**CHARACTER INHERITANCE: HERITABLE AND NON-HERITABLE TRAITS**

Heritable traits are defined by their ability to be passed from one generation to the next in a predictable manner. Visible or otherwise measurable properties of heritable traits are called phenotypes, while the genetic factors responsible for creating the phenotypes are called genotypes. The most basic question to be asked about a trait is whether or not the observed variation in the character is influenced genes at all. It is important to note that this is not the same as asking whether or not genes play any role in the character development. Gene mediated developmental process lies at the basis of every character, but variation from individual to individual is not necessary the result of genetic variation. Thus, the possibility of speaking a language at all depends critically on the structures of the central nervous systems as well as the vocal cords, tongues, mouth and ears which depends in turn on the nature of the human genome. There is no environment in which cows for example, will ever speak. Although, the particular language human speaks defers or varies from nation to nations, this variation is totally non genetic. Therefore, the question of whether or not a trait is heritable is a question about the role that differences in genes play in the phenotypic differences between individuals or groups.

In principle, it is easy to determine whether any genetic variation influences the phenotypic variation among organisms for a particular trait. If genes are involved, then on the average the biological relatives should resemble each other more than the unrelated individuals do. This resemblance would be reflected as a positive correlations between parents and offspring between siblings. Parents who are larger than average would produce offspring that are larger than the average. The more seeds a plant produces the more seeds the siblings will produce also. Such correlations between relatives are however, evidence of genetic variations only if the relatives do not share common environment more that the non-relatives do. It is absolutely fundamental to distinguish between familiarity and heritability at this point. Traits are familiar if members of the same family share them for whatever reasons. Inherited traits vary widely in complexity. Some appear in principles to be relatively limited. For example, human eye colour, which may

either be brown or blue. Whiles some apparently are more complex. e.g. the inheritance of the shape of the nose. Traits are heritable only if the similarity arises from shared genotypes. In experimental organisms, there's no problem in separating environmental from genetic similarities. The offspring of a cow producing milk at a high rate and the offspring of a cow producing at low rate can be raised together in the same environment to see whether despite the environmental similarity, each resembles its own parents. In natural populations, and especially in humans, this is difficult to do. Because of the nature of human societies, members of the same families not only share genes but also have similar environments. Thus the observation of simple familiarity of a trait is genetically un-interpretable. In general people who speak Yoruba have Yoruba parents and people who speak Ibo have Ibo parents, cross cultural activities over the years and the movement of people doing business at different locations in the country has demonstrated that this linguistic differences though familiar, are non genetic and non heritable. The distinction between heredity and familiarity are not always so obvious. For example, the disease pellagra (Vitamin deficiency disease) was ones thought to be heritable because it runs in families.

To determine whether a trait is heritable in human population, we must adopt studies that avoid the usual environmental similarities between biological relatives. Skin colour is clearly heritable as well as adult height but even in these traits also we have to be very careful. For example, the children of Japanese immigrants born in America are taller than there parents but shorter than the American average. So we might conclude that there are some influences of genetic differences. Yet there is also the effect of environmental cultural influences as second generation Japanese American are even taller than their American born parents. Personality traits, temperaments and cognitive performance (including IQ scores) and a whole variety of behaviours have been the subject of heritability studies in humans. Many showed familiarity. There is indeed a correlation between parents IQ and that of their children, but the correlation does not distinguish familiarity from heritability. To make that distinction requires that the environmental correlations between parents and children be broken.

**MUTATION**

A gene mutation may be defined as a change in the code of information transmitted by the DNA molecule on the chromosome to the ribosomes in the cytoplasm of the cell by means of mRNA, which gives it instructions to build a specific protein. A change in this code means that a different protein is formed in the place of the one normally produced by instructions from the gene. For example, the change in the code sent by a gene could produce an entirely different protein such as sickle cell hemoglobin which differs from the normal adult hemoglobin in the kind and number of amino acids contained in the protein portion of the hemoglobin molecule. Mutation in its wide sense means every change in the heritable substance which is not due to segregation or recombination of previously existing genes. Mutation can occur in genes carried either on the autosomes or in those on the sex chromosomes. They may also occur in body cells or in the cells of the germinal epithelium of the testes and ovary. Reverse mutation may also occur. Most new mutations are harmful but some are desirable in their effects.

Gene mutations that occur in the body cells are not transmitted to the progeny of the individual where they occur. In other to be transmitted to the progeny they must occur in the sex cells, the sperm and the egg. The failure of a new mutation to occur in the progeny, especially if it were dominant, would suggest it to be in the body cells. An example is the black spot on the red coat of the Hereford cattle. Black is dominant to red so new mutation from single red gene to black would show in the individual. Black spots of this nature in Hereford have been noted from time to time, but their transmission or failure to be transmitted have not been studied. A new somatic cell mutation may occur in a cell early in embryonic life. Later cells descending from this parent cell in which the new mutation occurred could show the new mutation, providing it were dominant and could have effects different than observed in other cells in the surrounding tissues. An example is the appearance of brown spot within the otherwise blue eye in humans.

**New** mutations which occur in the sex cells, sperm and egg, are transmitted from one generation to another. A new dominant mutation in the sex cells is followed by the transmission and appearance of the trait in the progeny of the individual where the first mutation occurred, providing the gene has a major effect on a trait and shows complete penetrance (or always shows up in the phenotype when present in the genotype). A new recessive mutation, however could occur and not appear in the descendants of the affected individual for many generations, or until two parents are mated which carry the same recessive mutation. Even then only about one of four offspring from such parents would be expected to show the mutation. A new mutation in a gene means that another allele at a particular locus on the chromosome has been produced which may affect the same trait in a different or alternative manner than the original gene. The new gene arising from the mutation reproduces itself exactly for succeeding generations as long as the individual carrying it survives and reproduces until a mutation of this gene occurs to produce still another gene in its place. A series of new mutation at the same locus is the explanation for the occurrence of several alleles in a multiple allelic series. e.g. The ABO blood type series in humans involving gene A for blood type A, B for blood type B and A for blood type O.

One of the most striking observations one can make in nature is the great variation among individuals in type, size, color, behavior, and etc. The genetic proportion of this variation is due to the accumulation of mutations within the species. If the genes could reproduces themselves exactly for generation after generation over a period of thousands of years without single mistake, members of a particular species would all be alike in colour, type and performance and would not be divided into distinct types and breeds. All variation that existed would be superficial environmental variations that could not be transmitted from parents to offspring.

Mutation can involve either a single gene, in which case it is called a point mutation or a whole chromosome or number of chromosomes or even their structures, in which case, it is called chromosomal mutation.

