COURSE CODE:	ABG 505
COURSE TITLE:	Heredity and Environment
NUMBER OF UNITS:	3 Units
COURSE DURATION:	Five hours per week

COURSE DETAILS:

Course Coordinator:	**Dr. M.N. Bemji**
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Other Lecturers:	**Dr. M.A. Adeleke**

COURSE CONTENT:

Qualitative and quantitative characters, Variation and measure of variation, Probability, Binomial distribution, Chi-square, Variance, standard deviation, standard of error means, Gene interactions (including modifier genes), Maternal influences, Extranuclear transmission, Penetrance, Expressivity, Pleiotropy, and Animal genetic resources: indigenous

COURSE REQUIREMENTS:

This is a compulsory course for all students in the Department of Animal Breeding and Genetics. In view of this, students are expected to participate in all the lectures and practical and <u>must</u> meet up with a minimum of 75% attendance to qualify for the final examination.

READING LIST:

Hartl. D.L. and Jones, E.W. 2005. Genetics: Analysis of genes and genomes, 6th edition, Jones and Bartlett publishers, Inc. Pg. 854.

Klung, W.S. and Cummings, M.R. 2000. Genetics, 6th edition, Prentice Hall, Inc. pg. 816.

Stansfield, W.D. 1986. Schaum's outiline of theory and problems of genetics, 2nd edition, McGraw-Hill Book Company. Pg. 392.

LECTURE NOTES

Introduction

Heredity: Tendency of living organisms to pass their characteristics onto offspring.
Hereditary: Passed on from parent to offspring or from one generation to another. E.g. Disease.
Heritable: Capable of being inherited.
Environment: Surroundings, circumstances or influences. It is the genetic or non-genetic factors that influence the phenotypic value.

Observed performance - the phenotype of an animal is the result of interaction between a genotype and its specific environment throughout life from the time of fertilization. i.e. the form and function of any organism is dependent on the interaction of two simultaneously operating factors: *heredity and environment*. The potential for growth and development is determined by heredity. The actual degree to which the potential is realized is governed by the environment. i.e. The expression of a gene or group of genes is a function of heredity and environment. The environment include both the genetic environment (other genes present) and the physical environment such as weather (*temperature, rainfall, humidity* etc), diet, location etc.

Qualitative (*Mendelian)* characters
Qualitative characters are sharply defined inherited characters which can be placed into distinct phenotypic classes or categories. Features of qualitative traits include:

1. They are governed by single or few pairs of genes each of which segregate independently of others during gamete formation. E g. coat colour in cattle, presence or absence of horns, quality of pea plants, its pods, seeds etc.

2. Individuals in a population can be placed into discrete phenotypic classes. Genes are not linked on the same chromosome and therefore assort independently of one another at gamete formation.

3. Their expression is usually not affected by environment.

4. The variation in qualitative characters is called discontinuous or discrete variation.

5. Their study depends on counting. With characters that show discontinuous distribution of phenotypic values, ratios are usually calculated. Test of these ratios with respect to hypothesis are performed using Chi-square statistic.

Individuals in a population segregating for the yellow/white genes in poultry can either have yellow skin or white skin with no intermediates. It was on characters showing discrete variation that Mendel developed his theories of genetic control of segregation.

Many simple inherited traits of Qualitative nature are important in animal breeding. They may be of direct economic importance or they exert harmful effects which completely out shadow or prevents the expression of genes controlling desired quantitative traits. The expression of many qualitative traits can be related to one or a few pairs of genes. Numerous qualitative traits have been identified as having a genetic basis in farm animals. For many the mode of inheritance is well established. In others a hereditary basis is known to exist but the exact mode of inheritance is not known with certainty.

It is sometimes assumed that continuous variation in a character is necessarily caused by a large number of segregating genes so that continuous variation is taken as *prima facie* evidence for control of the character by many genes. But this is not necessarily true. If the difference between genotypic mean is small compared with the environmental variation then even a simple one gene Z allele can result in continuous phenotypic variation.

Of course the range of a character is limited and if there are many segregating loci influencing it then we expect the character to show continuous variation because each allelic substitution must account for only a small difference in the trait.

Some examples:

Coat colour

Coat colour in mammal is due to the presence in hair or wool a pigment granule consisting of melanin in a protein framework. The melanins on this granule are formed by a series of metabolic pathways that convert tyrosine to eumelanin (dark colour) in phaeomelanin (light colour). Eumelanins are often described as black although they include brown and the derivative of black and brown. Phaeomelanin which are often called yellow can range from a rather bright yellow to red. The cells in which melanin production occurs are called melanocytes and the resultant pigment granules are known as Eumelanosomes or phaeomelanosomes.

Although much remains to be discovered about the genetic control of pigment formation, it is now generally acceptable that at least six autosomal loci each with multiple alleles influence the production and distribution of pigment. The most interesting aspect of these six loci is that they appear to exist in all mammals. Although not all species of mammals have all known alleles at any locus there are enough examples of similar coat colours and for pattern inherited in a similar way in several different species to present a convincing picture of homology of coat colour and coat pattern alleles among species. Because there is a series of more than two alleles of most of the coat colour loci, each locus is often referred to as Series.

