In other words, the banding pattern is repeatable.

ii) Q (quinacrine) banding: This gives a banding pattern which is similar to the bands, obtained in Giemsa staining. However ultraviolet fluorescent microscope is required to view these chromosomes.

iii) R (reverse) banding: In this method the chromosomes are denatured by heating and then stained with Giemsa. This gives light and dark bands which are the reverse of those obtained using conventional G banding.

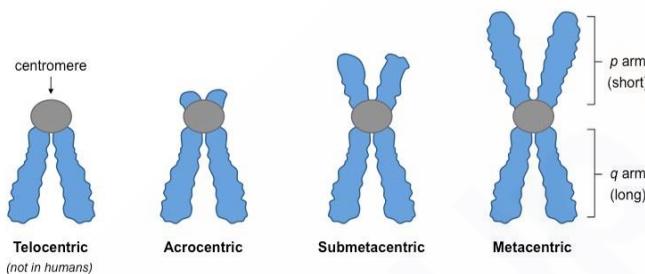
Meaning there will be a dark band in the region where the Giemsa stain shows up as a light band. Similarly it will be a light band in the corresponding region where the G staining gives a dark band.

iv) C (centromeric heterochromatin) banding: In this method, method of staining only the constitutive heterochromatin regions of chromosomes are stained. That is only the centromeres and the satellite region on chromosomes gets darkly stained.

Spectral Karyotyping (SKY)

Spectral karyotyping is a molecular cytogenetic technique used to simultaneously visualize all the pairs of chromosomes in an organism in different colours. Fluorescently labelled probes for each chromosome are made by labelling chromosome-specific DNA with different fluorophores.

On the Basis of Location of Centromere



Telocentric are rod-shaped chromosomes with centromere occupying the terminal position, so that the chromosome has just one arm.

Acrocentric are also rod-shaped chromosomes with centromere occupying a sub-terminal position. One arm is very long and the other is very short.

Sub-metacentric chromosomes are with centromere slightly away from the mid-point so that the two arms are unequal.

Metacentric are V-shaped chromosomes in which centromere lies in the middle of chromosome so that the two arms are almost equal.

Advantages

- 1) A sensitive method, can detect complex translocation involving two or more chromosomes.
- 2) Provides a critical screening method that can analyse all the chromosomes at once.

Disadvantages

- 1) Cannot detect inversions especially paracentric inversions.
- 2) Due to the nature of the probes they are very expensive.

Chromosomal Abnormalities or Aberrations

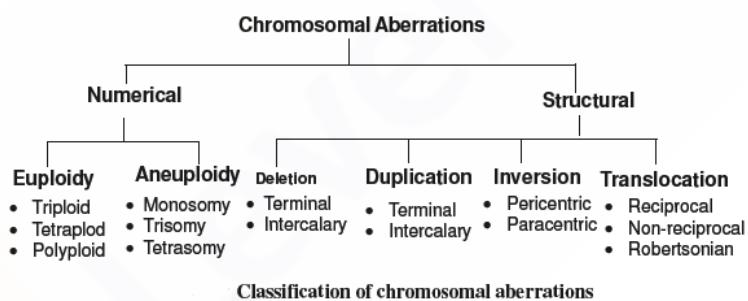
Almost all individuals of a species contain the same number of chromosomes specific for that species. For example, you and I contain, within each of our cells, a total of 46 chromosomes which is specific for *Homo sapiens*. However, there are individuals who show variations from this normal complement. These variations could be changes in number of chromosomes or

structural changes within and among chromosomes – together such changes are called chromosomal aberrations.

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

TYPES OF CHROMOSOMAL ABERRATIONS

Chromosomal aberrations are broadly classified as numerical or structural aberrations. They are further classified as shown in Figure



1) Numerical Aberrations

Numerical aberrations are those that cause a change (addition or deletion) in the number of chromosomes. They are further classified as euploidy changes or aneuploidy changes.

Euploidy is the condition when an organism gains or losses one or more complete set of chromosomes, thus causing change in the ploidy number. For example, triploid ($3n$), tetraploid ($4n$) etc.

Aneuploidy is the condition when an organism gains or losses one or more chromosomes and not the entire set. For example, trisomy ($2n + 1$), monosomy ($2n - 1$). In humans, euploidy conditions do not exist because the extent of abnormality is too large to sustain life.

Aneuploidy conditions, however, are more common and are manifested in disorders such as Down syndrome, Klinefelter syndrome and Turner syndrome.

Different types of numerical changes

Type of aberration	Representation	Explanation
Aneuploid	$2n \pm x$	Gain or loss of one or more chromosomes
Monosomy	$2n - 1$	Deletion of one copy of any one chromosome
Nullisomy	$2n - 2$	Deletion of both copies of any one chromosome
Trisomy	$2n + 1$	Addition of one extra copy of any one chromosome
Tetrasomy	$2n + 2$	Addition of two copies of any one chromosome
Euploid		Gain or loss of entire sets of chromosomes
Triploid	$3n$	Addition of one entire set to $2n$
Tetraploid	$4n$	Addition two entire sets to $2n$
Polyploid	$5n, 6n, 7n, \dots$	Addition of more than two entire sets to $2n$

ANEUPLOIDY CHANGES IN HUMANS

Aneuploidy conditions are non-lethal and result in abnormal phenotypes described as syndromes. The effects of aneuploidy changes differ significantly depending on the type of chromosome involved. For example, changes in chromosomes involved in sex determination (allosomes) results in changes in the primary and secondary sexual characters of that individual, whereas changes in other chromosomes (autosomes) do not.

Autosomal Trisomy

Trisomy is the condition where there is an additional copy of one chromosome. It is represented as $2n+1$. Individuals, who are trisomics, thus show three copies of the chromosome rather than the normal two. It is usually observed that trisomies of the smaller chromosomes are more tolerated than trisomies of the larger chromosomes. This is expected, because additional copies of larger chromosomes contribute to larger genetic imbalance than additional small chromosomes. You will find it no surprise that the most common trisomy is of the shortest chromosome in human – chromosome 21. The other trisomies that have been reported include trisomy 13 (Patau syndrome) and trisomy 18 (Edward syndrome).

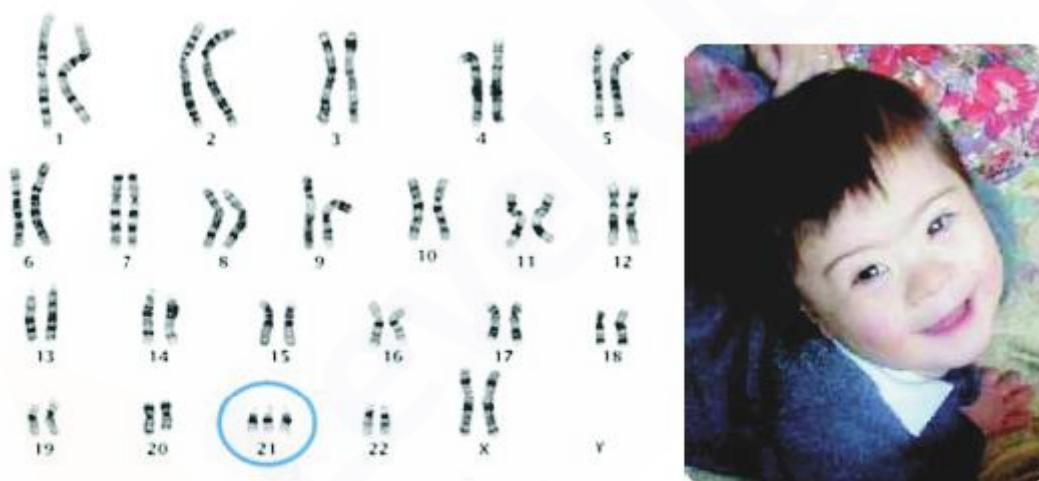
Down Syndrome

Down syndrome was one of the first reported chromosomal abnormalities in humans. It was described as Mongolian Idiocy by John Langdon Down in 1866. It wasn't until 1959 that it was shown to be caused by the presence of an extra chromosome 21, resulting in an increase of number of chromosomes to 47 (karyotype 47, XX / XY, +21). Thus, this disorder is also known as trisomy 21 or Down syndrome.

With an incidence of 1 in 800 live births, this is one of the common trisomies seen in humans. This incidence increases to 1 in 350 when the woman conceives beyond 35 years of age and to 1 in 25 when she conceives beyond 45 years.

There are many phenotypic manifestations that are typical in patients of this syndrome. However, as in other syndromes, not all affected individuals show all the symptoms. Any single individual usually expresses only a subset of the manifestations. Some of the most common are:

- i) Flat face, round head, and typical epicanthic fold of the eyes
- ii) Short, broad hands
- iii) Mental retardation
- iv) Hypotonia – poor muscle tone
- v) Short stature
- vi) Protruding furrowed tongue
- vii) Mild to moderate developmental disabilities
- viii) Typical dermatoglyphic patterns (palm and fingerprint patterns)



Karyotyping of the Down syndrome
www.hbml.org/news/media/981432.gif

The most common cause of this trisomy is the non-disjunction or the failure of separation of the chromosomes during meiotic division. Due to this one of the gametes undergoing fertilization contains two copies of chromosome 21 instead of the normal one copy (gametes are haploid containing one copy of each chromosome). This non disjunction can occur at either meiosis I or II. Chromosomal analysis has shown that 75% of the cases are due to nondisjunction occurring at meiosis I. When such a gamete is fertilized by a normal gamete, it results in trisomy 21.

Diagnosing Down's syndrome

During pregnancy

Pregnant women are offered screening for down's syndrome between 10 and 14 weeks of pregnancy to assess the chances of their baby having the condition.

This screening test is known as the combined test, and it also screens for Edward's syndrome and Patau's syndrome.

During the combined test you will have a blood test and a special ultrasound scan where the fluid at the back of the baby's neck (nuchal translucency) is measured.

If the combined test shows that you have a higher risk of having a baby with Down's syndrome, you will be offered a diagnostic test to find out for certain if your baby has the condition.

This involves analysing a sample of your baby's cells to check if they have an extra copy of chromosome 18.

There are two different ways of getting this sample of cells – **chorionic villus sampling**, which collects a sample from the placenta, **or amniocentesis**, which collects a sample of the amniotic fluid from around your baby.

After birth

If doctors believe a baby has Down's syndrome when it is born, they will take a blood sample from the baby. This will be examined to see if the baby's cells have extra copies of chromosome 21 by Karyotyping.

Living with Down's syndrome

Although there's no "cure" for Down's syndrome, there's support available to help children with the condition lead healthy, fulfilling lives.

This includes:

access to good healthcare – including a range of different specialists

support for your child's development – this may include speech and language therapy, physiotherapy, and home teaching

support groups – such as the Down's Syndrome Association, who can put you in touch with other families who have a child with Down's syndrome

Lots of people with Down's syndrome are able to leave home, have relationships, work, and lead largely independent lives.

Edwards Syndrome:

Edwards' syndrome, also known as trisomy 18, is a rare but serious genetic condition that causes a wide range of severe medical problems. Most babies with Edwards' syndrome will die before or shortly after being born. Some babies with less severe types of Edwards' syndrome, such as mosaic or partial trisomy 18, do survive beyond a year and, very rarely, into early adulthood. But they are likely to have severe physical and mental disabilities.

Cause of Edwards' syndrome: Each cell in your body normally contains 23 pairs of chromosomes, which carry the genes you inherit from your parents. But a baby with Edwards' syndrome has three copies of chromosome number 18, instead of two. The presence of this extra chromosome in cells severely disrupts normal development.

Edwards' syndrome is rarely inherited and is not caused by anything the parents have done. The development of three copies of chromosome 18 usually happens at random during the formation of either the egg or sperm.

As this happens randomly, it's extremely unlikely for parents to have more than one pregnancy affected by Edwards' syndrome. However, the chance of having a baby with Edwards' syndrome does increase as the mother gets older.

Mosaic trisomy 18

Mosaic trisomy 18 can be a less severe form of Edwards' syndrome, as only some of the cells have the extra copy of chromosome 18, rather than every cell.

How severely affected the baby is depends on the number of and type of cells that have the extra chromosome. Some babies may only be mildly affected, while some can be severely disabled.