**A point mutation** occurs at a certain gene locus or a part thereof. A gene can also be inactivated as in the case when gene C which is responsible for the animal capacity to produce pigment in the skin, hair and feather mutate to c. Individuals which are homozygote for the latter gene becomes albinos. The gene c has however been altered in many different ways so that a series of multiple alleles has been build up. In rabbits, at least 5 different alleles are known which influences the intensity of pigmentation. In some cases one or more genes may be lost when a piece of chromosome breaks off during cell division. If the segment is large, it is more of a case of structural alteration of the chromosomes. In many cases, a point mutation is a reversible process and the new mutant gene is recessive to the earlier allele.

**Chromosome mutation**: Chromosomes can change in two basic ways- by alternation in structure or in numbers. Both types of alterations have consequences besides their immediate effects on chromosomes. For examples individual heterozygous for chromosomes with different structures often have lower fertility, and individuals with altered numbers of chromosomes may be unviable or sterile.

**Structural changes**: The four possible types of changes in chromosomal structures are duplications, deletions (or deficiencies), inversions and translocations. When breaks occur in chromosomes, any two broken chromosomal ends may reunite. Structural changes are often a consequence of a break occurring at one or more places on the chromosome in which the same broken ends do not reunite. In some cases rejoining takes place and if non of the gen loci is lost or damaged, the chromosome behaves normally after rejoining. Generally such chromosomal mutation occur infrequently, but some researchers have estimated that more than one in a thousand have gametes may be some type of chromosomal mutation. In the case however, that parts of the chromosome separate from each other (fragmentation) in which case several things can happen.

1. **A Deletions can occur**. If several breaks occur in a chromosome and a middle portion of the chromosome is lost and the outer parts rejoined, a deletion has taken place. Where an internal part of the chromosome is missing, is called an **interstitial deletion.** But if there is only one break and the homologue fails to rejoin, a **terminal deletion or deficiency** has occurred. In this case, the tip of the chromosome is usually lost in cell division because it does not have a centromere. In both cases, a portion of the chromosome with all its associated genes has been lost. When deletions are homozygous, they are often lethal, because essential genes are missing. Even when heterozygous, it can cause abnormal development. A well-known example in humans is the deletion of a substantial part of the short arm of chromosome 5 (5p), which when heterozygous causes the cri du chat (cry-of-the-cat) syndrome. In facts with this syndrome patients generally have a characteristic high-pitched, catlike cry as well as microcephaly (small heads) and severe mental retardation. They generally die in infancy or early childhood. In addition, deletion heterozygotes usually shown abnormal chromosomal pairing in meiosis. Because the normal chromosome does not have a homologous region to pair within a deletion loop is formed. This phenomenon may be sen in meiotic chromosomes or in the polytene chromosomes of Drosophila and a few other organisms. Several other characteristics are useful in identifying deletions. First, deletions, unlike other mutations, generally do not revert, or mutate back to the wild-type chromosome. Second, in deletion heterozygotes, recessive alleles on the normal chromosome are expressed because the deletion chromosome is missing the homologous region. Expression of recessive alleles in such cases, called **pseudodominance,** is useful in defining the length of the deleted segment. For example, let us assume that genes B and c were deleted on one chromosome. If we have wild-type chromosomes with recessive mutants at different genes, these should be expressed if they are in the deleted region. Deletions can be used to map the sequence of the genes on the chromosome.

2. **Duplication**: When a chromosomal segment is represented twice, it is called a **duplication**. We can categories duplication by the position and order of the duplicated region. First, the duplication may be adjacent to the original chromosomal region. When this occurs, the order may either be the same as the original order, called a **tandem duplication**, or the opposite order, called a **reverse duplication**. Secondly, the duplicate region may not be adjacent to the original segment, resulting in a **displaced duplication**. In this place the displaced duplication may still be on the same chromosome or it may be on another chromosome. Chromosomal duplication can occur during crossing-over process, when a segment lost from one chromosome is added to another chromosome. If a gamete with the duplicated chromosome unites with a normal gamete, the zygote formed would have those genes on the duplicated chromosome segment in triplicate. When an individual is heterozygous for a duplication and a normal chromosome, the duplicated regions does not have a homologous segment to pair with a meiosis 1. As a result, a loop of the duplicated region may develop. In some cases, part of the chromosome may bend back and join. Individuals that are heterozygous or homozygous for a small duplicated segment may be viable, although they often exhibit some phenotypic effects noticeably due to gene duplication. If individuals are viable, there is a potential for further evolutionary changes in these extra genes. In fact it is though that this happen with the different globin genes, the genes that code for the components of the protein hemoglobin. These genes may have descended from an ancestral gene that was duplicated and then the duplicate copies diverged in their function.
3. **Inversions**: Most of the homologous chromosomes in a population have genes in the same sequence. However, in some instances the sequence may differ on different chromosome, followed by an incorrect reunion. Alterations in the sequence of genes called **inversions,** may be of two different kinds relative to the position of the centromere. If the inverted segment does not contain the centromere, it is called **paracentric inversion** (Greek: para = next to), but if the version spans the centromere, it is called a **pericentric inversion** (Greek: peri = around). Individual heterozygous for an inversion can be

recognized by the presence of inversion loops in meiotic pachytene chromosomes. These structures occur because of the affinity of the two homologues. The only was the two homogues can pair is if one twists on itself and makes a loop, while the other makes a loop without a twist. These loops can best be seen in the polytene chromosomes of organisms such as Drosophila pseudoobscura.

4. **Translocations:** A **translocation** is the movement (by breaking and rejoining) of a chromosomal segment from one chromosome to another, non-homologous chromosome. There are two types of translocations, an **interstitial translocation**, involving the one-way movement of a segment, and the more common **reciprocal translocation**, involving a two-way exchange of chromosomal segments. If two of the segments that join in a reciprocal translocation are large and the other two are small, the smaller translocated chromosomes are often lost. In this case, the number of chromosomes is reduced by the chromosomal exchange. Obviously, translocations can change both the size of chromosomes and the position of the centromere. Even though chromosomal segments have been exchanged between chromosomes in a reciprocal translocation, the affinity of the homologous regions results in pairing during meiosis I. If nearly equal parts of chromosomes are exchanged or not exchanged, the paired chromosomes in a translocation heterozygote have a cross appearance in metaphase I. During anaphase I, two major types of segregation occur: one in which adjacent centromeres goes to the same pole (adjacent I.) and two, the alternate centromere goes to the same poles. When alternate centromeres go to the same pole, the chromosomes often form a figure eight shape in early anaphase I. The products of this event, which is known as **alternate segregation**, are balanced so that each gamete has a full complement of chromosomes; either two untranslocated or two balanced translocated. On the other hand, when adjacent centromeres segregate together, **adjacent segregation**, the chromosomes appear as a ring at metaphase I. When this occurs, the products are unbalanced, resulting in duplications and deletions in the gametes. Some plants, and also a few animals, have a series of reciprocal translocations, so that chromosomal heterozygotes also have nearly