Agouti (A) series

The term Agouti refers to the salt and pepper appearance of coat of wild mice and rabbits. The distinctive colour of the Agouti *A* allele is due to a subterminal yellow band in otherwise black hairs.

Prolificacy

Another sheep gene that has created considerable interest is the fecundity gene F_1 that appears to be the major cause of the prolificacy seen in the Booroola strain of Australian Merino.

The effects of the F gene on ovulation rate and on litter size in Merino are illustrated in Fig 1. It can be seen that ff homozygotes have an ovulation approximately 3 times that of homozygous for the normal (f) gene and that heterozygotes F1 have an intermediate ovulation rate .The increases in ovulation rate are reflected in ff homozygous- having a litter size approximately double that of FF homo- with hetero- again being intermediate.

Polledness

In general, the presence or absence of horns can be attributed to the action of two alleles at an autosomal locus with the polled (P) being dominant to the horned (p). Many breeds of domestic livestock are horned and are therefore homozygous for p.
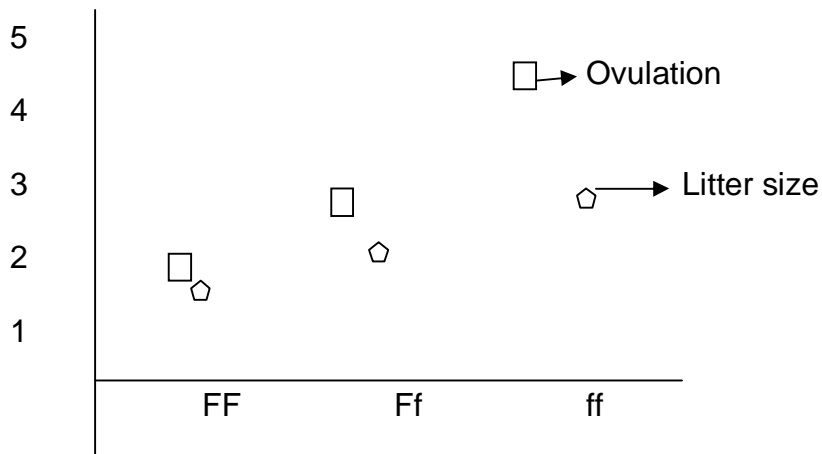

Fig 1.

Quantitative (Metric) characters

Quantitative characters are those that result from the combined effects of many different genes acting additively. Such traits cannot be placed into discrete phenotypic categories. *Hence a quantitative character could be defined as one for which the average phenotype difference between genotypes are small compared with the variation between individuals within genotypes.* Most of the *characters of economic value* to animal and plant breeders are metric characters. The main features of quantitative traits include:

1. They are governed by many pairs of genes.
2. They demonstrate considerable variation and are not easily categorized into distinct phenotypic classes. i.e. They show variation from one phenotypic extreme to another.
3. Their study depends on measurement instead of counting.
4. The traits are usually affected by environment to a large extend. Phenotypes are the outcome of interaction among genes and between genes and the environment.
5. The type of variation exhibited by quantitative characters is called continuous variation.

 Polygenes governing quantitative characters obey the same laws of transmission as those governing qualitative characters, but since it is not possible to place individuals

into distinct classes, one cannot talk of classical Mendelian ratios for quantitative characters.

Table 1. Quantitative traits and their heritabilities in domestic livestock

Specie	Trait	Heritability (h^2)
Sheep/goat	Litter size	10
	Birth weight	40
	Weaning weight	40
	Milk yield	
	Fleece weight	45
	Survival to weaning (dam trait)	
	Fertility (probability of conceiving)	
Cattle	Adult body weight	65
	Weaning weight	
	Milk yield	35
	Butter fat	40
	Efficiency of gain	35
Pigs	Back fat thickness	70
	Weight gain per day	40
	Feed conversion ratio	50
	Litter size	5
Poultry	Body weight at 32 weeks	55
	Egg weight at 32 weeks	50
	Egg production at 72 weeks	10
	Fertility, hatchability, livability	5 each

Characters with lowest heritability are those most closely connected with reproductive fitness. *Heritability expresses the proportion of the total variance that is attributable to the average effects of genes (What determines the degree of resemblance between relatives).* It has a predictive role, expressing the reliability of the phenotypic value as a guide to breeding value. Only phenotypic values can be measured, but it is the breeding value that determines the influence on the next generation.

The frequency distribution of most continuously varying characters approximate more or less closely to normal curves.