Around seven in every 10 babies born with mosaic trisomy will live for at least a year and, in rare cases, may survive into early adulthood.

Partial trisomy 18

In partial trisomy 18 only a section of the additional chromosome 18 is present in the cells, rather than a whole additional chromosome 18.

This type of Edwards' syndrome is more likely if one the parents has a minor alteration in their chromosomes, so blood samples are often requested from both parents to check for this and to help them understand the risks for future pregnancies.

How severely affected the baby is will depend on which part of chromosome 18 is present in the cells.

Symptoms of Edwards' syndrome

Babies with Edwards' syndrome can have a wide range of different problems.

Physical signs of Edwards' syndrome include:

1. low birthweight
2. a small, abnormally shaped head
3. a small jaw and mouth
4. long fingers that overlap, with underdeveloped thumbs and clenched fists
5. low-set ears
6. smooth feet with rounded soles
7. a cleft lip and palate
8. an exomphalos (where the intestines are held in a sac outside the tummy)

Babies with Edwards' syndrome also typically have:

1. heart and kidney problems
2. feeding problems – leading to poor growth
3. breathing problems
4. hernias in the wall of their stomach (where internal tissues push through a weakness in the muscle wall)
5. bone abnormalities – such as a curved spine
6. frequent infections of the lungs and urinary system
7. a severe learning disability

Diagnosing Edwards' syndrome

During pregnancy

Pregnant women are offered screening for Edwards' syndrome between 10 and 14 weeks of pregnancy to assess the chances of their baby having the condition.

This screening test is known as the combined test, and it also screens for Down's syndrome and Patau's syndrome.

During the combined test you will have a blood test and a special ultrasound scan where the fluid at the back of the baby's neck (nuchal translucency) is measured.

If the combined test shows that you have a higher risk of having a baby with Edwards' syndrome, you will be offered a diagnostic test to find out for certain if your baby has the condition.

This involves analysing a sample of your baby's cells to check if they have an extra copy of chromosome 18.

There are two different ways of getting this sample of cells – **chorionic villus sampling**, which collects a sample from the placenta, **or amniocentesis**, which collects a sample of the amniotic fluid from around your baby.

After birth

If doctors believe a baby has Edwards' syndrome when it is born they will take a blood sample from the baby. This will be examined to see if the baby's cells have extra copies of chromosome 18.

Treating Edwards' syndrome

There is no cure for Edwards' syndrome and the symptoms can be very difficult to manage. You are likely to need help from a wide range of health professionals.

Treatment will focus on immediately life-threatening issues, such as infections and heart problems. Child may also need to be fed through a feeding tube, as feeding is often a problem.

Patau's syndrome

Patau's syndrome is a serious rare genetic disorder caused by having an additional copy of chromosome 13 in some or all of the body's cells. It's also called trisomy 13. Each cell normally contains 23 pairs of chromosomes, which carry the genes you inherit from your parents. But a baby with Patau's syndrome has 3 copies of chromosome 13, instead of 2. This severely disrupts normal development and, in many cases, results in miscarriage, stillbirth, or the baby dying shortly after birth.

Babies with Patau's syndrome grow slowly in the womb and have a low birth weight, along with a number of other serious medical problems. Patau's syndrome affects about 1 in every 5,000 births. The risk of having a baby with the syndrome increases with the mother's age. More than 9 out of 10 children (over 90%) born with Patau's syndrome die during the first year. About 5 to 10% of babies with less severe forms of the syndrome, such as partial or mosaic trisomy 13, live for more than a year.

Symptoms and features

Babies with Patau's syndrome can have a wide range of health problems.

1. Their growth in the womb is often restricted, resulting in a low birth weight, and 80% will be born with severe heart defects.
2. The brain often doesn't divide into 2 halves. This is known as holoprosencephaly.
3. When this happens it can affect facial features and cause defects, such as:
 4. cleft lip and palate
 5. an abnormally small eye or eyes (microphthalmia)
 6. absence of 1 or both eyes (anophthalmia)
 7. reduced distance between the eyes (hypotelorism)
 8. problems with the development of the nasal passages

Other abnormalities of the face and head include:

1. smaller than normal head size (microcephaly)

2. skin missing from the scalp (cutis aplasia)
3. ear malformations and deafness
4. raised, red birthmarks (capillary haemangiomas)

Patau's syndrome can also cause other problems, such as:

1. an abdominal wall defect where the abdomen doesn't develop fully in the womb, resulting in the intestines being outside the body, covered only by a membrane – this is known as an exomphalos or omphalocele
2. abnormal cysts in the kidneys
3. an abnormally small penis in boys
4. an enlarged clitoris in girls
5. There may also be abnormalities of the hands and feet, such as extra fingers or toes (polydactyly), and a rounded bottom to the feet, known as rocker-bottom feet

Screening for Patau's syndrome

Mother is offered a screening test for Patau's syndrome – as well as Down's syndrome (trisomy 21) and Edwards' syndrome (trisomy 18) – from 10 to 14 weeks of pregnancy. The test assesses her chances of having a baby with these syndromes.

The screening test offered at 10 to 14 weeks of pregnancy is called the combined test because it involves a blood test and an ultrasound scan.

If the screening tests show that she has a higher risk of having a baby with Patau's syndrome, she'll be offered a diagnostic test to find out for certain whether her baby has the syndrome.

This test will check her baby's chromosomes in a sample of cells taken from her.

Two techniques can be used to obtain the cell sample – **amniocentesis or chorionic villus sampling (CVS)**.

Autosomal Monosomies

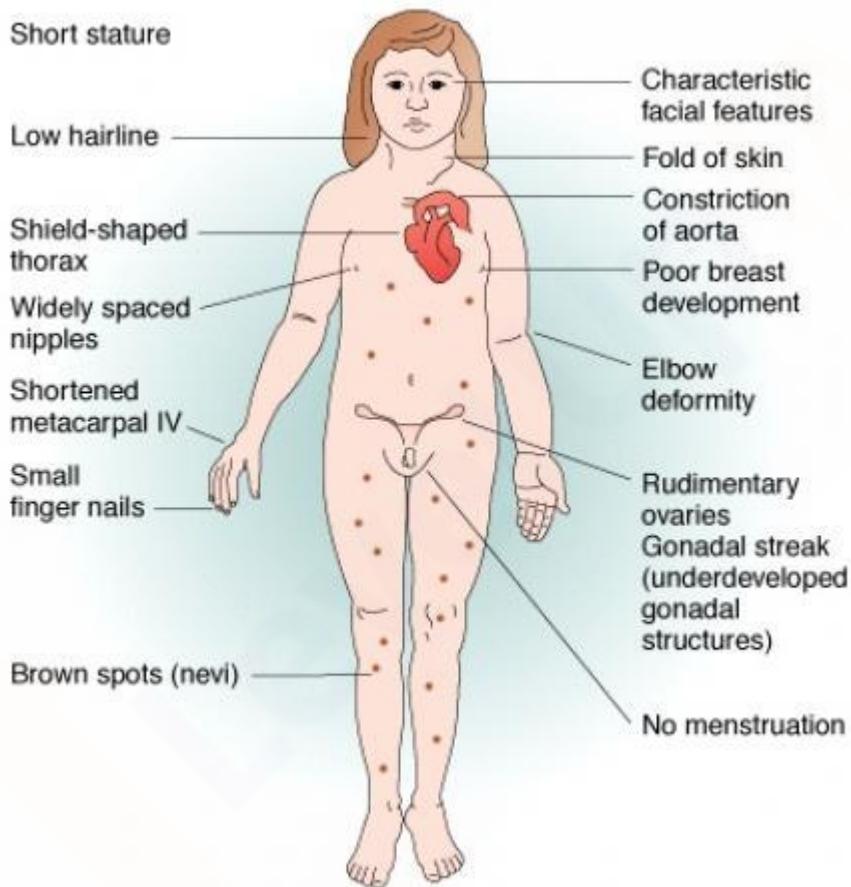
Autosomal monosomies have not been reported beyond birth in humans. Even the loss of the smallest chromosome is not compatible with life. Most known cases, therefore, are stillbirths and spontaneously aborted foetuses. It seems that loss of whole chromosomes causes too much genetic imbalance, which cannot support life.

Allosomal Aberrations

Changes in number of allosomes (X and Y chromosomes in humans) are termed allosomal aberrations. The gain or loss of these chromosomes alters the phenotype leading to syndromes. For example, the loss of one X chromosome in females leads to Turner syndrome (XO) and the excess of one X chromosome in males leads to Klinefelter syndrome (XXY). As mentioned earlier changes in allosomes cause changes in the primary and secondary sexual characters along with other manifestations.

Turner Syndrome

This syndrome is characterized by the partial or complete absence of one of the X chromosomes in females. This results in a reduction of the total number of chromosomes to 45 (karyotype – 45, X). Thus, this syndrome is also called Monosomy X. Its first description as a syndrome was by Henry Turner in 1938. Later, in 1954, the absence of Barr body (inactivated X-chromosome seen in buccal cells) and presence of only one X chromosome was noted. As we saw in Down syndrome, monosomy of X is not the only cause of this syndrome. Mosaicism, deletions and isochromosome have also been shown to cause this condition.



It is well known that, of the two X chromosomes in females, one is inactivated throughout her lifetime. If normal females have only one active X chromosome, then why should the loss of one X chromosome cause abnormal phenotype? The answer lies in the fact that although we speak of inactivated X chromosome, not all genes on that chromosome are being inactivated. There is a small subset of genes on the X chromosomes that are required to be expressed by both chromosomes for normal female development. Thus, individuals who lack one X chromosome fail to develop normal female character.

Some of the commonly seen manifestations of Turner syndrome are:

1. Primary hypogonadism – poor ovary development
2. Short stature
3. Minimal breast development

4. Broad shield-like chest with widely spaced nipples
5. Absence of menstrual periods
6. Absence of secondary sexual characteristics
7. Horseshoe-shaped kidney
8. Inability to produce gametes – sterility.

Girls with Turner syndrome also have distinctive features and associated health conditions, some of which may be apparent from birth.

They may be born with swollen hands and feet, caused by a build-up of excess fluid (lymphoedema) in the surrounding tissues, but this usually clears soon after birth.

Other features that may have developed in the womb include:

1. thick neck tissue
2. swelling of the neck (cystic hygroma)
3. being a small baby
4. heart conditions
5. kidney abnormalities

Growth

Babies with Turner syndrome may grow at a normal rate until they're 3 years old. After this, their growth slows down.

At puberty, usually between 8 and 14 years, a girl with Turner syndrome will not have the normal growth spurt, even with female oestrogen hormone replacement (HRT).

Girls with Turner syndrome are typically short in relation to the height of their parents. On average, adult women with untreated Turner syndrome are 20cm (8in) shorter than adult women without the syndrome. Treatment with additional high-dose growth hormone reduces this difference by about 5cm (about 2in) on average.

Ovaries

Ovaries are the pair of female reproductive organs that produce eggs and sex hormones. During puberty, a girl's ovaries usually begin to produce the sex hormones oestrogen and, once fully mature, progesterone. These trigger periods to begin.

Around 90% of girls with Turner syndrome don't produce enough of these sex hormones, which means:

1. they may not begin sexual development or fully develop breasts without female hormone replacement therapy (HRT)
2. they may begin sexual development but not complete it.
3. they may not start their monthly periods naturally.
4. it's likely they'll be unable to have a baby without assistance (infertile)

Even though many women with Turner syndrome have undeveloped ovaries and are infertile, their vagina and womb develop normally. This means they're able to have a normal sex life following treatment with female hormones.

Most girls need hormone replacement therapy (HRT) with oestrogen from around 10 to 12 years of age to begin breast development, and about 3 years later with added progesterone to bring on monthly periods.

A minority (10%) of girls with Turner syndrome experience some physical changes naturally during puberty, but only a very small number (1%) become pregnant naturally.

Associated conditions

Turner syndrome is often associated with a number of other health conditions, including:

heart murmur – where the heart makes a whooshing or swishing noise between beats; this is sometimes linked to a narrowing of the main blood vessel in the heart (the aorta) and high blood pressure

kidney and urinary tract problems – this can increase the risk of developing urinary tract infections (UTIs) and high blood pressure this occurs in around 10 to 30% of women with Turner syndrome; regular blood tests are needed to detect it early before it causes symptoms

Learning difficulties

Most girls with Turner syndrome have good language and reading skills. However, some have behavioural, social and specific learning difficulties.