all the chromosomes associated in a large ring (or rings) in meiosis. However, at anaphase these chromosomes may undergo an orderly alternate segregation, producing only zygotes with a balance chromosomal complement. Although translocations can resulting in normal chromosomes, they can also cause several human diseases. For example, about 5% of individuals with **Down syndrome** have one parent who is heterozygous for a translocation. In this instance, chromosome 14 is translocation onto chromosome 21. Half of the time, the heterozygote produces either the normal set or a balanced translocated set of chromosomes, making the progeny either normal or translocation heterokaryotypes, respectively. The other half of the time, unbalanced chromosomes are produced, either a 14 without the translocated 21 segment or a translocated 14 without the translocated 21 segment or a translocated 14 with the attached 21 plus a normal 21. In the first case, offspring get only one 21 chromosome, a lethal chromosomal component. In the second instance, three 21 chromosomes are received, resulting in Down syndrome. Overall then, approximately one-third of the live births from some a translocation heterokaryotype can be expected to have Down syndrome. In actual fact, the proportion is less than this, primarily because some Down individuals do not survive gestation. Note that this cause of Down syndrome has implications for genetic counseling. First, Down syndrome could recur in children of a transolocation heterokaryotye, whereas normally Down syndrome does not recur in sibs Second, half of the phenotypically normal sibs of Down individuals are themselves translocation heterokaryotypes, and therefore could produced Down progeny.

**Changes in chromosomal number**

The numbers of chromosomes may vary in two basic ways: **euploid** variants, in which the number of chromosomal sets differ, and **aneuplid** variants, in which the number of a particular chromosome is not diploid. As one might expect, changes in chromosome number, either euplid or aneuploid, generally have a greater effect on survival than do changes in chromosome structure. In fact, in humans, more than half of

the spontaneous abortions that occur in the first three months of pregnancy involve fetuses with aneuploidy, polyploidy, or other large chromosomal aberrations.

**Polyploidy (Euploidy Variation)**: Organisms with three or more complete sets of chromosomes are called **polyploids**. If we let the haploid number of chromosomes be x, then organisms with three chromosomes sets have 3x chromosomes and are called triploids; those with 4x chromosomes are tetraploids; those with 6x chromosomes are hexaploids; and so on. However, for organisms that are regularly polyploidy, such as many plants, x usually refers to the number of chromosomes in a set and n to the number in a gamete. Thus, in a hexaploid organism with 60 chromosomes, $6x = 2n = 60$, so that $x = 10$ and $n = 30$. Polyploidy is relatively common in plants but rare in most animals, occurring only in certain beetles, earthworms, salamanders, fishes, and a few other organisms. On the other hand, nearly half of all floweing plants are polyploids, as are many important crops. For example, potatoes are tetraploid ($4x = 48$), bread wheat is hexaploid ($6x = 42$), and strawberries are octoploid ($8x = 56$). Polyplidy is less frequent in animals than in plants for several reasons. First, sex determination is often more sensitive to polypoidy in animals than in plants. Second, plants can often self-fertilize, so a single new polyploidy plant with an even number of chromosomal sets (tetraploid, hexaploid, etc.) can still reproduce. Finally, plant generally hybridize more easily with other related species, an important attribute, because the different sets of chromosomes in a polypoid often have different origins. We can distinguish two types of polyploids: those that receive all their chromosomal sets from the same species, **autopolyploids,** and those that obtain their chromosomal sets from different species, **allopolyploids.** For example, if any unreduced or diploid pollen grain from a diploid organism fertilizes a diploid egg of the same species, the offspring are **autotetraploids,** or AAAA, where A indicates a complete chromosomal set, **genome,** of type A. On the other hand, if diploid pollen of one species fertilizes a diploid egg of another, related species, the offspring are **allotetraploids.** Or AABB, where B indicates a genome from the second species. All the chromosomal sets in an autopolyploid are

homologous, just as they are in a diploid. But in allopolyploids, the different chromosomal sets generally vary somewhat and are called **homeologous** or partially homologous.

Triploid organisms are usually **autopolyploids** (AAA) that result from fertilization involving a haploid and a diploid gamete. They are normally sterile because the probability of producing balanced gametes is quite low. For example, most bananas are triploids; they produced unbalanced gametes, and as a result, are seedless (they are propagated by cuttings). **Allopolyploids:** Most naturally occurring polyploids are allopolyplods, and they may result in a new species. For example, the bread wheat Tritium aestipum is an allohexaploid with 42 chromosomes. By examining wild related species, it appears that bread wheat is descended from three different diploid ancestors, each of which contributed two sets of chromosomes (in this case designated as AABBDD). Pairing occurs only between the homologous sets, so that meiosis is normal and results in balanced gametes of n = 21.

**Aneuploidy:** The cause of aneuploidy is non-disjuction; that is, two homogolous chromosomes fail to separate properly during meiosis or mitosis. Non-disjuction in meiosis itself is thought to result from improper pairing of homologous chromosomes on opposite sides of the metaphase plane, or from failure of chiasma formation. As a result, both chromosomes may go to the same pole, leaving one daughter cell with an extra chromosome and the other daughter cell with no chromosome. When these gametes are fertilized by a normal gamete, they either have an extra chromosome, 2n + 1, termed **trisomy,** or are missing a chromosome, 2n – 1, termed **monosomy.** Non-disjuction is most common in meiosis 1, but it can occur in meiosis II as well. Non-disjuction can also take place in mitosis, resulting in mosaics for normal and aneuploid cells. Other combinations of extra chromosomes are possible, the most important being a tetrasomic with 2n + 2 chromosomes and a nullisomic with 2n – 2 chromosomes, in which no copies of a particular homologue exist. Trisomics are known in many different species. They are viable in many plants, but are less frequently viable in animals. For example, among the aneuploids that have been most thoroughly studies are those in the Jimson weed, or thorn apple. A series of Datura mutants with strange