An example of metric character is illustrated in the Fig. 2 below. The variation is represented graphically by the frequency distribution of the measurement. The measurements are grouped into equally spaced classes and the proportion of individual falling in each class is plotted on a vertical scale. The resulting histogram is discontinuous only for the sake of convenience in plotting if the class ranges were

made smaller and the number of individuals measured were increased indefinitely, the histogram used become a smooth curve. In the study of metric characters therefore, it is possible to make use of the properties of the normal distribution and to apply the appropriate statistical techniques.
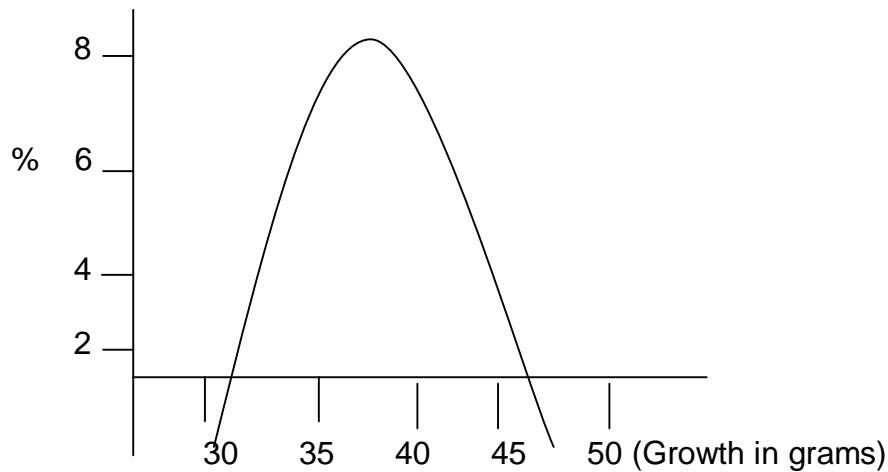

Fig. 2.

Many of the applications of quantitative genetics involve the assumption that data follow a normal distribution. It can be concluded that quantitative characters are determined by the combined actions of alleles at many loci most of which have a relatively small effect on the character and a number of non-genetic environmental factors.

VARIATION

The examination of most animal species reveals the existence of phenotype difference between individuals for example in cattle there are obvious differences in coat colour and the presence and absence of horns. If cattle are weighed or if milk production is recorded, there will be difference in performance between individuals. This difference between individuals of the same species or breed for the same trait or character is called Variation. This may be classified into two or more categories depending on the character examined and upon the unit of measurement used.

Those characters for which there are two or only relatively few categories are described as showing discrete variation. The number of categories is large and limited to the units

and accuracy of measurement used for classification. These characters are described as showing continuous variation. Two categories, discrete and continuous variations are the extremes of a scale of variation which can be found by investigating a number of characters. Variation among animals in size, rate of growth, efficiency of feed utilization, carcass characteristics, disease resistance etc has been observed.

Both heredity and environment are important in producing difference among individual animals. In some instances, there are specific hereditary and environmental influences that may produce variability which is not directly attributable to either but which is a result of their joint action or interaction.

Causes of Variation

Traits generally are grouped into those which show qualitative differences and those which show quantitative differences. In the former the variation fall into a few clearly defined classes which is usually due to the fact that these traits are under the control of one or a few pairs of genes whose final expression is not greatly influenced by external environmental factors. The polled or horn consideration in cattle is an example of qualitative traits. Quantitative variation on the other hand shows all manner of variations from small to large as are found in milk production and rate of gain.

The study of variation consists of two stages. The first is a description of the phenotypic variation. The second is a translation of this phenotype into genetic terms and the description of the variation genetically. A measure of genetic variation is the amount of heterozygosity at a locus in a population which is given by the total frequency of heterozygotes at a locus. Phenotypic variation refers to the observable or measurable difference among individuals within a population for a particular trait. If there were no variation among individuals there would be no need to select or cull animals for breeding purposes, because from the genetic standpoint they would all look and perform alike. The phenotypic variations are seldom if ever completely due to different genes.

Causes of phenotypic variation in farm animals

1. **Heredity**

The genotype of an individual is fixed at conception and having a mutation remains the same for the remainder of its life. Its genetic makeup is determined by the genes that it receives from both parents.

The individual as well as its parent possess thousand of genes. The exact number has not been determined probably only two animals resulting from sexual reproduction that are alike genetically are identical twins produced by a single fertilized egg. Members of an inbred line are more likely to be alike genetically than non inbred individuals.

The degree of genetic similarity among individuals within an inbred line increases as the amount of inbreeding increases especially if there is directional Selection.

Parents homozygous for many pairs of genes will have more offspring that are more alike genetically than parents that are heterozygous for several of genes. In fact genetic variability within a species is almost unlimited.

A qualitative trait affected by only one pair of genes may vary in a population because of a difference in the frequency of the two alleles. At the same locus, economic trait may also vary genetically for the same reason but they also vary because of difference in the frequency of genes at several different loci.

2. **Environment**

Phenotypic variations in economic traits due to environment are also of great importance.

The environmental portion of the phenotypic variation may be denoted by the symbol σ^2_e. Environment includes all such factors as disease, nutrient supply, temperature effects accident and others which the individual may encounter from the time of conception until its death.

Phenotypic variations due to environment are important because:

(1) They are not transmissible,

(2) They overshadow variation due to heredity,

(3) The environmental component is necessary for an individual to reach its genetic potential and

(4) Rapid improvement can be made in the efficiency of livestock production by supplying uniform and superior environmental conditions to breeding animals.