Social intelligence

About a third of girls with Turner syndrome have problems understanding social relationships because of the way their brain develops. This can make it difficult to sustain friendships and leads to relationship problems in later life, both at home and at work.

Attention and hyperactivity problems

Typically, girls with Turner syndrome will go through a phase in childhood that involves:

1. physical overactivity, such as constant fidgeting and restlessness
2. acting impulsively, such as breaking rules or having no sense of danger
3. having a short attention span and being easily distracted
4. Attention and hyperactivity problems usually begin when the girl is a toddler but may not be serious problem until the girl starts school at 4 or 5. Girls with Turner syndrome may have difficulty settling in class.

The physical hyperactivity usually reduces around the time the girl starts secondary school at 11 years of age, although problems with inattention can last longer, into the teens.

Causes

A girl with Turner syndrome only has one normal X sex chromosome, rather than the usual two (XX). Everyone is born with 23 pairs of chromosomes. One pair of chromosomes, the sex chromosomes, determines the baby's gender. One sex chromosome comes from the father and one from the mother. The mother's contribution is always an X chromosome. The father's contribution can either be an X or a Y chromosome. A baby girl usually has two X chromosomes (XX), and boys have an X and a Y chromosome (XY). A female with Turner syndrome is missing part or all of one sex chromosome. This means she has just one complete X chromosome. The Y chromosome determines "maleness", so if it's missing, as in Turner syndrome, the sex of the child will invariably be female. This chromosome variation happens randomly when the baby is conceived in the womb.

Only **non disjunction of chromosomes during sperm or egg formation** can be a possible reason.

Diagnosis

Pregnancy and birth

1. Turner syndrome may be suspected in pregnancy during a routine **ultrasound scan** if, for example, heart or kidney abnormalities are detected. Lymphoedema, a condition that causes swelling in the body's tissues, can affect unborn babies with Turner syndrome, and may be visible on an ultrasound scan.
2. **Absence of Barr body** in females may indicate turner's syndrome.
3. Use of **amnioncentesis and chorionic villi sampling**.

Childhood

If a girl has the typical **characteristics and symptoms** of Turner syndrome, such as short stature, a webbed neck, a broad chest and widely spaced nipples, the syndrome may be suspected. It's often identified during early childhood, when a slow growth rate and other common features become noticeable. In some cases, a diagnosis isn't made until puberty when breasts don't develop or monthly periods don't start.

Treating Turner syndrome

There's no cure for Turner syndrome but many of the associated symptoms can be treated.

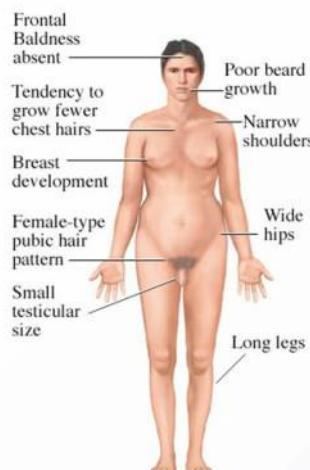
Girls and women with Turner syndrome will need to have their heart, kidneys and reproductive system checked regularly throughout their lives. However, it's usually possible to lead a relatively normal and healthy life.

Life expectancy is slightly reduced, but it can be improved with regular health checks to identify and treat potential problems at an early stage.

Klinefelter Syndrome

The presence of an additional X chromosome in males causes abnormal sexual development and is described as Klinefelter syndrome. This set of characteristics was first described by Harry Klinefelter in 1942. In 1959 it was shown to be due to the presence of an additional X chromosome in males by the presence of barr bodies in these males (normal males do not show barr body). The additional X chromosome results in an increase in the total number of chromosomes to 47 (karyotype 47, XXY). It has an overall incidence of 1 in 1000 live male births. While most patients show the XXY condition, individuals showing variations like XXXY or XXYY have also been reported.

Klinefelter syndrome



- Lower IQ than sibs
- Tall stature
- Poor muscle tone
- Reduced secondary sexual characteristics
- Gynaecomastia (male breasts)
- Small testes/infertility

The additional X chromosome arises due to non-disjunction during meiosis. Due to this, the gamete contains two X chromosomes rather than one. When such an egg containing XX is fertilized by sperm containing Y, an XXY zygote is formed that develops into a Klinefelter male. The extra X chromosome may be either of maternal or paternal origin, but it is more often to be of maternal origin. Individuals with this syndrome show hypogonadism and reduced fertility. These males do not develop masculine secondary sexual characteristics and show female type characteristics. Some of the clinical manifestations include:

1. Primary male hypogonadism
2. Reduced facial, body and pubic hair
3. Small and soft testes
4. Slight learning difficulties
5. Increased breast tissue – gynecomastia
6. Long limb bones and lanky body
7. Azoospermia – absence of sperm production leading to infertility

Health issues in Klinefelter syndrome

Most boys and men with Klinefelter syndrome will not be significantly affected and can live normal, healthy lives. Infertility tends to be the main problem, although there are treatments that can help.

But men with Klinefelter syndrome are at a slightly increased risk of developing other health problems, including: **type 2 diabetes, weak and fragile bones (osteoporosis) cardiovascular disease and blood clots, autoimmune disorders (where the immune system mistakenly attacks the body), such as lupus, an underactive thyroid gland (hypothyroidism), anxiety, learning difficulties and depression, male breast cancer – although this is very rare.**

These problems can usually be treated if they do occur and testosterone replacement therapy may help reduce the risk of some of them.

Causes

Klinefelter syndrome isn't directly inherited – the additional X chromosome occurs as a result of either the mother's egg or the father's sperm having the extra X chromosome (an equal chance of this happening in either), so after conception the chromosome pattern is XXY rather than XY. But the risk of a woman having a son with Klinefelter syndrome may be slightly higher if the mother is over 35 years of age.

Diagnosis

1. **Ultrasound scan during pregnancy**
2. **Amnioncentesis and chorionic villi sampling**
3. **Presence of a barr body in male karyotype**

Treatments for Klinefelter syndrome

There's no cure for Klinefelter syndrome, but some of the problems associated with the condition can be treated if necessary.

Possible treatments include:

testosterone replacement therapy

speech and language therapy during childhood to help with speech development

educational and behavioural support at school to help with any learning difficulties or behaviour problems

physiotherapy to help build muscle and increase strength

psychological support for any mental health issues

fertility treatment – options include artificial insemination using donor sperm or possibly intra-cytoplasmic sperm injection (ICSI), where sperm removed during a small operation are used to fertilise an egg in a laboratory

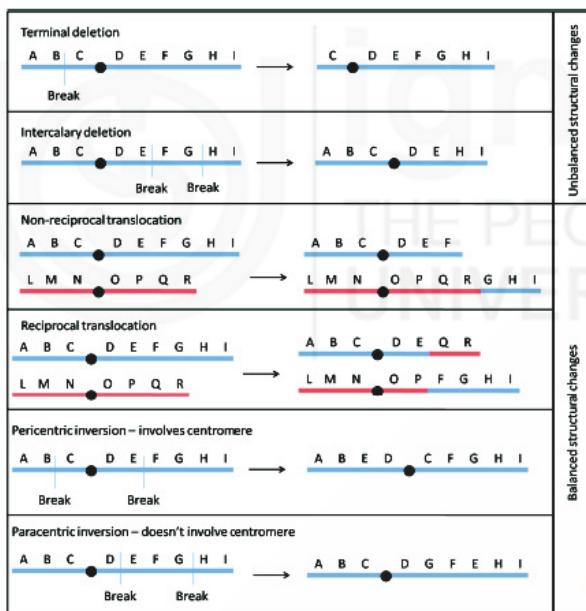
breast reduction surgery to remove excess breast tissue

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

2) Structural Aberrations

Structural aberrations are those that involve a change in the chromosome structure. These include deletions, duplications and rearrangements (inversions and translocations). Structural changes occur when chromosomes break and later rejoin in combinations that are different from the original. When there is a **net loss or gain or chromosomal segments**, the change is called an **unbalanced structural change**. When there is **no net loss or gain of chromosomal segments, instead there is only a rearrangement; it is called a balanced structural change**. Thus, balanced changes usually do not show any abnormal phenotypes, which unbalanced changes do. You should keep in mind that these changes are not mutations in genes; they only cause the number and order of genes to be changed.



Balanced and unbalanced structural changes in chromosomes

a) Deletions

A deletion refers to the loss of a segment of a chromosome. This leads to the loss of the genes present in the missing region. A single break in the chromosome leads to the loss of the terminal segment and is called terminal deletion. Intercalary deletion, however, involves two breaks in the chromosome, loss of the segment, and rejoining of the two chromosomal parts. Very large deletions are usually lethal because the monosomic condition of the large number of genes of the missing fragment reaches the level of genetic imbalance that cannot sustain life. Usually any deletion resulting in loss of more than 2% of the genome has a lethal outcome.

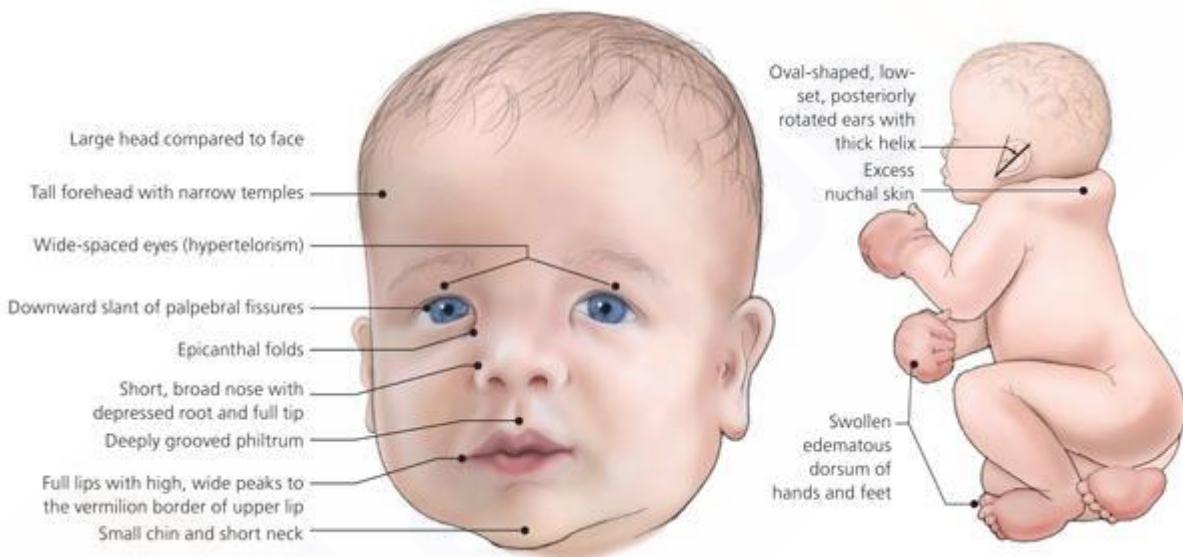
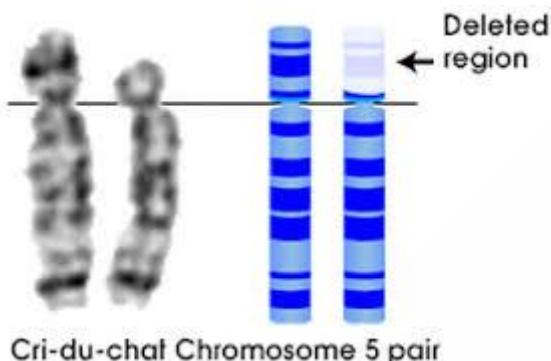
Cri-du-chat Syndrome

This syndrome results from a deletion on the short arm of chromosome 5. It is also known by other names such as 5p deletion syndrome and Lejeune's syndrome. The disorder gets its name from the characteristic cat-like cry of affected infants.

Described first by Jérôme Lejeune in 1963, this disorder has an incidence of 1 in 25,000 live births. This disorder, being autosomal, should affect males and females in equal frequencies; but incidence is seen to be more in females by a ratio of 4:3 of females: males affected.