properties, turned out to be trisomics for different chromosomes. In fact, a trisomic for each of the twelve different chromosomes was found, and each had a particular phenotype. The effects on the appearance of the seed capsule were quite different for trisomies of the different chromosomes, suggesting that different chromosomes have different hereditary effects on this trait. Trisomics have been investigated in crop plants such as corn, rice and wheat in an effort to identify the chromosomes carrying different genes. Crosses involving plants with trisomic chromosomes give unusual segregation ratios. For example, if a homozygous dominant trisomy, AAA (The A symbol again indicates a dominant allele), is crossed to a recessive diploid, aa, half the progeny are trisomic AAa half are diploid Aa. When the trisomic progeny are backcrossed to aa individuals, approximately one-sixth of the progeny are recessive aa. If the gene had been on a chromosome that was not trisomic, the F1 would be Aa, and one-half, not one-sixth, of the backcross progeny would be homozygous recessive (aa). In animals, trisomics and other aneuploid chromosomal complements are more unusual. From analysis of the chromosomal constitution of spontaneous abortions in humans, it appears that nearly all monosomics and many trisomics are fetal lethals. However, several trisomics that sometimes come to full term compose a substantial part of congenitally abnormal births. One of the most common is Down syndrome, trisomy of chromosome 21, with a frequency of one in seven hundred live births. Down syndrome, first described nearly 150 years ago, is generally characterized by mental retardation, distinctive palm prints, and a common facial appearance. In general, mortality is higher than normal: the average life span is the middle tens to the forties, depending upon the country, but some individuals live much longer. People with Down syndrome generally have a positive disposition, and some are able to be partially independent. The chromosomal basis of Down syndrome was first discovered in 1959, shortly after the correct human diploid number was determined. Detailed banding of human chromosomes has shown that Down syndrome actually results from a trisomy of the smallest chromosome, which is actually chromosome 22. However, because Down syndrome is known so prevalently as trisomy 21, this association was not changed, and the smallest chromosome is still

called chromosome 21. The current nomenclature to indicate an individual with trisomy 21 is 47 + 21, in which 47 indicates the total number of chromosome sand +21 indicates that there are three, rather than two, copies of chromosome 21. The other autosomal trisomies are much rarer, mostly because they are not viable as fetuses.

Nondisjunction of the sex chromosomes in human is the source of several conditions. Four common viable, but abnormal chromosomal types XO, XXX, XXY and XYY, are produced through nondisjuction. The symbol O here indicates the lack of a sex chromosome in a gamete or zygote.

**Klinefelter syndrome,** XXX (or 47, XXY), occurs fairly frequently and generally results in a relatively mild abnormality. These individuals are sterile males with some female characteristics. Individuals with **Turner syndrome** (XO or 45, X) are sterile females, short in stature, with some neck webbing. The frequency of XYY (or 47, XXY) is about one per one thousand males, but such males do not appear to have any congenital problems. At one point, it was suggested that XYY individuals had criminal tendencies, but further study indicates minimal correlation with behavior, if any. The frequency of XYY (or 47, XYY) individuals in prisons is significantly higher than that of the general populations; however, less than 5% of all XYY individuals are actually institutionalized. Abnormal chromosome numbers in a fetus can be diagnosed using **amniocentesis.** In this procedure, a sample of fluid is withdrawn from the amniotic sac with a needle. The fetal cells contained in this fluid are cultured for two or three weeks. Dividing cells are then stained, and the chromosomes are examined and counted to check for chromosomal abnormalities. The X chromosome is different from the other chromosomes in that only one is active in given cell. Normal males have only one X, which is active in all cells. In normal females, only one X is active in a given cell and the other X is heterochromatinized, or mostly inactive. The mostly inactivated X forms a structure called a **Barr body** that can be identified in a cell. Therefore, normal males and XO individuals have no Barr bodies; normal females and XXY individuals have one: XXX individuals have two: and so on. In other words, by counting the number of Barr bodies in a cell, chromosomal abnormalities involving the X chromosome can

be determined. The incidence of Down syndrome, and to some extent, other aneuploidies, increases with the age of the mother. The incidence of Down for mothers of age forty-five is nearly 50-fold that for teenage mothers. Although the exact mechanism for this increase is unknown, it appears to be related to the difference in gametogenesis between females and males. In females, oocytes are formed before birth and held in a resting stage (actually prophase of meiosis 1) until just before ovulation. In older mothers, an oocyte may remain at this stage for over forty years, during which time it may be affected by environmental factors that may cause a non-disjunction.

**Causes of Mutations**

Mutation can either be spontaneous or induced. In **spontaneous mutation,** mutagens are not involved. Base pairs changes and chromosomal aberrations can occur spontaneously, e.g. Adenine molecule can exist in two forms called tautomers. In its more stable configuration, it form two hydrogen bond with thymine in the DNa. If it however, undergoes a tautomeric shift such that a hydrogen atom moves from the 6-ammonia group to the 5N position, then hydrogen bonding with cytosine can occur at the A-T position. If the A-C pairing occur while DNA is replicating, then at the ensuring round of replication, one of the daughter DNA helical will have a G-C pair instead of an A-T pair at that position.

**Induced mutation**: Mutation can be induced either physical or chemical means. Irradiation is an example of physical mutagens with X-ray, gamma-ray, ultraviolet light being the most commonly use metagens. Their mode of action is through breakage of chromosomes which may result in chromosomal rearrangement. On the other hand, chemical mutagens can act in a variety of ways depending on the properties of the chemical and its reactions with the bases of the DNA. Some examples of chemical mutagens are 5-bromouracil, a base analogue whose structure resembles the structure of one of the bases in the DNA. In its **keto** state, it pairs with guanine. Mutation can therefore be induced by 5-bu in two ways.

The first involves the incorporation of the normal 5-bu into DNA during replication. If it shifts to its enol state during the next round of replication, then the result will be a transition mutation from A-T to G-C.

Other chemical mutagens are **2-minopurine** which is also a base analogue that can bond with both thymine and cytosine in its two forms. **Nitrus acid NA)** a deaminating agent is another chemical mutagen. It removes the ammonia group ($NH_2$) from the bases altering their base pairing abilities and hence inducing mutation. When adenine is treated with NA, it changes to hypoxanthine which can pair with cytosine thus resulting in A-T to G-C mutation. **Hydroxylamine $NH_2OH$)** induces mutation in a specific way in that it can react with cytosine hydroxylating it so that it can only pair with adenine thereby inducting a G-C to A-T pairing. **Acridine** treatment results in the addition or deletion of one base pair in the DNA.

**LETHALS AND GENETIC ABNORMALITIES**

Death of an organism may occur at any stage of development – immediately following fertilization, during embryonic differentiation, at parturition, or postnatally. Death may be due to a variety of causes, such as injury, diseases, malnutrition, and harmful irradiations such as X-rays and gamma rays. Any cause of death is termed lethal effects. Among the may causes of death are gene changes which are incompatible with development or survival. These genes are known as lethal (deadly) genes. They are deleterious genes with drastic effects causing the death of the young during pregnancy or at time of birth. Some other genes which are deleterious to the organisms may not be lethal, provided that environmental factors especially are favorable. If not, they however, can cause the death of the young after birth or sometimes later in life. These genes are called semi-lethal or sub-lethal genes. Still other genes do not cause death, but definitely reduce viability or vigor. These genes are referred to as nonlethal or detrimental genes.

A lethal gene may have its effect any time from the formation of the gamete until birth or shortly afterward. In a strain of horse, a sex-linked recessive lethal gene has been reported that kills approximately half of the male offspring of carrier females, so there are approximately twice as many females as males at

birth. Dwarfism in Herefords resulting from the mating of Comprest with Comprest is an example of a gene with semi-lethal effect. The dwarfs are born alive, as a general rule, but most invariably die before they are one year of age.