3. **Interaction between heredity and Environment**

The interaction between heredity and environment means that animals of a certain genotype may perform more satisfactorily in some environment than in another. In other words one environment permits the expression of the genetic characters in a breed or strain while another does not.

Many kinds of heredity X environmental interaction are possible. It is well known that the Braham crosses perform very well satisfactorily in the tropics and some arid regions as compared to the British breeds because they are more resistant than the British breeds to certain diseases, parasites and high temperature. In more temperate regions of the world however where disease and heat are not as important they might not perform as well as British crosses.

Measures of variation

Extrapolation of phenotype back to chromosomal gene is dangerous for characters showing both discrete and continuous variation, since the physiological processes involved between the 2 stages are extremely complex. However, a body of mathematical theory was developed by Wright, Fisher, Lush and others to interpret genetic control of characters showing continuous variation. This approach has been shown by experiment to be satisfactory in describing biological variation under different environmental circumstances and predicting changes in means and variations of populations under selection. The theory assumes that genes at any one locus act according to Mendelian principles and that genetic control of a quantitative character is the result of the combined action of genes at many loci. Since quantitative variation is a statistical concept, statistical methods are used in investigation it. *Two statistical concepts used to describe these observations are mean (x) and standard deviation (σ)*.

Variance

The amount of variation is measured and expressed as the variance when values are expressed as deviation from the population mean. *The variance is usually denoted by σ^2 and is defined as the average of the squared deviations from the mean.* It is the most useful measure of variation for studying the variability of population.

Backfat thickness of live pigs measured at a market weight of approximately 800 lb.

Back fat thickness (mm) X_i	Variation from the mean $(X_i\text{-}\bar{X})$	Square of deviation $(Xi\text{-}\bar{X})^2$	Square of each observation X_i^2
47	8.50	72.25	2209
38	-0.05	0.25	1474
39	-0.50	0.25	1521
32	-6.50	42.25	1024
34	-4.50	20.25	1156
37	-1.50	2.25	1369
31	-7.50	56.25	961
43	4.50	20.25	1809
41	2.50	6.25	1681
43	4.50	20.25	1849
385	0	240.50	15,063

The deviation of each observation from the X_i was determined $(X_i\text{-}\bar{X})$ in column 2. Each deviation was squared and all of the squared deviations from the mean totaled $\sum (Xi\text{-}\bar{X})^2$ to give 240.50. The last column represent each item squared whereas $(\sum x^2)$ represents the sum of items squared 15, 063 which will be used in the calculation of the variance. Since the number of items in column 1 is 10 and the sum of all 10 observation is 385 the mean of 10 observations is 385/10=38.50.

A frequently asked question is why we don't use the average of the variation instead of the average of the squared variations. If when we add all the deviations and may start alteration of the sign of each deviation the sum of the deviation is equal to zero. Thus, the average of the deviation from the mean would be zero also.

Another and probably more important reason for squaring the deviations and averaging them magnify and give more weight to extreme values in the group of observation. Squaring the deviations and averaging them also make it possible to perform other statistical measurement in a correct mathematical manner.

Once the sum of the squared deviations from the mean is determined, the variance σ^2 may be calculated by dividing by the total number of observation in the sample minus one (n-1).

From the table, variance σ^2 therefore would be 240.30/9=26.72

If we were to calculate the variance for a group of 200-300 pigs, it would be very time consuming to go through the procedure above and the chance of error would be greatly increased. By using the following equation therefore variance can be estimated.

$$\sigma^2 = \frac{\sum x^2 - (\sum x)^2/n}{n-1}$$

where $\sum x$ is the sum of all sires of all dams

$\sum x^2$ is the sum of all items squared

n is the number of observations in the sample

$$\sigma^2 = \frac{15063 - 385^2/10}{9} = 240.5/9 = 26.72$$

One of the most useful properties of the variance is that it can be separated by special analysis into its various component parts. The standard deviation is a much more accurate measure of variation on a population than is the range and can be used very extensively together with the mean to describe a population.

The Standard deviation is the square root of the variance. The following formula may be used.

S.D (σ) = $\sqrt{\dfrac{\sum x^2 - (\sum x)^2/n}{n-1}}$

= √2405/9

= √26.75

= 5.17

Coefficient of Variation

It is sometimes desirable to compare the variability of traits measured in different units. The standard deviation expressed as a percentage of the mean is termed the coefficient of variation and the formula for computing it from a sample population is

CV = $\dfrac{\sigma}{\bar{X}}$ x 100

Assignment

Draw a frequency distribution or graph of first lactation milk yield in a population of Friesian cows having the following records. Determine the mean, SD and CV of the distribution.

No. of cattle	2	3	8	7	3	2
Milk yield, kg	1500	2000	3000	3500	4000	4500

Correlations

Correlation deals with the relationship between two variables. Many variables in nature vary together but in an imperfect or approximate way. Correlated characters are of interest for 3 main reasons:

1. In connection with the genetic causes of variation through pleiotropic action of genes. Pleiotropy is a common property of major genes.