The deletion occurring on the short (p arm) arm of chromosome 5 varies in different affected individuals. The phenotypic effects are also shown to vary between individuals. Most cases show deletion of 30 to 60% of the terminal region of the short arm. Studies show that larger deletions tend to result in more severe intellectual disability and developmental delay than smaller deletions. Figure below shows the chromosome 5 pair from a karyotype of an individual with this syndrome. You can see that one of the chromosomes (left) has the normal length of the short arm while the other (right) has significantly reduced short arm. More

specifically, a dark band is prominently seen in the normal chromosome, which is missing in the deletion chromosome.



Characteristics

Affected individuals characteristically show a distinctive, high-pitched, catlike cry in infancy with growth failure, microcephaly, facial abnormalities, and mental retardation throughout life. Some common clinical manifestations are:

1. Cry that is high-pitched and sounds like a cat
2. Downward slant to the eyes
3. Low birth weight and slow growth
4. Low-set or abnormally shaped ears
5. Mental retardation (intellectual disability)
6. Partial webbing or fusing of fingers or toes
7. Slow or incomplete development of motor skills
8. Small head (microcephaly)
9. Small jaw (micrognathia)

10. Wide-set eyes

Causes

Cri-du-chat syndrome is caused by a deletion of the end of the short (p) arm of chromosome 5. This chromosomal change is written as 5p-. The size of the deletion varies among affected individuals; studies suggest that larger deletions tend to result in more severe intellectual disability and developmental delay than smaller deletions.

The signs and symptoms of cri-du-chat syndrome are probably related to the loss of multiple genes on the short arm of chromosome 5. Researchers believe that the loss of a specific gene, CTNND2, is associated with severe intellectual disability in some people with this condition. They are working to determine how the loss of other genes in this region contributes to the characteristic features of cri-du-chat syndrome.

There is a 10-15% chance that the syndrome is inherited from a parent. A parent, should be offered a genetic test to see if he or she is a carrier. This means that if he or she has the missing piece of the fifth chromosome, but not in the right place; a translocation.

Diagnosis

CdCS is usually diagnosed within the first few days of birth, though for some babies this takes longer. The syndrome is diagnosed by looking at the combination of symptoms, physical examination by a specialist, and finally by genetic testing.

Diagnosis can sometimes happen before birth with a genetic test (via an amniocentesis or CVS test), though there are few known signs that would indicate that a pre-birth test is needed.

b) Duplications

Part of a chromosome is duplicate. A particular kind of mutation involving the production of one or more copies of any piece of DNA, including sometimes a gene or even an entire chromosome. A duplication is the opposite of a deletion. Duplications have been important in the evolution of the human genome (and the genomes of many other organisms). Duplications typically arise from an event termed unequal crossing-over (recombination) that occurs between misaligned homologous chromosomes during meiosis (germ cell formation). The chance of this event happening is a function of the degree of sharing of repetitive elements between two chromosomes. The recombination products of such an event are a duplication at the site of the exchange and a reciprocal deletion.

Charcot–Marie–Tooth (CMT) Disorder

This disorder results from duplication in the short arm of chromosome 17 in the region 17p12. It is a hereditary motor and sensory neuropathy that affects the nerve cells of the individual. Affected individuals typically show loss of touch sensation and muscle tissue.

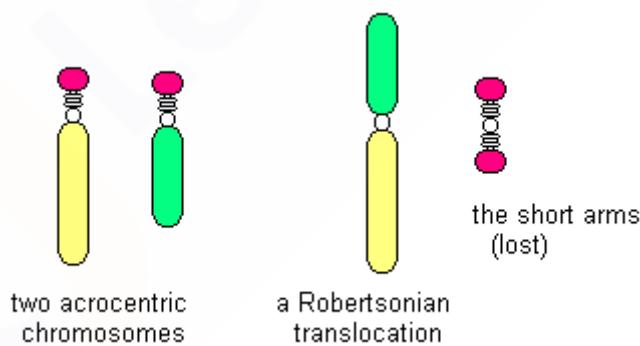
- Weak feet and lower leg muscles
- Foot deformities (eg: high arch)
- Difficulty with fine motor skills due to muscle atrophy
- Mild to severe pain as age progresses
- May lead to respiratory muscle weakness

c) Translocation

In genetics, a chromosome translocation is a chromosome abnormality caused by rearrangement of parts between non-homologous chromosomes. A gene fusion may be created when the translocation joins two otherwise-separated genes. It is detected on cytogenetics or a karyotype of affected cells. Translocations can be balanced (in an even exchange of material with no genetic information extra or missing, and ideally full functionality) or unbalanced (where the exchange of chromosome material is unequal resulting in extra or missing genes)

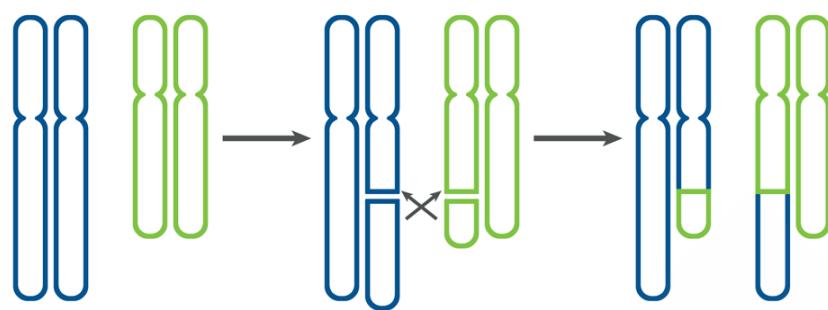
Robertsonian translocations

Robertsonian translocations result in the loss of small parts of the chromosomes involved. The fusion of two acrocentric chromosomes with the subsequent loss of the two short arms is termed Robertsonian translocation or centric fusion. One of the commonly seen such translocation is between chromosome 14 and 21, that gives rise to individuals showing characteristics of Down syndrome. Since this translocation is functionally a balanced translocation, individuals with this aberration usually do not show any abnormal phenotype. Their effects are only seen in the next generation due to production of abnormal gametes.



Reciprocal Translocation

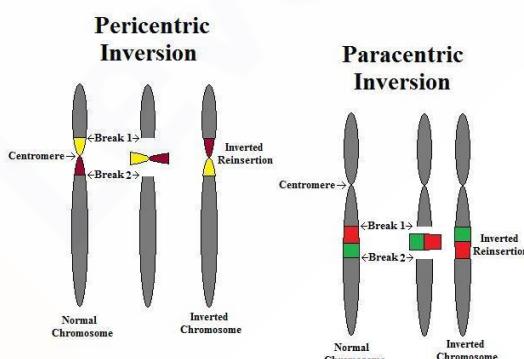
Reciprocal translocation involves breaks in two chromosomes and the subsequent exchange of segments between the two chromosomes. Reciprocal translocation do not change the number of chromosomes. However, they may change the size and type of chromosome if the segments being exchanges are differing in size. For reasons not yet clear, reciprocal translocations involving chromosomes 11 and 22 are fairly common in the population.



d) Inversions

An inversion is a condition wherein a segment of a chromosome is inverted. This is caused by two breaks in the chromosome and the subsequent rejoining in a reverse manner. This changes the order of genes on that chromosome and does not cause any changes in the chromosome number. Depending on the involvement of the centromere, inversion are of two types – pericentric and paracentric.

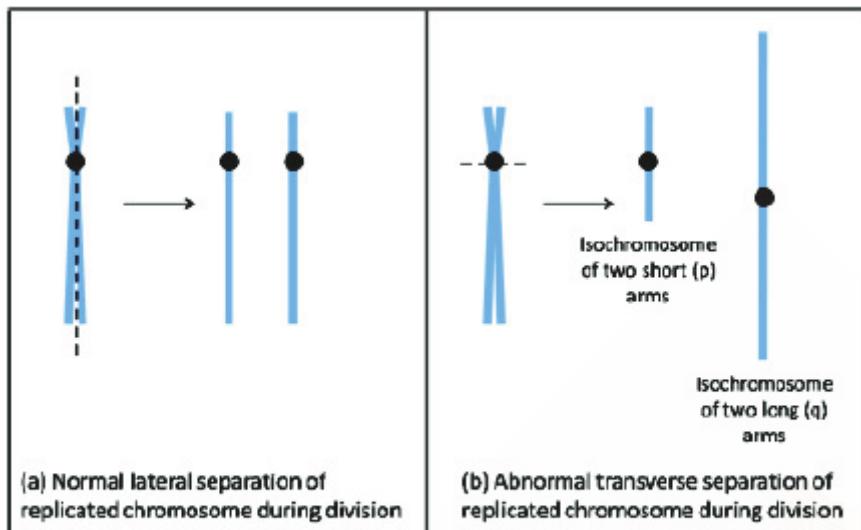
- **Pericentric inversions** occur when the inverted segment that includes the centromere. The product after inversion can differ significantly in the arm length and thus change the type of chromosome
- **Paracentric inversions** occur when the inverted segment does not include the centromere. The product after inversion remains the same type as the original except for a change in the order of genes.



Isochromosomes and Ring chromosomes

Isochromosomes

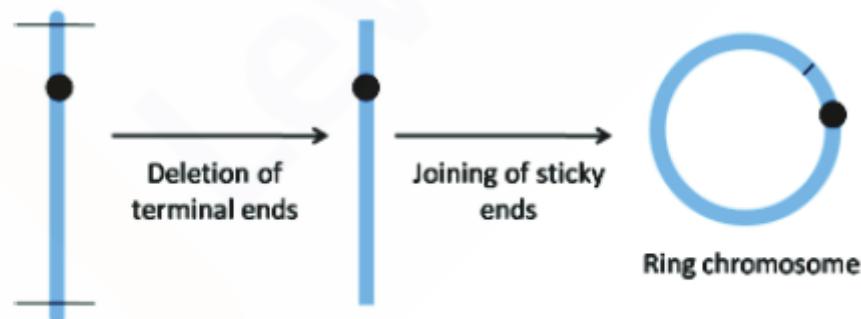
An isochromosome is an abnormal chromosome with two identical arms – either having two short (p) arms or two long (q) arms. An isochromosome, thus, has an entire arm deleted along with the duplication of the other arm. This type of aberration is caused due to the transverse separation of the centromere during cell division instead of the normal lateral separation



Origin of isochromosome by transverse separation of centromere

Ring chromosomes

Ring chromosomes are formed when a chromosome loses its telomere regions and joins back on itself end-to-end. Breaks at the terminal regions cause the chromosome to have “sticky ends” because of loss of telomere region. These end, thus, join with each other causing the chromosome to become circular or ‘ring-like’. Since the two terminal fragments are lost, loss of genes in those regions can have an effect on the phenotype. If these regions have important genes, their consequences can be serious abnormality in the phenotype.



Formation of a ring chromosome

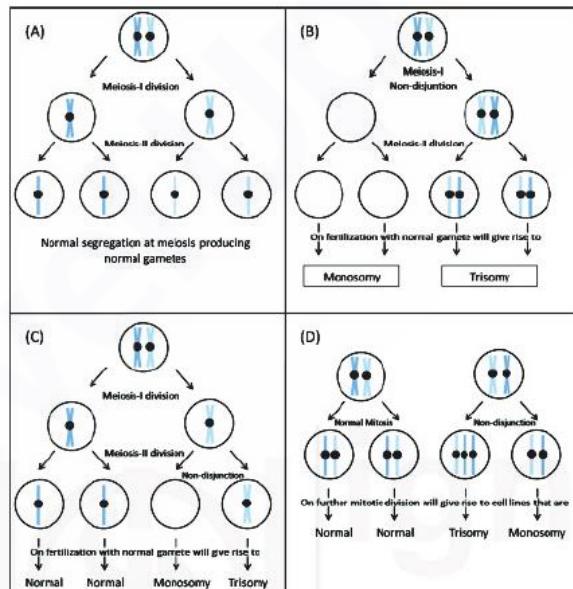
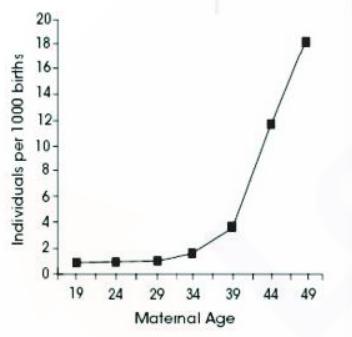
Non-disjunction

Non-disjunction is the failure of separation of the chromosomes during mitosis or meiosis. Normal division involves the separation of the two arms (mitosis and meiosis-II) of the chromosomes or separation of the two chromosomes (meiosis-I) during the anaphase

stage. This ensures that one copy of each is moved to each pole and consequently each daughter cell receives one copy. When this separation fails, both copies will move to one pole. Hence, one of the daughter cells will now have two copies while the other has no copies of that chromosome. Simply put, this is the basis of aneuploidy changes where there is one extra copy present or one copy missing in the cells.