Most detrimental and lethal genes are either recessive or partially dominant and must be present in the homozygous state to have their full effect. In some instances, the partial dominant genes affect the heterozygous individuals so that they are intermediate in phenotype between the normal and the homozygous recessives. Some lethal genes however, are sex-linked. Examples of sex linked lethals are the hemophilia and Duchene muscular dystrophy genes. A slight scratch or accident injury which would not be serious in normal person often results in fatal bleeding for the affected hemophilia individual. Duchene muscular dystrophy is a disease in which the affected individual though apparently normal in early childhood exhibit progressive wasting away of the muscles resulting in confinement to wheel chair about the age of twelve and death in the teen years. Like hemophilia, it is due to a recessive sex-linked gene.

Detrimental recessive genes are generally present at low frequencies in a population, and in many cases, only inbreeding, line breeding or chance will cause their occurrence in the homozygous state.

Typically, a lethal or other abnormality would first come to the attention of the breeder when one or more defective individuals appear in the herd or flock. There are no absolute rules for determining whether the abnormality is hereditary or environmental in origin, whether it is due to some combination of hereditary and environmental influences or whether it is merely an accident or development.

**However, the following would indicate hereditary based defects.**

1. If previous studies on a scale large enough to be conclusive has shown a hereditary basis for a phenotypically similar condition in the same species or breed.
2. If the condition appears only in some breeding groups or families.

3. If it occurred in herds where there had been inbreeding. Inbreeding does not create abnormalities, but since most abnormalities are recessive, it tends to bring them to light as a result of increased homozygosity resulting from inbreeding.
4. If it occurred in more than one season when rations and environment differed.

**The following indicates an environmentally base defect.**

1. If it occurred when ration of dam was known to have been deficient or when she had been under stress.
2. If it had previously been reliably reported as due to ration or environment.
3. If it did not recur after rations or environment were changed.

In strict sense every abnormality are the product of heredity and environment. If the gene or genes conditioning an abnormality are uniformly expressed over a range of environments which includes the 'normal', we see only the genetic effects and think of it as genetic.

**Recessive Defects with Some Expression in Heterozygote**

Most lethals and abnormalities are recessive in inheritance, whether due to one or several genes. The death or culling of affected individuals usually keeps the frequency of the gene or genes at low levels and in equilibrium with mutation rate. A few cases are known in which recessive-ness is not complete, and the heterozygotes or carriers have characteristics which make them more favored or desired by breeders than the homozygote normal. A classical example of this is the Dexter breed of cattle. Cattle of this type are always heterozygous for a semi dominant gene which when homozygous produces a lethal acondroplasia (bulldog calves). Dexters themselves show the effects of the gene by shortness of leg. When inter-mated, Dexter produces ¼ long legged individuals known as kerrys, ½ short legged Dexter and ¼ bulldog calves.

Apparently, the hereditary situation is as follows:

Preference of British breeders for the short legged Dexters has resulted in the development of bred carrying lethal gene at a frequency of 0.5. Since the heterozygous individuals are easily identified. It would be an easy matter for breeders to cull them of they so desired. The Dexter type can be propagated without the production of lethals by avoiding the inter-mating of Dexter. Kerry X Dexter matings give 50% each of kerry and Dexter types. A mnore intriguing situation occurred in a Swedish dairy breed. A type of infertility characterized by gonadal hypoplasia was found to be highly hereditary but not a clear cut case of a single gene pair of gene action. Although it was not demonstrated beyond reasonable doubt, evidence indicated that unilaterally affected cows, on average, produced milk with higher than average fat percentage and were favored in selection. The gene or genes responsible for the condition attained such frequency in the breed that bilateral gonadal hypoplasia (with resultant sterility) reach a level constituting a serious problem to the breed. International selection against the condition subsequently reduced the frequency markedly.

In the mid years of the twentieth century, a type of dwarfism characterized by small size, high mortality, bulging foreheards, undershot jaws, difficult breathing, a tendency to bloat, and poor coordination reached a frequency in at least two breeds of cattle in the U.S. high enough to constitute an economic problem. The common name 'snorter' dwarf was applied to these animals. Initially the condition appeared to be inherited as a simple recessive. Although definite proof is lacking, the apparent increase in frequency strongly suggested that the gene was not completely recessive, but has some effect in the heterozygous condition making animals shorter-bodied and lower-set.

A partial deficiency of urdine monophosphate (UMP) synthase was also discovered in Holstein cattle. The enzyme is responsible for the conversion of orotic acid to UMP, the precursor of all other pyrimide nucleotides. Affected animals have half the normal activity for this enzyme when heterozygous for the condition. Hmozygous recessive genotypes apparently are lethal in utero. Advances in molecular genetics have permitted the identification of carriers through DNA probes. More often however breeders

have to use pedigree information and progeny testing method for reducing the frequency of such conditions.

**Semilethal Recessive Related to Economically Desirable Traits.**

Fortunately, few characters of this kind are known. In several breeds of swine in both the U.S. and Europe, a port quality problem became apparent in the mid fifties and sixties in type selected for muscularity and thin back fat. It is known as pale, soft and exudative pork (PSE). In the carcasses of the affected individuals the lean tissue is light in color and lack firmness; fluid may seep from cut surfaces. A second condition highly associated with PSE but not completely linked, is the so called port stress syndrome (PSS) in which the affected pigs are unable to withstand even short periods of strenuous physical exercise and may die quickly when subjected to such stress. In some cases susceptible animals may live to market weight and even reproductive ages if not subjected to undue stress. However, death rate may be high, particularly during marketing, and for this reason PSS can be a highly important economic problem. A test involving exposure of pigs to standard level of halothane anesthetic for a prescribed period was devised to identify stress susceptible animals. In this test stress susceptible animals develop muscular rigidity, while normal pigs are unaffected. PSS has been found to be inherited as a simple recessive gene trait. Interestingly it is related to certain blood groups. The most dramatic example of the relationship of PSS to economic traits was reported from Switzerland, where two lines of pigs were selected from the same base population. One for superiority and the other for inferiority on an index based on daily gain and back fact thickness. After six generations, 42 percent of the superior line was halothane susceptible whereas none of the inferior line was affected.

**Detrimental Genes**

Most livestock breeds have standard colors or color patterns which serves as breed trademarks. Most of these are unrelated to productivity, but a few are of economic worth. For example, white udders

in beef cows lead to 'snow burn' if cows calve in spring before snow is gone. Again, pigment in and around the eyes of white-faced cattle reduces the incidence of eye and eyelid cancers. In hot areas with intense sunlight, light coat colors in cattle reflect more heat and thus are an aid in maintaining normal body temperature.