2. It is important to know how the improvement of one character through selection will cause simultaneous change in other character.

3. In natural selection, the relationship between a metric character and fitness is the primary agent that determine.

Causes of correlation

In genetic studies, it is necessary to distinguish two causes of correlation between characters, *genetic* and *environmental*. The genetic cause of correlation is chiefly *pleiotropy*, though linkage is a cause of transient correlation particularly in population derived from crosses between divergent strains. Pleiotropy is simply the property of a gene whereby it affects two or more characters. It causes simultaneous variation in the character it affects. eg gene that increases growth rate increases both stature and weight, so that they tend to cause correlation between these two characters. Genes that increase fatness however, influences weight without affecting stature and are therefore not a cause of correlation. The degree of correlation arising from pleiotropy expresses the extent to which the characters are influenced by the same genes.

The environment is a cause of correlation if characters are influenced by the same environmental conditions. Again the correlation resulting from environmental causes is the overall effect of all the environmental factors that vary, some may tend to cause a positive correlation others a negative one.

Measure of correlation

The measure of the relationship between 2 variables X and Y is the correlation coefficient. The correlation coefficient measures the degree of association between 2 traits or variables in a sample from the population. It ranges in value from **-1 to +1.**

It is calculated in part from the product of the deviation of each observation of X from the mean of the Y values - a quantity called Covariance of X and Y.

$$COV_{xy} = \frac{(X_1 - \bar{X})(Y_1 - \bar{Y}) + (X_2 - \bar{X})(Y_2 - \bar{Y}) + (X_n - \bar{X})(Y_n - \bar{Y})}{n}$$

$$= 1/n \sum (X_i - \bar{X})(Y_i - \bar{Y})$$

$$\text{Corr } (r) = r_{xy} = \frac{\text{Cov}_{xy}}{\sum_X \sum_Y}$$

$$r = \frac{\sum \hat{X}\hat{Y}}{\sqrt{(\sum \hat{X}2)(\overline{\sum}\hat{Y}2)}}$$

$$= \frac{\sum XY - (\sum X)(\sum Y)/n}{\sqrt{(\sum X^2) - (\sum X)^2/n}(\sqrt{(\sum Y^2)} - (\sum Y)^2/n}$$

Correlation coefficients are subject to sampling fluctuations and the value obtained will be limited in its representation of the association between the two traits in the population. Correlation and variance are related and in many respects represents two different ways of viewing variation. The square of the correlation coefficient is a measure of the portion of the variance in one variable, say Y that can be accounted for by variation in a related variable X.

Regression

The measurement of correlation provides us with estimates of the precision of relationship between 2 variables. A related situation is predicting the value of one variable given the value of the other. If two variables are linearly related, then the relationship can be expressed as:

Y=bx+a

Where b is the slope of the line relating Y to X and a is the Y intercept of that line. The regression coefficient b measures the amount of change in one variable (y) associated with a unit change in the second variable (X).
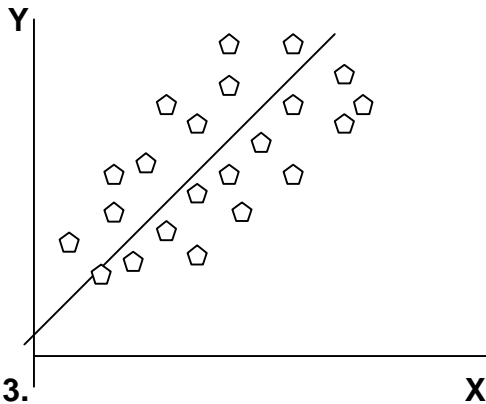
Fig 3.

Fig. 3 shows a scattered diagram of points for 2 variables Y and X together with a straight line expressing the general linear trend of Y with increasing X. This line called the regression line of Y on X has been positioned so that the deviations of the points from the line are as small as possible. Specifically, If dY is the distance of any point from the line in the Y direction, then the line has been chosen so that $\sum dY^2$ is at its minimum.

Slope b of the line is calculated by:

b= $\dfrac{COVxy}{S^2_x}$

Or $\sum XY/ \sum X^2$

a = y-bx

So that the line passes through the point X,Y. Estimates of b and a will yield the least squares prediction equation. Note that the prediction equation cannot predict Y exactly from a given X because they are scattered around the line. The equation predicts the average Y from a given X value.

PROBABILITY

Practically everything we embark upon is based on a conscious consideration of the probability that something will or will not happen. We can never be absolutely sure about what will happen or why a certain event occurs. We often attribute things to chance which simply means that the causal condition are so complicated that an individual case cannot be analysed but nevertheless they follow certain laws which can be revealed by studying a large number of random events.