The occurrence of non-disjunction is itself dependent on many factors. Some of these factors are:

- Advanced maternal age has been well correlated with an increase in the chances of non-disjunction. This is well illustrated in the fact that incidence of Down syndrome increases drastically as the maternal age increases. Increase in the time between ovulation and fertilization is well documented in animals to increase the rate of non-disjunction.
- Exposure to mutagens in general increases the chances of non-disjunction. Especially those who are constantly exposed to radiations have a high risk of non-disjunction.

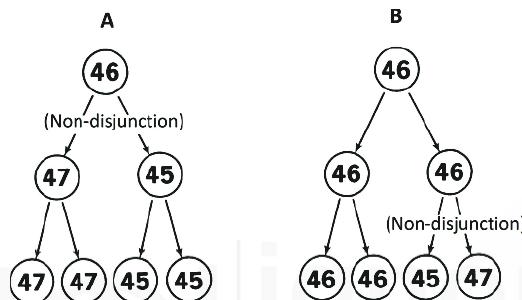


MOSAICISM

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. 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.



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.

Bio-Chemical Methods

Biochemistry is carried out at the cellular or subcellular level, generally on cell extracts. Biochemical methods are applied to the main chemical compounds of genetics—notably DNA, RNA, and protein. Biochemical techniques are used to determine the activities of genes within cells and to analyse substrates and products of gene-controlled reactions. In one approach, cells are ground up and the substituent chemicals are fractionated for further analysis. Special techniques (e.g., chromatography and electrophoresis) are used to separate the components of proteins so that inherited differences in their structures can be revealed.

For example, more than 100 different kinds of human haemoglobin molecules have been identified. Radioactively tagged compounds are valuable in studying the biochemistry of whole cells. For example, thymine is a compound found only in DNA; if radioactive thymine is placed in a tissue-culture medium in which cells are growing, genes use it to duplicate themselves. When cells containing radioactive thymine are analysed, the results show that, during duplication, the DNA molecule splits in half, and each half synthesizes its missing components.

Chemical tests are used to distinguish certain inherited conditions of humans; e.g. urinalysis and blood analysis reveal the presence of certain inherited abnormalities—phenylketonuria (PKU), cystinuria, alkaptonuria, gout, and galactosemia. Genomics has provided a battery of diagnostic tests that can be carried out on an individual's DNA. Some of these tests can be applied to foetuses in utero.

Many of the biochemical human traits are called Genetic markers like haptoglobin, ABO blood group, HLA complex, transferrin, G6PD etc. (to be studied in unit 9.6)

Electrophoresis is a technique commonly used in the lab to separate charged molecules, like DNA, according to size.

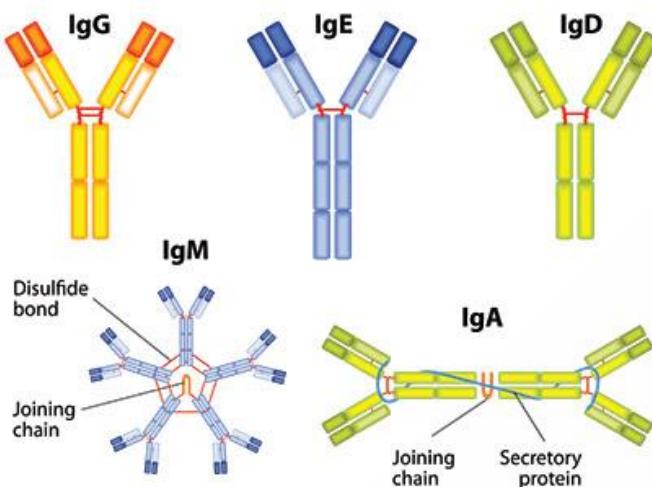
- Gel electrophoresis is a technique commonly used in laboratories to separate charged molecules like DNA, RNA and proteins according to their size.
- Charged molecules move through a gel when an electric current is passed across it.
- An electric current is applied across the gel so that one end of the gel has a positive charge and the other end has a negative charge.
- The movement of charged molecules is called migration. Molecules migrate towards the opposite charge. A molecule with a negative charge will therefore be pulled towards the positive end (opposites attract!).
- The gel consists of a permeable matrix, a bit like a sieve, through which molecules can travel when an electric current is passed across it.
- Smaller molecules migrate through the gel more quickly and therefore travel further than larger fragments that migrate more slowly and therefore will travel a shorter distance. As a result the molecules are separated by size.

Immunological Methods

The abilities of our bodies and cells to resist invasion by foreign objects is subject of interest of immunology. Like all life processes, the basis for immune reactions can be traced to gene action. Because of the profound influence of molecular genetics on biology an area of genetics known as immunogenetics has developed. We know that immune reactions are the result of complex gene regulation in our WBCs. It deals with the structure, function and cellular control of immunoglobulins, immune responsiveness, histocompatibility etc or simply the study of antigen and antibody and their reactions.

Basically an immune reaction involves the 2 factors, an outside agent that is unacceptable to the special cells of the body involved in immune reactions and the body factor that responds to this invader. The foreign factor are called antigens. Response of body leads to production of special proteins called antibodies. Cells respond differently to every antigen by producing different antibody. The variation in the antibody are made use of in immunological methods.

Antibodies also known as immunoglobulin is a large Y-shaped protein, produced by plasma cells. Tip of Y contains paratope (lock) that is specific for one particular epitope(key) of an antigen. They 2 bind together with precision. 5 main class antibody are IgA, Ig D, Ig E, Ig G, Ig M). They are made of 2 heavy chain proteins and 2 light chain protein. Knowledge about the bio-synthesis and structure of these antibodies is important for their detection and use both as diagnostic and therapeutic tools.



Many substances are antigenic; i.e. when introduced into a vertebrate body, they stimulate the production of specific proteins called antibodies. Various antigen exist in RBCs, including those that make up the major blood groups of man. These and other antigens are genetically determined; their study constitutes immunogenetics. Blood antigen of man include inherited variations and the particular combination of antigens in an individual is almost as unique as fingerprints and has been used in such areas as paternity testing.

Immunological techniques are used in blood group determinations, in blood transfusions, in organ transplants and in determining rhesus incompatibility in child birth. Specific Antigens of the Human Leucocyte Antigens(HLA) genes are correlated with human diseases and disease predisposition. Antibodies also have a genetic basis, and their seemingly endless ability to match any antigen presents is based on special types of DNA shuffling processes between antibody genes.

DNA technologies/Recombinant DNA Technology

Recombinant DNA technique involves the generation of DNA fragments using restriction endonucleases, the incorporation of these fragments into a suitable vector, the introduction of the vector into a host of organism (usually E.coli) and subsequent selection of clones containing specific DNA sequence.

The technique has been used for analysing Gene structure, diagnosis of genetic disorders of both adults and foetus and various therapeutic purposes.

Analysis of Gene Structure:

The technique has enabled us to learn a great deal about human genes, particularly the Beta-Globin gene region. By arranging the fragments generated by various restriction enzymes, it

has been possible to know the genes and their arrangement in this region. There are in total 7 genes in this regions. For example, using this technique it has been possible to know that beta globin genes are localises near centromere of short arm of chromosome 11.

The HBB gene provides instructions for making a protein called beta-globin. Beta-globin is a component (subunit) of a larger protein called haemoglobin, which is located inside red blood cells. In adults, haemoglobin normally consists of four protein subunits: two subunits of beta-globin and two subunits of another protein called alpha-globin, which is produced from another gene called *HBA*.

DNA probes are important means of study in recombinant DNA technique. For example, if you know structure of protein or mRNA, DNA can be synthesized which is radioactively labelled as ^{32}P . this DNA probe can be used to locate similar DNA in the genome of any organism. The DNA probe will hybridize with similar sequence and its radioactivity can signal its presence. DNA probes have many Functions.

- a) They can identify mutation or change in any gene by not perfectly hybridizing with it.
- b) such probes have been used in DNA fingerprinting.

Restriction Fragment Length Polymorphism (RFLP)

RFLP has been used in study of genetic variation in man. Since different individuals differ in DNA bases every 200 base pairs, it follows that different length of DNA fragments will be produced if cleaved by same restriction Endonuclease. It is referred to as RFLP. This can be recognised by the altered mobility of DNA fragments in electric fields, such as gel electrophoresis where rate of migration in gel depends on their sizes. It can be used in identification of individuals while solving a criminal case.

Variable Number Tandem Repeat (VNTR)

This is also known as hypervariable region in which a core sequence of 10- 15 base pairs is repeated. Such hypervariable regions are distributed throughout the genome, its number and distribution varying in different individuals. Like other genes, VNTR is also inherited in Mendelian Fashion; hence progeny tends to inherit a particular from their parents.

Protein Synthesis (generation of Interferons)

the transfer of DNA fragment of interest from an organism to a self replicating genetic element such as bacterial plasmid. We take for example, the gene for insulin production in humans and paste it into the plasmid DNA of *E.coli* bacterium that inhabits the human digestive tract. The bacterial cells divide very rapidly making billions of copies themselves and each bacterium carries in its DNA a replica of the gene for insulin production.

DNA PROFILING/DNA FINGERPRINTING

DNA profiling (also called **DNA fingerprinting**) is the process of determining an individual's DNA characteristics, which are as unique as fingerprints. DNA analysis intended to identify a species, rather than an individual, is called DNA barcoding.

DNA profiling is a forensic technique in criminal investigations, comparing criminal suspects' profiles to DNA evidence so as to assess the likelihood of their involvement in the crime. It is also used in parentage testing, to establish immigration eligibility, and in genealogical and medical research. DNA profiling has also been used in the study of animal and plant populations in the fields of zoology, botany, and agriculture.

The technique was developed in 1984 by British geneticist Alec Jeffreys, after he noticed that certain sequences of highly variable DNA (known as mini satellites), which do not contribute to function of genes are repeated with genes. Jeffreys recognised that each individual has a unique pattern of minisatellites.

The procedure for creating DNA fingerprinting consist of first obtaining a sample of cells which contain DNA. The DNA is extracted from the cells and purified. In Jeffrey's original approach, based RFLP technology, DNA was cut at specific points along the strands with protein known as restriction enzymes. The enzymes produced fragments of varying lengths that were sorted by placing them on a gel and then subjecting the gel to electric current (**ELECTROPHORESIS**). the shorter the fragment, the more quickly it moved toward (+)ve pole(anode). The sorted double stranded DNA fragments were then **subjected to a blotting technique** in which they were split into single strands and transferred to a nylon sheet. The fragments underwent autoradiography in which they were exposed to several DNA probes (pieces of synthetic DNA that were made radioactive and that bound to the minisatellites). A piece of X-ray film was then exposed to the fragments, and a dark mark was produced at any point where a radioactive probe had attached. The resultant pattern of probe could then be analysed.

The assay developed by Jeffreys has been supplanted by approaches that are based on use of PCR and so called microsatellites (short tandem repeat). PCR amplifies the desired fragment of DNA many times over, creating thousands of copies of the fragment. Once an adequate amount of DNA has been produced with PCR, the exact sequence of nucleotide pairs in a segment of DNA can be determined by using various DNA sequencing methods.

Some concerns about DNA fingerprint are sample contamination, Faulty preparation on procedures and erroneous interpretation of results. In addition, RFLP required large amount of high quality DNA.

Polymerase Chain Reaction (PCR)

The polymerase chain reaction (PCR) was originally developed in 1983 by the American biochemist Kary Mullis. He was awarded the Nobel Prize in Chemistry in 1993 for his pioneering work.