Most basic color variations are inherited in a fairly simple faction, and in many cases maintenance of the breed trademark constitutes no special problem. Shades of color have been a concern in several breeds of both cattle and swine. In spite of the fact that, there is no known relationship between shade of color and productivity, fads for certain shades have sometime developed.

Experiments with small laboratory animals, indicates that in some instances gene affecting coat color also affect the vigoar of the individual. One of the first of this effects was found in a certain strain of yellow mice. When yellow mice were mated, they produced approximately two yellow to one non yellow offspring rather than the 3:1 ration expected if yellow were dominant and non-yellow recessive and yellow mice were heterozygous. It was found that homozygous yellow individuals died at an early stage of gestation, and the surviving yellow animals were heterozygous. Thus, a lethal gene was related to the homozygous yellow color. Platinum foxes are also known to be heterozygous, because they produced two platinum to one silver offspring when mated. The homozygous platinum individual apparently die before birth as a general rule.

Some lethal coat colors have also been reported in farm animals. Sheep of certain gray breed, when mated together, produce progeny of which one-fourths are gray. This indicates that black is recessive. A large proportion of the gray lambs possess as abnormal abomasums as well as other defects of the digestive tract, that causes death within a few months after birth. A recessive gene for gray coat color in Collie dogs is accompanied by an increase susceptibility to infections and death at a young age. Blue-eyed white cats are usually deaf.

In most breed of sheep and cattle, the presence or absence of horns depends fairly upon simple genetic patterns. The size and shape of horns are apparently modified by many pairs of genes, each with minor effects, In most European breeds, the presence or absence of horn usually behaves as if under the control of a single pair of allelic factors with dominant allele resulting in the absence of horns or polledness. In most fine – wool sheep, the presence or absence of horns depends upon a single pair of alleles with heterozygote being horned in males. Females of all genotypes are polled or have a slight amount of horny growth known as knobs. The polled gene is related in some way in breeds of this type to cryptorchidism, a defect in which testicles are retained in the abdominal cavity rather than descended in to the scrotum. Whether the cryptorchidism is due to a apleiotropic effect of the same gene or to a closely linked gene is not known with certainty. A few normal ram have been progeny tested at high levels of probability and are apparently homozygous for the polled gene. This would indicate either: 1. Close linkage which has been broken off. 2. Presences of modifying genes which prevented the expression of cryptorchidism even though this is a normal plieotropic effect of the gene.

**Genetic Abnormalities Affected by Environment Variations.**

The expression of abnormalities in laboratory animals and plants varies within the range of normal environments. The bar-eye condition in the fruit flies. (*Drosophilia melanogaster*) is one of the best known of these. The normal compound eye of this insect has many subunit or facets – usually 800 or more. In bar-eye individuals the number is much reduced, but the reduction is much larger at high rearing temperatures than low. Expressive of abnormality of this type is said to exhibit genetic-environmental interactions. In swine, scrotal hernia has a hereditary base, but its incidence is also influenced by a maternal effect. The nature of the effect is not known, but it appears to have differential effects on different genotypes.

Several defects in farm animals are conditioned partially by hereditary variations of quantitative nature and partially by environmental factors. The best known of these is cancer eye in cattle. It occurs

more frequently in Herefords than in other breeds. Although, it occurs in most geographical locations; within this breed it is more frequent in location with high average annual hours of sunshine. Latitude and altitude are also related to incidence, probably are a result of differences in the ultraviolet component of sunlight. It is usually an affliction of older cattle. Its incidence increases, and it occur at younger sage in cattle maintained on high level of nutrition. Hereditary variations affect the age of cancer development as well as occurrence or nonoccurrence. Hereford cattle with pigmented eyelids and corneoscleral areas are less susceptible than white eyed types. Selection against defects of this type is difficult because they are expressed more frequently at advanced age. A sire may have left many offspring before it is discovered that his daughters have an unusually high susceptibility to a condition such as cancer eye. Selection for pigmented eye should be an effective indirect method of selecting against cancer-eye susceptibility.

**Strategy for Control of Genetic Defects**

The action to be taken if a lethal or genetic abnormality is discovered in a herd depends upon the type of herd and the seriousness of the abnormality. In a commercial herd, the only action usually necessary is to cull the sire or sires which produced the defective offspring and replace them with unrelated males. For most traits the frequency is so low that the probability of obtaining new sires which also carry the defective gene. The probability of acquiring replacement sires which do not carry the delecterious gene or gene can be increased by knowledge of the pedigree lines to avoid. Corrective measures may need to be more drastic in sed-stock herds since the owner has an obligation to provide stocks which will performe well for future customers.

For seed-stock herds, the following should be considered as possible measures for elimination of the defect or for reducing its frequency.

1. Cull all sires which have produced defective offspring.

2. Replace the herd sires culled with animals whose pedigrees indicate there should be only minimal probabilities of the new sires being heterozygous for the defects.
3. Remove all females which have produced defective offspring from the seed-stock herd itself. They may be placed in an auxiliary herd and used to progeny – test future herd sires to determine whether they are heterozygous for the gene(s) responsible for the defect.
4. Cull other close relatives of affected individuals including normal offspring of sires and dams which have produced defective individuals.
5. If the affected individuals are viable and fertile, retain them for progeny – testing prospective breeding animals.
6. Progeny – test prospective herd sires before using them extensively in the herd.

**Penetrance and Expressivity**

A gene does *not* determine a phenotype by acting alone; it does so only in conjunction with other genes and with the environment. In the examples of gene interactions, the genetic basis of the dependence of one gene on another has been worked out from clear genetic ratios. However, in other situations, where the phenotype ascribed to a gene is known to be dependent on other factors but the precise inheritance of those factors has not been established, the terms *penetrance* and *expressivity* may be useful in describing the situation.

Penetrance is defined as the percentage of individuals, with a given genotype which exhibit the phenotype associated with that genotype. For example, an organism may have a particular genotype but may not express the phenotype normally associated with that genotype because of modifiers, epistatic genes or suppressors in the rest of the genome or because of modifying effect of the environment. Penetrance can b used to measure such an effect when it is not known which of these types of modification underlies the effect. On the other hand, expressivity describes the extent

to which a given genotype is expressed phenotypically in an individual. Again, the lack of full expression may be due to the allelic constitution of the rest of the genome or to environmental factors.

Human pedigree analysis and predictions in genetic counseling can often be thwarted by the phenomena of variable penetrance and expressivity. For example, if a disease-causing allele is not fully penetrant (as often is the case), it is difficult to give a clean genetic bill of health to any individual in a disease pedigree (for example, individual R in Figure below).

On the other hand, pedigree analysis can sometimes identify individuals who do not express but almost certainly do have a disease genotype (for example, individual Q in the figure below).