The concept of probability or chance is the basis of most decisions in life. Farmers consider the probability of producing good crops or animals before planting in any season or setting up any production system. An appreciation of the law of chance is basic to the understanding of transmission of hereditary traits or characters. Genetic ratios are most properly expressed as probabilities. E.g. ¾ tall and ¼ dwarfs. These values predict the outcome of each fertilization event such that the probability of each zygote having the genetic potential for becoming tall is ¾ while the potential for becoming dwarf is ¼.

Terms in probability

1. *Mutually exclusive events*

Two events are said to be mutually exclusive when the occurrence of one simply means that the other cannot occur. E.g. In treating a sick animal, success may mean survival and failure death. The probability must be a number between 0 and 1.

2. *Independent and dependent events*

In repetitive processes, the occurrence of one event may or may not depend on the other. If a die is thrown twice, the appearance of one number in the second throw does not depend on what appeared in the first throw. These events are independent.

Outcomes are not independent when the probability of occurrence of an event depends on the other.

Theorems in probability

1. **Addition theorem** (*Either or*)

For mutually exclusive events, the probability of the occurrence of either A or B is

$$P(A \text{ or } B) = P(A) + P(B)$$

The sum law is therefore applied where possible outcome of 2 events are independent of one another but can be accomplished in more than one way.

Ex.1. What is the probability that a litter size of 2 lambs will consist of all males (M) or all females (F)?

Solution: $(a+b)^2 = a^2 + 2ab + b^2$

                  (MM+MF,FM+ FF)

Assumptions: prior to parturition, P(M) = 0.5 and P(F) = 0.5

                  P(all Males or Females) = (½)(½) + (½)(½) = ½

Ex. 2. A small ruminant unit contains 50 ewes, 10 rams and 16 goats. Find the probability of getting an ewe or goat in a single trial.

      P(ewe) = 50/76 = 0.66

      P(goat) = 16/76 = 0.21

      P(ewe or goat) = 0.66+0.21 = 0.87

2. **Multiplication theorem** (*Both*)

When two events are independent, both can occur in a single trial or successfully in a series or runs.

      $$P(A \text{ & } B) = P(A) \times P(B)$$

The law of product probability was derived which states that the probability of two independent events occurring simultaneously is the product of their separate probabilities.

The outcome of each event does not affect the outcome of any of the others under consideration.

E.g. The dihybrid ratio is also obtained by multiplying the expected monohybrid ratios for 2 gene pairs considered separately as in the inheritance of coat colour and horness/pollness in cattle.

Assignment

1. Draw the monohybrid and dihybrid crosses to illustrate this.

2. What is the probability that a litter size of 3 kids will have (i) 3 males (ii) 1 male and 2 females (iii) 1 female and 2 males (iv) all females?

The probability laws are useful in transmission genetics such as Mendel's dihybrid and trihybrid inheritance. To know the results of a cross, calculation of the probability of each possible outcome is needed. The results can be used to predict the proportion of offspring expressing each phenotype or each genotype. It is important to note that predictions of possible outcomes are based on large samples sizes. If it is predicted that 9/16 of the offspring of a dihybrid cross will express both dominant traits, it is very unlikely that in a small sample, exactly 9 out of 16 offspring will express this phenotype. Instead, the prediction should be that, of a large number of offspring, approximately 9/16 of them will do so. The deviation from predicted ratio in smaller sample sizes is attributed to chance. The impact of deviation due strictly to chance is reduced as the sample size increases.

When we toss a coin the chances are equal that it will come down with the head or tail. The probability of each of these two occurrences is half (1/2). If we throw a die, the probability that it will turn up any particular number of the six possible sides is one-sixth (1/6).

In summary,

1) The sum of the probability of an event happening and an event not happening is always equal to one.

2. For mutually exclusive events, the probability of the occurrence of either A or B is the sum of their individual probabilities.

3) If two events are independent the probability that both will occur is the product of their individual probabilities.

e.g, If a coin is tossed thrice the probability of getting two heads in succession is 0.5x0.5 $=0.5^2$ =0.25. Obtaining a head 3 times in succession is 0.5^3 = 0.125 and so on. If two coins are tossed simultaneously there are four possible combinations: H+H, H+T, T+H and T+T.

Two of these possibilities are however equivalent and one can say that the combination of H+T has twice as great a chance of occurring as each of the other 2 combinations. The probability of obtaining different combination can be calculated is as follows:
 H+H= 0.5x 0.5 =0.25, H+T=2x0.5x0.5=0.5 and T+T =0.5x 0.5=0.25.
The probability of getting at least one head in spinning two coins simultaneously is obtained by adding the individual probabilities for H+H and H+T=0.25+0.5=0.75

The above examples have a direct application to Mendelian inheritance. Several species of mammals give birth to more males than females. The sex ratio is therefore somewhat higher than 0.5. The deviation is however quite small and can be disregarded. It can be assumed therefore that the probability of a calf being a heifer is equal to the probability of being a bull =0.5. If a cow had 6 calves during her lifetime, the probabilities of each of the 7 possible sex combinations are as follows.