PCR is used in molecular biology to make many copies of (amplify) small sections of DNA or a gene.

Using PCR it is possible to generate thousands to millions of copies of a particular section of DNA from a very small amount of DNA.

PCR is a common tool used in medical and biological research labs. It is used in the early stages of processing DNA for sequencing, for detecting the presence or absence of a gene to help identify pathogens during infection, and when generating forensic DNA profiles from tiny samples of DNA.

How does PCR work?

The principles behind every PCR, whatever the sample of DNA, are the same.

Five core 'ingredients' are required to set up a PCR. These are:

- i) the DNA template to be copied
- ii) primers, short stretches of DNA that initiate the PCR reaction, designed to bind to either side of the section of DNA you want to copy
- iii) DNA nucleotide bases (also known as dNTPs). DNA bases (A, C, G and T) are the building blocks of DNA and are needed to construct the new strand of DNA
- iv) Taq polymerase enzyme to add in the new DNA bases
- v) buffer to ensure the right conditions for the reaction.

PCR involves a process of heating and cooling called thermal cycling which is carried out by machine.

There are three main stages:

Denaturing – when the double-stranded template DNA is heated to separate it into two single strands.

Annealing – when the temperature is lowered to enable the DNA primers to attach to the template DNA.

Extending – when the temperature is raised and the new strand of DNA is made by the Taq polymerase enzyme.

These three stages are repeated 20-40 times, doubling the number of DNA copies each time.

A complete PCR reaction can be performed in a few hours, or even less than an hour with certain high-speed machines.

After PCR has been completed, a method called electrophoresis can be used to check the quantity and size of the DNA fragments produced.

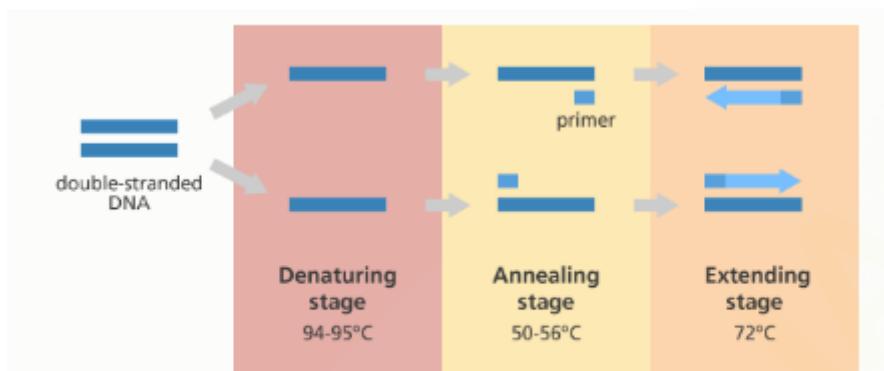


Illustration showing the main steps in the polymerase chain reaction (PCR).

Image credit: Genome Research Limited

The versatility of the PCR technique finds its application in archaeology, medicine, forensics besides evolutionary studies, gene mapping, and mutagenesis in molecular biology laboratories. Knowledge and understanding of properties of DNA molecule (such as complementary base pairing, its synthesis), availability of primers and the discovery of polymerases laid the foundation for invention of the technique in 1980s by Kary Mullis and his co-workers. Initially done manually by maintaining the heating and cooling cycles, now automated thermal cyclers are available.

DNA Fingerprinting can be used for

- Evaluating genetic relationships
- Reconstruction of evolutionary history (Phylogenetic) or population history
- Dating evolutionary history
- Detecting selection
- Assessing geographical variation
- Criminal investigation
- Medical research

DNA Barcoding

The taxonomic system we use to identify and name species dates back nearly 300 years. The pioneer taxonomists such as Ray and Linnaeus (see Chapter 2) invented this system with no knowledge about evolution or the mechanisms of genetics. Today, we know a considerable amount about these areas, and some biologists argue that we could make better use of this knowledge as we try to organize and understand the world's biodiversity.

One proposal to modernize taxonomy involves something known as *DNA barcoding* (see the website for the Consortium for the Barcode of Life, (<http://www.barcodeoflife.org>)).

Unlike the grocery store, where barcodes are arbitrarily assigned to different items, in DNA barcoding, the source of the identifying code is an intrinsic part of the organism's genome. DNA barcoding is based on the premise that, because genetic variation between species exceeds that within species, it should be possible to identify species based on a short, standardized sequence of the genome (Hajibabaei et al., 2007). For animals, the most commonly used genetic sequence is a 650-base pair fragment found at one end of the mitochondrial gene

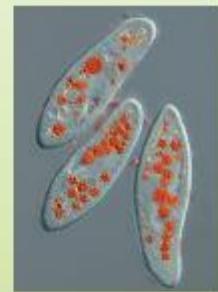
cytochrome oxidase I. What are the advantages of using something like DNA barcoding? There are tens of millions of eukaryotic species in the world, the vast majority of which are unidentified (Waugh, 2007). With a standardized, easily reproducible system of biologically meaningful identification, the first step toward understanding species would be significantly streamlined. Naturally enough, critical taxonomic features vary widely among divergent groups of animals. The DNA barcode system provides a common basis for species identification.

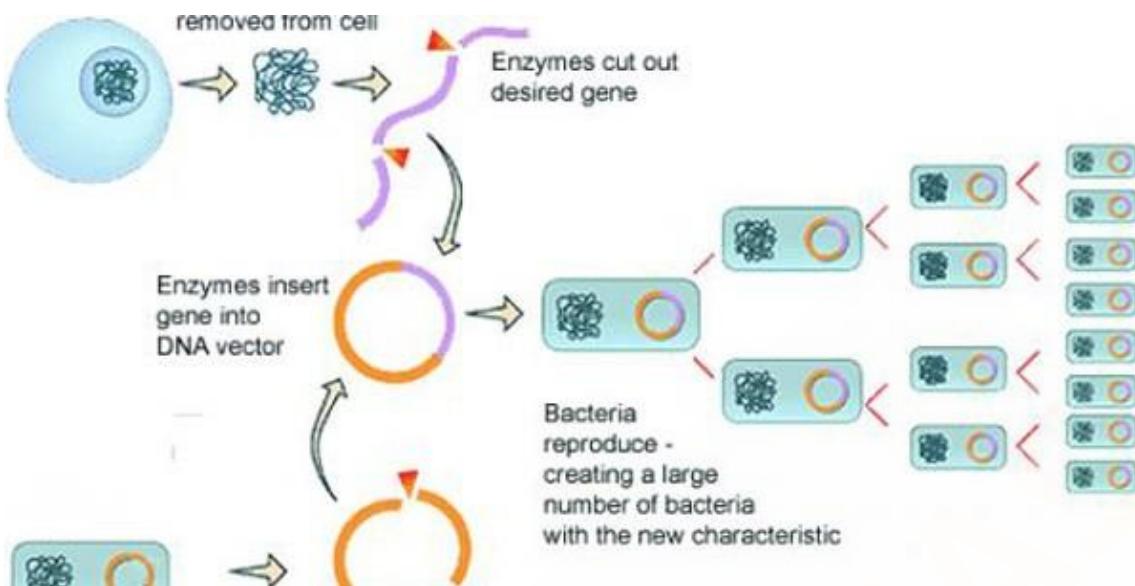


It is easy to see where DNA barcoding would be of great value in the identification of insect and microorganismal species (Hajibabaei et al., 2007). The vast majority of these species have yet to be identified, and they are easier to collect than to analyze. Identifying these species is not just a matter of "stamp collecting,"

however. Understanding species diversity at the microbiotic level is essential for understanding entire ecosystems and how they may be changing in the face of human activity. The taxonomy of larger animals may also benefit from the barcode approach. Indeed, it is only within the last 10 years that molecular evidence has been found to support the claim that there are two distinct species of African elephant (Roca et al., 2005). DNA barcoding may be useful in identifying similar issues in other groups of large animals. Within primates, understanding species diversity within genera such as *Papio* (baboons) and *Macaca* (macaques) is complicated by the existence of hybrids between different species and the maintenance of widely dispersed and isolated populations belonging to a single species. DNA barcoding also provides an efficient means to investigate species designations in extinct animals known only from scrappy remains. This has already been applied to the many recently extinct species of flightless birds in New Zealand (Waugh, 2007), and could be useful in studying the sub/fossil lemurs of Madagascar (Orlando et al., 2008).

DNA barcoding has several shortcomings. There is no independent way of determining how much DNA change is "enough" to identify a new species; a variety of genetic segments will likely have to be used if all life forms are going to be barcoded. Some critics worry that barcoding conveys an impression of species as fixed and static entities with some essential single quality. But the advocates of DNA barcoding make it clear that it is a taxonomic tool and not a replacement for classic taxonomy. It is meant to be used in conjunction with knowledge about anatomy, behavior, and physiology. DNA barcoding is just one of the many ways that the ready availability of DNA sequencing technology is changing the biological sciences.





CRISPR CAS9

CRISPR-Cas9 is a genome editing tool that is creating a buzz in the science world. It is faster, cheaper and more accurate than previous techniques of editing DNA and has a wide range of potential applications.

CRISPR-Cas9 is a unique technology that enables geneticists and medical researchers to edit parts of the genome by removing, adding or altering sections of the DNA sequence.

It is currently the simplest, most versatile and precise method of genetic manipulation and is therefore causing a buzz in the science world.

How does it work?

The CRISPR-Cas9 system consists of two key molecules that introduce a change (mutation) into the DNA. These are:

- an enzyme called Cas9. This acts as a pair of 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome so that bits of DNA can then be added or removed.

- a piece of RNA called guide RNA (gRNA). This consists of a small piece of pre-designed RNA sequence (about 20 bases long) located within a longer RNA scaffold. The scaffold part binds to DNA and the pre-designed sequence 'guides' Cas9 to the right part of the genome. This makes sure that the Cas9 enzyme cuts at the right point in the genome.

The guide RNA is designed to find and bind to a specific sequence in the DNA. The guide RNA has RNA bases that are complementary to those of the target DNA sequence in the genome. This means that the guide RNA will only bind to the target sequence and no other regions of the genome.

The Cas9 follows the guide RNA to the same location in the DNA sequence and makes a cut across both strands of the DNA.

At this stage the cell recognises that the DNA is damaged and tries to repair it.

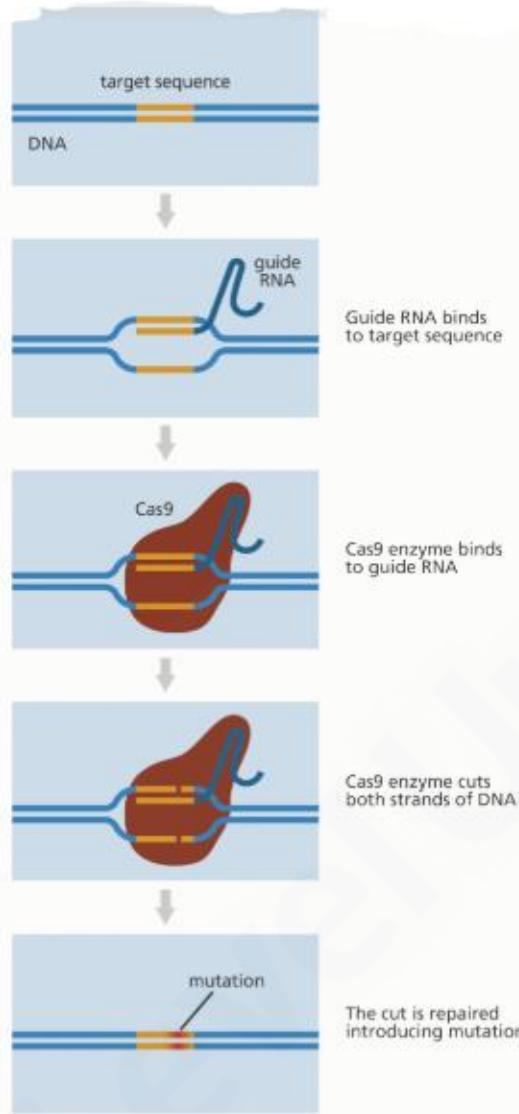
Scientists can use the DNA repair machinery to introduce changes to one or more genes in the genome of a cell of interest.