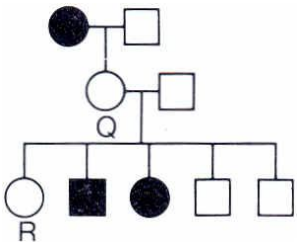



**Figure:** Lack of penetrance illustrated by a pedigree for a dominant allele. Individual Q must have the allele (because it was passed on to her progeny), but it was not expressed in her phenotype. An individual such as R cannot be sure that his or her genotype lacks the allele.

**Phenocopies**

An environmentally caused trait may mimic a genetic trait, for instance a heat shock delivered to *Drosophila* pupae may cause a variety of defects which mimic those caused by mutations in genes affecting wing or leg development. In humans, the drug thalidomide taken during pregnancy caused phenocopies of the rare genetic disease phocomelia, children were born with severe limb defects.

**Pedigree Analysis**

A family history, known as a pedigree, is an orderly diagram of a family's relevant genetic features, extending back to at least both sets of grandparents and preferably through as many more generations as possible. From systematic pedigree analysis in the light of Mendel's laws, geneticists can tell if a trait is determined by alternative alleles of a single gene and whether a single-gene trait is dominant or recessive. A pedigree analysis is the interpretation of these data that allows a better understanding of the transmission of genes within the family. *Pedigrees* are a convention for keeping track of genetic traits used to infer genotype. Pedigree analysis in its broadest sense is the process of making inferences about a particular pedigree-or set of pedigrees-on the basis of partial information. The information available may be of three types: the genealogical structure (how the members of the pedigree are related to each other), the phenotypes (the "data" collected on each pedigree member), and the mode of transmission (the genetic-or other-mechanism underlying the distribution of phenotypes over the members of the pedigree). Pedigree analysis is then used to make inferences about the information that is missing. *Pedigrees* are the human equivalent of test crosses. Usually, at least one member of the family has a genetic disease, and by examining the pedigree, clues to the mode of inheritance of the disorder and the potential risk to other family members can be obtained. A member of a family who first comes to the attention of a geneticist is called the **propositus.** Usually the phenotype of the propositus is exceptional in some way. Many pairs of contrasting human phenotypes are determined by pairs of alleles inherited in exactly the same manner shown by Mendel's peas. Pedigree analysis can reveal such inheritance patterns, but the clues in the

pedigree have to be interpreted differently depending on whether one of the contrasting phenotypes is a rare disorder or whether both phenotypes of a pair are part of normal variation.

Traits associated with dominant, recessive, sex linked, etc. alleles and loci display characteristic patterns in *pedigrees* just as they do when following traits in any organism by any means (i.e., in addition to historical).

Pedigree analysis can also allow estimation of gene penetrance and gene expressivity. Pedigree is initiated by using a symbol to represent the proband or individual seeking counselling. Immediate family members (parents, siblings, spouse, children) are added next, followed by aunts, uncles, cousins, grandparents, and others in the proper orientation. Males are indicated as squares and females as circles. The square or circle is filled in for any affected individuals to reflect their disease status. When two people marry or have children together, a single line is drawn between them. A vertical line descends from this marriage line and then connects to another horizontal line, the sibship line. Short vertical lines descend from the sibship line, one for each of the children of this union. All members of one generation are shown adjacent to one another. There are special symbols to denote, identical twins (a single line from the sibship line that bifurcates for each twin), fraternal twins (an inverted V drops from the sibship line), divorce and remarriage (cross hatches on the marriage line to show discontinuity between the divorced partners and a second marriage line to the new partner), and so on (see fig 1).

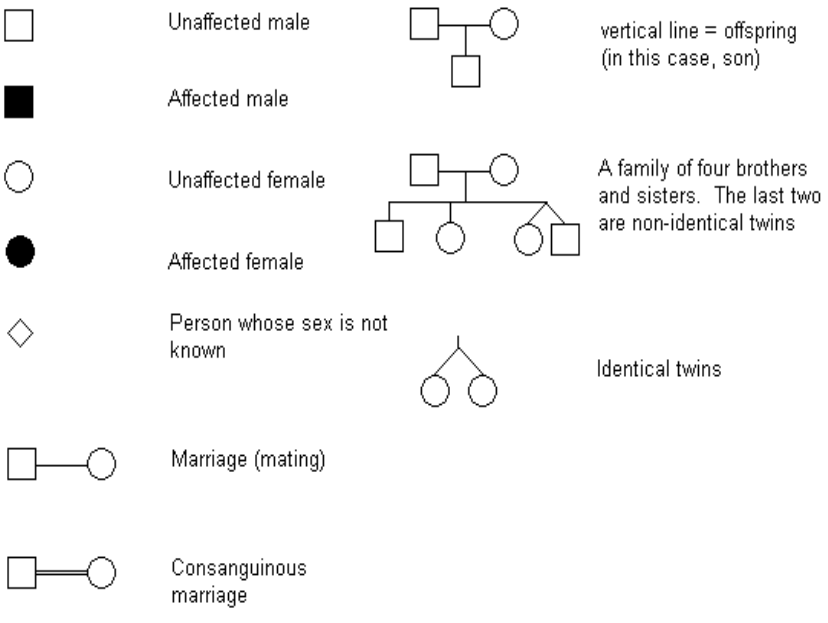


**Fig. 1: Symbols used to draw pedigrees.**

Generations are numbered from the top of the pedigree in uppercase Roman numerals, I, II, III etc. Individuals in each generation are numbered from the left in arab numbers as subscripts, $III_1$, $III_2$, $III_3$ etc.

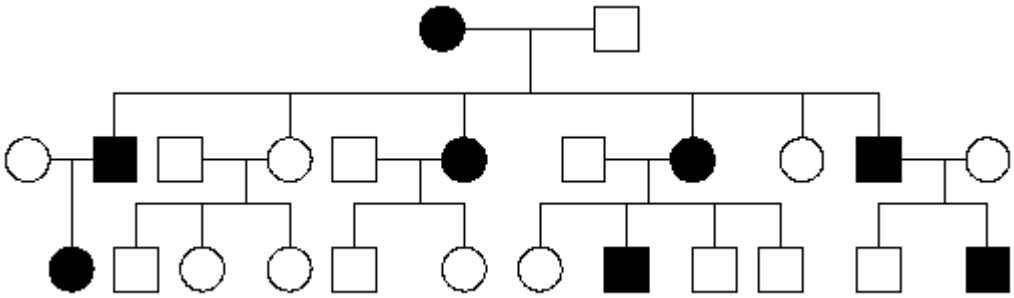
Each generation is labelled at the left with a Roman numeral beginning with the first generation. The members of each generation are consecutively numbered left to right with Arabic numbers, always starting each generation with one. In this way, each person can be specifically identified. For example, the second person in the first generation would be individual I-2, and the sixth person in the fourth generation would be IV-6.