6f	5f+1m	4f+2m	3f+3m	2f+4m	1f+5m	6m
1/64	6/64	15/64	20/64	15/64	6/64	1/64

These probabilities are obtained by developing the binomial $(1/2+1/2)^6$ or in generalized form $(p+q)^n$ 'where p is the probability of the one event, *q* the other probability of the other event and n the total number of events. A distribution of this type is said to be binomial.

$(p+q)^6 = p^6+6p^5q+15p^4q^2+20p^3q^3+5p^2q^4+6pq^5+q^6$

The probability that all the progenies will males = $(0.5)^6$

$=0.5^6=(1/2)^6=1/2x1/2x1/2x1/2x1/2x1/2=1/64$

If dominance occur e.g in mating between black animals which are heterozygous for red colour the expected proportion of the progeny are 3black:1red. If only 4 progenies are obtained, there are 5 different combinations and the probability for each of these can be calculated by developing the binomial.

The probability of obtaining 3 black and 1 red is 0.422 and the probability of obtaining 4 red calves is only 4 in 1, 000.

The coefficient for the binomial distribution can be obtained from **Pascal's triangle** as illustrated under binomial distribution.

BINOMIAL DISTRIBUTION

Binomial distribution takes into consideration a nominal scale data that comes from a population with only 2 categories. Ex. Members of a mammalian litter classified as male or female, victims of an epidemic as dead or alive. Any mathematical term made up of 2 quantities is known as a binomial term. Thus a+b, p+q and x+y are all binomial expressions.

Sampling a binomial distribution is like drawing individual animals from a herd with replacements, unlike hyper-geometric distribution (drawing samples without replacements). Frequency of samples consisting of no male, 1 male, 2 males, 4 males, 4 females etc would be described by a binomial distribution. The probability associated

with an event such as drawing a particular sex is constant from trial to trial. The events are said to be mutually independent or simply independent. In a single binomial event, there are two possible outcomes only one of which can occur. Mathematicians refer to this as 'success' or 'failure'.

Binomial probabilities

The usual sampling procedure consists of observing a number of events and recording the numbers of successes or failures. Thus the probability distribution usually required is the distribution of number of successes. If a random sample of size n is taken from a binomial population, the probability of x individuals being in one category (and therefore n-x individuals in the second category) is given by:

$$P\left(X = \underline{x}\atop N\right) = \binom{n}{x} P^x (1-P)^{n-x}$$

i.e. 'The probability that the number of successes, x will equal x in n random trials …'
where $\binom{n}{x} = {}^nC_x = \dfrac{n!}{x!(n-x)!}$

In other words,

$$\mathbf{P(X)} = \frac{n!}{x!(n-x)!} \; P^x q^{n-x}$$

which refers to the probability of a sample consisting of a particular arrangement of x items, each having a probability P, and n-x items each with probability, q.

$\dfrac{n!}{x!(n-x)!}$ is a binomial coefficient and expresses the number of ways x items of one kind can be arranged with n-x items of a second kind. The binomial coefficient is often written in a combinational notation, ${}^nC_x = \dfrac{n!}{x!(n-x)!}$

Example:

1. What is the probability that a litter size of 6 piglets will (a) consist of 6 females? (b) all of the same sex?

Assumption:

- The binomial distribution holds

- Prior to parturition, $P(m) = P(f) = 0.5$ or $\frac{1}{2}$

- Events are independent

(a) The required probability is: $P(X) = \dfrac{n!}{x!(n-x)!} P^x q^{n-x}$

$$= \dfrac{6!}{6!(6-6)!} \tfrac{1}{2}^6 \tfrac{1}{2}^{6-6} \quad = 1/64 \quad = 0.016$$

(b) The probability of the piglet being all of the same sex is:

$$2 \times 0.016 = 0.0312$$

Note:

Permutation: To permute a number means to produce different arrangements.

   E.g. 9! (9 factorial) = 9x8x7x6x5x4x3x2x1

Combination: If you have n items to choose from, taking x at a time without regard to arrangement, we are concerned with the number of combinations. E.g. $^nC_x = \dfrac{n!}{x!(n-x)!}$

Pascal's triangle

n	Binomial coefficients
0	1
1	1 1
2	1 2 1
3	1 3 3 1
4	1 4 6 4 1
5	1 5 10 10 5 1
6	1 6 15 20 15 6 1

Note: the coefficient in each term indicate the number of ways each different combination can occur.

$(a+b)^0 = 1$
$(a+b)^1 = a+b$
$(a+b)^2 = a^2+2ab+b^2$
$(a+b)^3 = a^3+3a^2b+3ab^2+b^3$
$(a+b)^4 = a^4+4a^3b+6a^2b^2+4ab^3+b^4$
$(a+b)^5 = a^5+5a^4b+10a^3b^2+10a^2b^3+5ab^4+b^5$
$(a+b)^6 = a^6+6a^5b+15a^4b^2+20a^3b^3+15a^2b^4+6ab^5+b^6$

$(a+b)^3 = a^3+3a^2b+3ab^2+b^3$ indicates that there are 8 possible combinations: only one way of getting all successes or all failures in 3 trials; 3 ways of getting 2 successes and 3 ways of getting only one success.