How was it developed?

Some bacteria have a similar, built-in, gene editing system to the CRISPR-Cas9 system that they use to respond to invading pathogens like viruses, much like an immune system.

Using CRISPR the bacteria snip out parts of the virus DNA and keep a bit of it behind to help them recognise and defend against the virus next time it attacks.

Scientists adapted this system so that it could be used in other cells from animals, including mice and humans.



LETHAL GENES

For the alleles that Mendel studied, it was equally possible to get homozygous dominant, homozygous recessive, and heterozygous genotypes. That is, none of these genotypes affected the survival of the pea plants. However, this is not the case for all genes and all alleles.

Many genes in an organism's genome are needed for survival. If an allele makes one of these genes non-functional, or causes it to take on an abnormal, harmful activity, it may be impossible to get a living organism with a homozygous (or, in some cases, even a heterozygous) genotype.

Lethal alleles (also referred to as lethal genes or lethals) are alleles that cause the death of the organism that carries them. They are usually a result of mutations in genes that are

essential to growth or development. Lethal alleles may be recessive, dominant, or conditional depending on the gene or genes involved. Lethal alleles can cause death of an organism prenatally or any time after birth, though they commonly manifest early in development.

Lethal alleles were first discovered by **Lucien Cuénot** in 1905 while studying the inheritance of coat colour in mice. The agouti gene in mice is largely responsible for determining coat colour. The wild-type allele produces a blend of yellow and black pigmentation in each hair of the mouse. This yellow and black blend may be referred to as 'agouti' in colour. One of the mutant alleles of the agouti gene results in mice with a much lighter, yellowish colour. When these yellow mice were crossed with homozygous wild-type mice, a 1:1 ratio of yellow and dark grey offspring were obtained. This indicated that the yellow mutation is dominant, and all the parental yellow mice were heterozygotes for the mutant allele.

By mating two yellow mice, Cuénot expected to observe a usual 1:2:1 Mendelian ratio of homozygous agouti to heterozygous yellow to homozygous yellow. Instead, he always observed a 1:2 ratio of agouti to yellow mice. He was unable to produce any mice that were homozygous for the yellow agouti allele.

It wasn't until 1910 that W. E. Castle and C. C. Little confirmed Cuénot's work, further demonstrating that one quarter of the offspring were dying during embryonic development. This was the first documented example of a recessive lethal allele.

Types of lethal alleles

Recessive lethals

A pair of identical alleles that are both present in an organism that ultimately results in death of that organism are referred to as recessive lethal alleles. Though recessive lethals may code for dominant or recessive traits, they are only fatal in the homozygous condition. Heterozygotes will sometimes display a form of diseased phenotype, as in the case of achondroplasia. One mutant lethal allele can be tolerated, but having two results in death. In the case of homozygous achondroplasia, death almost invariably occurs before birth or in the perinatal period.

Other examples of human diseases caused by recessive lethal alleles include sickle-cell anaemia.

Dominant lethals

Alleles that need only be present in one copy in an organism to be fatal are referred to as dominant lethal alleles. These alleles are not commonly found in populations because they usually result in the death of an organism before it can transmit its lethal allele on to its offspring. An example in humans of a dominant lethal allele is Huntington's disease, a rare neurodegenerative disorder that ultimately results in death. A person exhibits Huntington's disease when they carry a single copy of a repeat-expanded Huntington allele on chromosome 4.

Conditional lethals

Alleles that will only be fatal in response to some environmental factor are referred to as conditional lethals. One example of a conditional lethal is favism, a sex-linked inherited condition that causes the carrier to develop hemolytic anemia when they eat fava beans.

Gametic Lethals

Some genes make the gametes incapable of fertilization. Such genes are said as gametic lethals. Some times the term 'Meiotic drive' is used to describe gametic lethals. Meiotic drive may be called a mechanism that leads to the production of unequal numbers of functional gametes by a heterozygote.

It has been found in certain males of **Drosophila pseudoobscura**, produce only half amount of sperm as compared to normal males. When these males are mated to normal females, most of the progeny are females. It demonstrates that the sperm cells produced by these males contain the 'X' chromosome only and their sperms having 'Y' chromosome are non-functional.

Semilethal or Sublethal Genes

Haemophilia is a hereditary disease caused by deficiencies in clotting factors, which results in impaired blood clotting and coagulation. Because the allele responsible for haemophilia is carried on the X chromosome, affected individuals are predominantly males, and they inherit the allele from their mothers. Normally, clotting factors help form a temporary scab after a blood vessel is injured to prevent bleeding, but haemophiliacs cannot heal properly after injuries because of their low levels of blood clotting factors. Therefore, affected individuals bleed for a longer period of time until clotting occurs. This means that normally minor wounds can be fatal in a person with haemophilia. The alleles responsible for haemophilia are thus called semilethal or sublethal genes, because they cause the death of only some of the individuals or organisms with the affected genotype.

Examples of diseases caused by recessive lethal alleles in humans

Brachydactyly - A genetic state in which the fingers are unusually short in heterozygotic condition. But, this condition is lethal during early years to homozygous recessive individuals due to major skeletal defects

- **Sickle Cell Anaemia** - A genetic state that is often fatal in the homozygous recessive condition. Concerned gene codes for the manufacture of haemoglobin, which is an O₂ transport protein found in red blood cells.

- **Tay-Sachs Disease** - A genetic state that is fatal to every homozygous recessive members by the age of 4. Not curable Metabolic Disorder which causes brain deterioration.

- **Cystic Fibrosis** - A genetic state that is fatal to every homozygous recessive person by age 30. Not curable disorder in which sticky mucus accumulates in the lungs giving rise to constant and risky respiratory infections.

- **Congenital Ichthyosis:** It is an instance of homozygous recessive fatal gene in individuals. Children with this disease are born with crusted leathery skin with deep splits. These splits lead to bleeding, infection and death.

Examples of diseases caused by dominant lethal allele in humans :

- **Huntington's Disease** - A genetic state caused by a dominant lethal allele. This dominant allele is still persists in the population because the disease does not have an effect on peoples until after reproductive period of life (40-50 years of age) Symptoms include jerking and depression and also results in brain degeneration and death within 5 years of arrival.

On the basis of effect of survivability the genes may be grouped in to 5 classes:

1. Vital genes
2. Lethal genes
3. Sub-lethal genes
4. Sub-vital genes
5. Super-vital genes

1. Vital genes:

The genes which do not affect the survival of the individuals in which they are present are said as vital genes. It does not mean that these genes are necessary for the survival of the concerned individual. Wild type alleles of all the genes of an organism are said as vital genes. In other words, the survival of the organism is not influenced by the vital genes, whether may be present in homo or heterozygous condition.

2. Lethal genes:

Has been described above

3. Sub-lethal or semi-lethal genes:

Such genes do not lead the organism to the death that carry them in appropriate genotype. 90% of the individuals die, however, only less than 10% of the individuals survive. Some Xantha mutants of several plants are sub-lethal or semi-lethal in the homozygous state.

Haemophilia is a hereditary disease caused by deficiencies in clotting factors, which results in impaired blood clotting and coagulation. Because the allele responsible for haemophilia is carried on the X chromosome, affected individuals are predominantly males, and they inherit the allele from their mothers. Normally, clotting factors help form a temporary

scab after a blood vessel is injured to prevent bleeding, but haemophiliacs cannot heal properly after injuries because of their low levels of blood clotting factors. Therefore, affected individuals bleed for a longer period of time until clotting occurs. This means that normally minor wounds can be fatal in a person with haemophilia. The alleles responsible for haemophilia are thus called semilethal or sublethal genes, because they cause the death of only some of the individuals or organisms with the affected genotype.

4. Sub-vital genes:

Most of the mutant genes reduce the viability of individuals having them in appropriate genotype as compared to that of normal individuals. Most of the mutant genes are sub-vital in their effect and kill less than 90% of the individuals which carry them. The examples are some virdis mutants of barley, miniature wings in Drosophila. Retinoblastoma or eye cancer in humans - A small percentage of retinoblastomas are caused by **deletions** in the region of chromosome 13 that contains the **RB1** gene.

5. Super-vital genes:

Most of the mutant genes increase the survival of such individuals which carry them in appropriate genotype as compared to that of wild type allele. Such genes are called as super-vital genes.

Super-vital genes protect the individuals carrying them against the various disease thus increasing the chance of their survival. Likewise, the genes providing resistance or tolerance to different environmental pressure or strain like high and low temperature, low and high light intensity, drought, salinity, alkanity etc.

GENETIC SCREENING AND GENETIC COUNSELLING

Genetic screening is a type of medical test that identifies changes in chromosomes, genes, or proteins. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.

Several methods can be used for genetic testing:

- Molecular genetic tests (or gene tests) study single genes or short lengths of DNA to identify variations or mutations that lead to a genetic disorder.
- Chromosomal genetic tests analyse whole chromosomes or long lengths of DNA to see if there are large genetic changes, such as an extra copy of a chromosome, that cause a genetic condition.
- Biochemical genetic tests study the amount or activity level of proteins; abnormalities in either can indicate changes to the DNA that result in a genetic disorder.

Genetic screening is voluntary. Because screening has benefits as well as limitations and risks, the decision about whether to be tested is a personal and complex one. A geneticist or genetic counsellor can help by providing information about the pros and cons of the test and discussing the social and emotional aspects of testing.

Genetic testing can provide information about a person's genes and chromosomes. Available types of testing include:

Newborn screening

Newborn screening is used just after birth to identify genetic disorders that can be treated early in life. Millions of babies are tested each year in the United States. All good hospitals currently test infants for phenylketonuria (a genetic disorder that causes intellectual disability if left untreated) and congenital hypothyroidism (a disorder of the thyroid gland). Most developed countries also test for other genetic disorders.

Diagnostic testing

Diagnostic testing is used to identify or rule out a specific genetic or chromosomal condition. In many cases, genetic testing is used to confirm a diagnosis when a particular condition is suspected based on physical signs and symptoms. Diagnostic testing can be performed before birth or at any time during a person's life, but is not available for all genes or all genetic conditions. The results of a diagnostic test can influence a person's choices about health care and the management of the disorder.

Carrier testing/ Heterozygote screening

Carrier testing is used to identify people who carry one copy of a gene mutation that, when present in two copies, causes a genetic disorder. This type of testing is offered to individuals who have a family history of a genetic disorder and to people in certain ethnic groups with an increased risk of specific genetic conditions. If both parents are tested, the test can provide information about a couple's risk of having a child with a genetic condition.

Prenatal testing

Prenatal testing is used to detect changes in a foetus' genes or chromosomes before birth. This type of testing is offered during pregnancy if there is an increased risk that the baby will have a genetic or chromosomal disorder. In some cases, prenatal testing can lessen a couple's uncertainty or help them make decisions about a pregnancy. It cannot identify all possible inherited disorders and birth defects, however.

Preimplantation testing

Preimplantation testing, also called preimplantation genetic diagnosis (PGD), is a specialized technique that can reduce the risk of having a child with a particular genetic or chromosomal disorder. It is used to detect genetic changes in embryos that were created using assisted reproductive techniques such as in-vitro fertilization. In-vitro fertilization involves removing

egg cells from a woman's ovaries and fertilizing them with sperm cells outside the body. To perform preimplantation testing, a small number of cells are taken from these embryos and tested for certain genetic changes. Only embryos without these changes are implanted in the uterus to initiate a pregnancy.

Predictive and presymptomatic testing.

Predictive and presymptomatic types of testing are used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing. Predictive testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. Presymptomatic testing can determine whether a person will develop a genetic disorder, such as hereditary hemochromatosis (an iron overload disorder), before any signs or symptoms appear. The results of predictive and presymptomatic testing can provide information about a person's risk of developing a specific disorder and help with making decisions about medical care.

GENETIC COUNSELLING

The word "counselling" refers to information giving or communication as opposed to psychotherapy or psychology thus doing **genetic counselling means communicating genetic information in a meaningful way to patients**. But it does not just mean having a conversation that happens to involve genetic information; it goes much further than that. Genetic counselling provides an individual or family with information and support regarding health concerns which run in their family. Genetic counselling may involve the diagnosis of a genetic condition, the provision of information and supportive counselling (advice and guidance) by a team of health professionals, so that families and individuals may be better able to adjust to diagnosis.