Once the family members are properly arranged, important medical facts can be added. Proper interpretation of the pedigree is dependent upon obtaining accurate information about each individual in a pedigree. The first step in pedigree analysis is to observe the number and relationships of all individuals who express the same or similar clinical features. From this, it should be possible to determine if the disorder is dominant or recessive, autosomal or X-linked by looking for the typical patterns of inheritance. For example, an autosomal disease can usually be distinguished by seeing male-to-male transmission of the mutation, but since males pass only the Y chromosome to their sons, there should never be father to son transmission of an X-linked gene. Males will be most commonly affected in an X-linked disease, whereas males and females should be equally affected in autosomal disorders. In general, a dominant disease will be seen in approximately half of the individuals in each generation, but recessives occur very rarely. If the mutation is in the mitochondrial genome, affected mothers will pass the trait to all of their children, but none of the offspring of an affected male should have the disease.

Most human genes are inherited in a Mendelian manner. We are usually unaware of their existence unless a variant form is present in the population which causes an abnormal (or at least different) phenotype. We can follow the inheritance of the abnormal phenotype and deduce whether the variant allele is dominant or recessive.

**Autosomal dominant**

A dominant condition is transmitted in unbroken descent from each generation to the next. Most matings will be of the form M/m x m/m, i.e.heterozygote to homozygous recessive. We would therefore expect every child of such a mating to have a 50% chance of receiving the mutant gene and thus

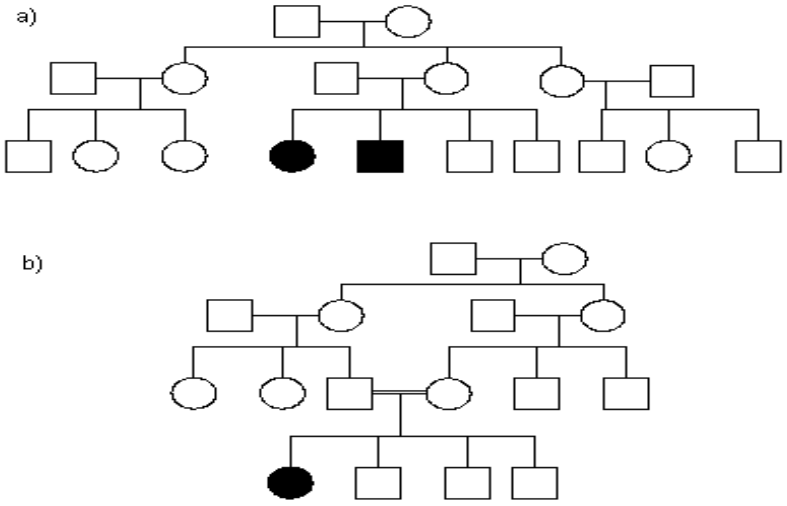


Examples of autosomal dominant conditions include *Tuberous sclerosis*, *neurofibromatosis* and many other cancer causing mutations such as *retinoblastoma*

**Autosomal recessive**

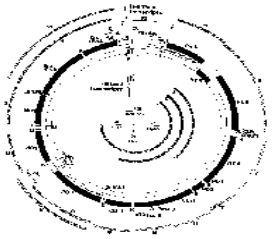
A recessive trait will only manifest itself when homozygous. If it is a severe condition it will be unlikely that homozygotes will live to reproduce and thus most occurrences of the condition will be in matings between two heterozygotes (or carriers). An autosomal recessive condition may be transmitted through a long line of carriers before, by ill chance two carriers mate. Then there will be a ¼ chance that any child will be affected. The pedigree will therefore often only have one 'sibship' with affected members.

a) A 'typical' autosomal recessive pedigree, and b) an autosomal pedigree with inbreeding:




If the parents are related to each other, perhaps by being cousins, there is an increased risk that any gene present in a child may have two alleles identical by descent. The degree of risk that both alleles of a pair in a person are descended from the same recent common ancestor is the degree of inbreeding of the person. Let us examine b) in the figure above. Considering any child of a first cousin mating, we can trace through the pedigree the chance that the other allele is the same by common descent. Let us consider any child of generation IV, any gene which came from the father, $III_3$ had a half chance of having come from grandmother $II_2$, a further half chance of being also present in her sister, grandmother $II_4$ a further half a chance of having been passed to mother $III_4$ and finally a half chance of being transmitted into the same child we started from. A total risk of½ x ½ x ½ x ½ = 1/16

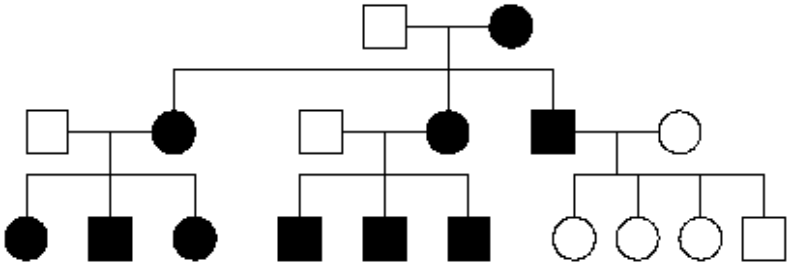
This figure, which can be thought of as either the chance that both maternal and paternal alleles at one locus are identical by descent or the proportion of all the individual's genes that are homozygous because of identity by common descent, is known as the coefficient of inbreeding and is usually given the symbol F.



**Mitochondrial inheritance**

The human mitochondrion has a small circular genome of 16,569 bp which is remarkably crowded. It is inherited only through the egg, sperm mitochondria never contribute to the zygote population of mitochondria. There are relatively few human genetic diseases caused by mitochondrial mutations but, because of their maternal transmission, they have a very distinctive pattern of inheritance.

*A mitochondrial inheritance pedigree*



All the children of an affected female but none of the children of an affected male will inherit the disease.

**Once** the inheritance pattern of the disorder is determined, the status of family members in the pedigree can be evaluated. By carefully observing the position of affected individuals, mutation carriers may be identified. From this data, the risk of carrier status for other family members or the chance that a couple may have an affected child can be estimated.

Pedigrees are also maintained for many animals, though the purpose of pedigree analysis is somewhat different. The data contained in the pedigree are generally utilized to select individuals

with specific characters for breeding purposes. Animals with unfavourable traits are eliminated from consideration so that the next generation will include individuals with more of the preferable traits. For each species, the characters of choice will vary. In the thoroughbred world, pedigree analysis tries to combine speed with stamina and a will to win that will yield winning racehorses. For cows, sheep, and pigs, such characteristics as high milk production, higher muscle content, or better wool are desirable. Even some plants have pedigrees as researchers strive to find drought and pest resistant species with high crop yields.

**Questions**

1. The following pedigree could be the result either of the segregation of an autosomal dominant condition or of an autosomal recessive. In the former case what is the risk for individual $III_6$ of having a child affected with this condition. In the latter case, who in the pedigree is an obligate carrier? And which other members of the pedigree are at risk of being carriers. Write down their risks.