Genetic counselling is “the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease.” Traditionally, this process includes collecting and interpreting the family and medical history, risk assessment, a comprehensive educational process for potential genetic testing, informed consent, and psychosocial assessment and support (National Society of Genetic Counsellor's Definition Task Force et al. 2006). The term 'genetic counselling' was coined by Sheldon Reed in 1947. Genetic counselling is an educational process that aims to inform and advise patients and relatives at risk of a genetic condition about the nature of the disorder, the probability of developing it and the risk of passing it on to future generations.

Genetic counselling is the process of:

- evaluating family history and medical records
- ordering genetic tests

- evaluating the results of this investigation
- helping parents understand and reach decisions about what to do next

In general, a genetic counselling session aims to:

- Increase the family understands about a genetic disease(s), the risks and benefits of genetic testing and disease management, and available options.
- Identify with the individual and family the psychosocial tools required to adjust to potential outcomes.
- Reduce the family's anxiety.

WHO REQUIRES GENETIC COUNSELLING?

The best time to seek genetic counselling is before becoming pregnant, when a counsellor can help assess your risk factors. But even after you become pregnant, a meeting with a genetic counsellor can still be helpful. A genetic counsellor can help determine what testing is appropriate for your pregnancy. Experts recommend that all pregnant women, regardless of age or circumstance, be offered genetic counselling and testing to screen for Down syndrome. Every mother wants to give birth to a healthy baby. To rule out any chances of birth defects and complications, genetic testing is done. Genetic testing is not a norm for all pregnancy cases. It is done only in certain cases or those with a family history of certain diseases. Genetic testing improves the chances of giving birth to a healthy baby. Genetic tests are carried out during different stages of pregnancy. Genetic counselling helps expecting parents to understand the family traits that can be passed to the baby.

It's especially important to consider genetic counselling if any of the following risk factors apply:

- A standard prenatal screening test (such as the alpha fetoprotein test) yields an abnormal result
- An amniocentesis yields an unexpected result (such as a chromosomal defect in the unborn baby)
- Either parent or a close relative has an inherited disease or birth defect
- Either parent already has children with birth defects, intellectual disabilities, or genetic disorders.

the mother-to-be has had two or more miscarriages or babies that died in infancy.

- The mother-to-be will be 35 or older when the baby is born. Chances of having a child with Down syndrome increase with the mother's age: a woman has about a 1 in 350 chance of conceiving a child with Down syndrome at age 35, a 1 in 110 chance at age 40, and a 1 in 30 chance at age 45.
- Either parent is concerned about the effects of exposures they have had to radiation, medications, illegal drugs, infections, or chemicals.

Risks and Limitations of Genetic screening and counselling:

The physical risks associated with most genetic tests are very small, particularly for those tests that require only a blood sample or buccal smear (a method that samples cells from the inside surface of the cheek). The procedures used for **prenatal testing** carry a small but **real risk of losing the pregnancy** (miscarriage) because they require a sample of amniotic fluid or tissue from around the foetus.

Many of the risks associated with genetic testing involve the **emotional, social, or financial consequences of the test results**. People may feel angry, depressed, anxious, or guilty about their results. In some cases, genetic testing creates tension within a family because the results can reveal information about other family members in addition to the person who is tested. The possibility of **genetic discrimination** in employment or insurance is also a concern.

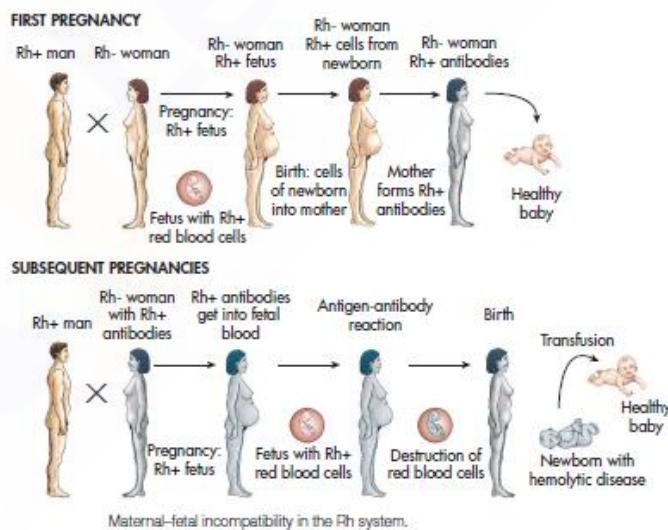
GENETIC LOAD

The burden load or risk of death or disease due to genetic reasons is called genetic load. **Crow** defines genetic load as the proportion by which fitness of the average genotype in the population is reduced in comparison with best genotype.

TYPES OF GENETIC LOAD

INCOMPATIBILITY LOAD

It is encountered when certain genotypes are unable to survive in the environment of specific genotypes. The concept of rh+ve child to rh-ve mother is a common example of this type of genetic load. In this situation Erythroblastosis foetalis is caused by Rh factor incompatibility between a pregnant woman and next foetus.



MUTATIONAL LOAD

Genetic load caused due to mutation. Deletion of some vital gene or insertion, deletion etc. Eg: sickle cell anaemia,

Hemophilia A, also called factor VIII (FVIII) deficiency or classic hemophilia, is a genetic disorder caused by missing or defective factor VIII, a clotting protein. Although it is passed down from parents to children, about 1/3 of cases are caused by a spontaneous mutation, a change in a gene.

The gene for hemophilia is carried on the X chromosome. Hemophilia is inherited in an X-linked recessive manner. Females inherit two X chromosomes, one from their mother and one from their father (XX). Males inherit an X chromosome from their mother and a Y chromosome from their father (XY). That means if a son inherits an X chromosome carrying hemophilia from his mother, he will have hemophilia. It also means that fathers cannot pass hemophilia on to their sons.

But because daughters have two X chromosomes, even if they inherit the hemophilia gene from their mother, most likely they will inherit a healthy X chromosome from their father and not have hemophilia. A daughter who inherits an X chromosome that contains the gene for hemophilia is called a carrier. She can pass the gene on to her children. Hemophilia can occur in daughters, but is rare.

SEGREGATIONAL LOAD

This is due to breaking down of genetic correlation and linkages. Especially useful linkages or correlation happen when 2 beneficiary alleles co-occur. By breaking down this relationship, possibility of inheriting bad gene increase. Hence genetic load. It acts at a single locus. Recombination load when it acts on 2 different loci.

INBREEDING

Inbreeding increases the rate of homozygosity, an inbreeding depression will be observed when the offspring's receive two recessive and deleterious alleles resulting in a lower fitness. A declining population will experience high rate of mutation. An increase in the rate of mutation in alleles will increase the pairing frequency alleles. Due to a decline in population because of higher mutation rate, there is a chance of mating between the remaining organism to breed with their relatives and it will help in pushing out some of the harmful mutations.

Tay-Sachs disease is a rare inherited disorder that progressively destroys nerve cells (neurons) in the brain and spinal cord. Tay- Sachs disease is due to simple recessive gene and the percentage of first cousin marriage amongst the parents is about 15%.

Alkaptonuria is transmitted as a simple recessive. It is very rare, and proportion of affected persons whose parents are first cousins is no less than something between 30% and 40%.

MIGRATION

Migrational load results when an organism non-adaptive to a particular environment comes in contact with individual adapted to that environment. The offspring produced as a result of such mating are not as fit as they would have been if both of their parent where adapted to same environment. The offspring will have a lower variability rate as well as a lower overall

fitness and higher will be the genetic load if individuals are from remarkably different environment.

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 descendants of the exposed persons, and that too for many generations after the exposure.

Mention social factors like lack of health facilities immunisation, education, sanitation, poverty, cultural elements like endogamy intensify genetic load.

However, for survival of a species it is necessary that population size matches with carrying capacity of the environment. It is necessary that self-thinning of population must occur in order to match with the carrying capacity of the environment. To this end, phenotypic load with or without genetic load is essential because some individuals must be weak or die out in order to secure survival of the rest. Thus contrary to earlier beliefs genetic load increases population fitness by bringing about thinning of population through phenotypic load.

GENE IMPRINTING

People inherit two copies of their genes—one from their mother and one from their father. Usually both copies of each gene are active, or “turned on,” in cells. In some cases, however, only one of the two copies is normally turned on. Which copy is active depends on the parent of origin: some genes are normally active only when they are inherited from a person’s father; others are active only when inherited from a person’s mother. This phenomenon is known as genomic imprinting.

Genomic imprinting is a process of silencing genes through DNA methylation. The repressed allele is methylated, while the active allele is unmethylated. This stamping process, called methylation, is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. Genes that undergo genomic imprinting, the parent of origin is

often marked, or “stamped,” on the gene during the formation of egg and sperm cells. This stamping process, called methylation, is a chemical reaction that attaches small molecules called methyl groups to certain segments of DNA. These molecules identify which copy of a gene was inherited from the mother and which was inherited from the father. The addition and removal of methyl groups can be used to control the activity of genes.

Only a small percentage of all human genes undergo genomic imprinting. Researchers are not yet certain why some genes are imprinted and others are not. They do know that imprinted genes tend to cluster together in the same regions of chromosomes. Two major clusters of imprinted genes have been identified in humans, one on the short (p) arm of chromosome 11 and another on the long (q) arm of chromosome 15 .

Uniparental disomy

Uniparental disomy (UPD) occurs when a person receives two copies of a chromosome, or part of a chromosome, from one parent and no copies from the other parent. UPD can occur as a random event during the formation of egg or sperm cells or may happen in early foetal development.

In many cases, UPD likely has no effect on health or development. Because most genes are not imprinted, it doesn't matter if a person inherits both copies from one parent instead of one copy from each parent. In some cases, however, it does make a difference whether a gene is inherited from a person's mother or father. A person with UPD may lack any active copies of essential genes that undergo genomic imprinting. This loss of gene function can lead to delayed development, intellectual disability, or other health problems.

Several genetic disorders can result from UPD or a disruption of normal genomic imprinting. The most well-known conditions include Prader-Willi syndrome, which is characterized by uncontrolled eating and obesity, and Angelman syndrome, which causes intellectual disability and impaired speech. Both of these disorders can be caused by UPD or other errors in imprinting involving genes on the long arm of chromosome 15. Paternal inheritance of a deletion is associated with Prader-Willi Syndrome (characterised by hypotonia, obesity and hypogonadism). Maternal inheritance of same deletion causes Angelman syndrome (characterised by epilepsy, tremors and perpetually smiling face).

Other conditions, such as Beckwith-Wiedemann syndrome (a disorder characterized by accelerated growth and an increased risk of cancerous tumours), are associated with abnormalities of imprinted genes on the short arm of chromosome 11.

Evolution of Gene- Imprinting:

Conflict Theory by Haig: Theory proposes that imprinting has evolved mainly in mammals that directly supply nutrients to their growing embryos. The theory maintains that there are conflicting demands of maternal and paternal genes- paternal genes trying to obtain as much nutrition for growth of current embryos in which it has contributed, whereas maternal genes

trying to save some energy for its future embryos in whose making the present paternal genes may not participate. Hence paternal genes are active as it provides selective advantage.

Non Conflict Theory: Possibly the oldest proposed explanation for the evolution of imprinting begins by noting the absence of naturally occurring parthenogenesis in mammals. This observation extends to extensive laboratory experiments attempting to generate viable mice from reduplication of the chromosomes of a single sperm or a single egg. Such experiments had universally failed. This implies that both maternal and paternal contributions are essential to the developing mammalian zygote, which would obtain if one or more essential genes were expressed from only the maternal copy and others only from the paternal. Thus, imprinting may have been selected to prevent the establishment of parthenogenetic lineages.

Ovarian time-bomb: The ovarian time-bomb hypothesis is similar to the prevention of parthenogenesis hypothesis. **Varmuza and Mann** (1994) argued that imprinting evolved to prevent ovarian trophoblastic disease arising from a parthenogenetically developing (unfertilized) egg in the ovary of a female mammal. If the maternal copy of an essential gene were inactivated and hence a paternal contribution necessary for correct development, this 'ovarian time-bomb' could be defused.