Also note that the power attached to the first quantity in the term decreases by one down the line while those of the second term increase. Thus the binomial expansion can be used to work out the probability of occurrence of an event, given a number of trials, n. The probability will be in the term $(a+b)^n$.

Assignment

1. Using Pascal's trianlge, calculate the probability that a litter size of 6 piglets will consist of (a) 6 females (b) all of the same sex (c) 4 males (d) 3 females.

2. Solve the following using permutation and combination:

(a) If a sample of 5 is taken from a population composed of 50% females or 50% females, determine the probability of the sample containing 0 male, 1 male, 2 males, 3 males, 4 males and 5 males.

(2) Draw a graphical representation of the binomial distribution for p=0.5 and q=0.5, where n=5 and describe the distribution.

Chi-square goodness of fit

In general, the x^2-test tells us how often observation deviate from expectations purely on basis of chance. How well a given set of results fits those to be expected on the basis of a particular genetic hypothesis can be tested by x^2. This test is often termed the test of goodness of fit. The procedure is as follows.

1) **State a simple hypothesis** that gives a precise expectation. In our example the best hypothesis is lack of linkage which yields an expected 1:1:1:1 ratio.

Null hypothesis (H0): Observed ratio (1:1:1:1) = Expected ratio

Alternative hypothesis (HA): Observed ratio (1:1:1:1) ≠ Expected ratio

2) **Calculate x^2**

- Draw up a table to show the expected ratios, observed values and calculate the expected values.

- Find the difference between each observed and corresponding expected values.

- Square the differences.

- Divide each squared difference by corresponding expected value.

- Sum the resulting quotient to obtain your X^2 value.

$$X^2 = \sum \frac{(O-E)^2}{E}$$

3. **Inference**: The calculated X^2 value is compared with Tabulated or Table X^2 value at 5% level of significance (95% confidence level) and 3 degrees of freedom (df). Since there are 4 classes phenotypic classes, df = n-1 = 4-1 = 3.

Conclusion

If calculated X^2 is less than tabulated X^2 value at 0.05 level of significance and 3 df, accept the null hypothesis and conclude that the two loci are not linked. The genes are indeed located on the same chromosome, F on linkage group I and R on linkage group II.

Example 1.

Consider a double cross between heterozygous frizzled rose-combed chicken (FfRr) and double recessive normal single-combed individuals (ffrr) which results in 46 offsprings as follows:

Frizzled rose   FfRr   13

Frizzled single Ffrr   9

Normal rose   ffRr   11

Normal single   ffrr   13

Use X^2 to test if the genes are on separate chromosomes or linked.

The statistic x^2 is always calculated from actual numbers never from percentages, fractions or decimal fractions. The usefulness of x^2 test is that it takes sample size into consideration.

GENE INTERACTION

The genes of an individual do not operate isolated from one another but obviously are functioning in a common cellular environment. Thus, it is expected that interactions between genes would occur. While one gene may make only one protein, the effects of those proteins usually interact. Bateson and Punnett performed a classical experiment that demonstrated genetic interaction. Novel phenotypes often result from the interactions of two genes, as in the case of comb types in chickens.

Parental cross   RRpp (Rose comb) X   rrPP (Pea comb)

F_1 genotype/phenotype   RrPp (Walnut)

F_2 genotype/phenotype

Phenotype	Genotype	Frequency
Walnut	R_P_	9/16
Rose	R_pp	3/16
Pea	rrP_	3/16
Single	Rrpp	1/116

Classical Mendelian ratio = 9:3:3:1

The development of any individual is obviously the expression of all the genes that are part of its genetic makeup. Therefore, it is an expected conclusion that more than one gene could be responsible for the expression of a single phenotype. The interaction between two or more genes to control a single phenotype is called epistasis. The Mendelian dihybrid ratio (9:3:3:1) could be modified through non-allelic interaction. Epistasis involves two or more genes which are not alleles. A gene or gene pair at one locus is said to be epistatic to a gene or gene pair at a second locus when the gene product of the first locus suppresses the expression of the second.

An epistatic gene therefore is one that covers up the phenotypic expression of a gene at different locus. Epistatic genes are sometimes called inhibiting genes because of their effect on other genes which are described as hypostatic (hypo = under), which cannot express themselves.

Epistasis is similar to dominance because one gene covers the expression of another, in both phenomena. This happens at the same locus in dominance but at different loci in epistasis.

The interaction of the two genes which control comb type was revealed because we could identify and recognize 9:3:3:1. Other genetic interactions were identified because the results of crossing two dihybrid produced a modified Mendelian ration.

Epistatic Interactions

When epistasis is operative between two gene loci, the number of phenotypes appearing in the offspring from dihybrid parents will be less than four. There are six types of epistatic ratios commonly recognized, three of which have 3 phenotypes and the other three having only 2 phenotypes.

1. Dominant Epistasis.

   When the dominant allele at one locus, for example the *A* allele, produces a certain phenotype regardless of the allelic condition of the other locus, then the *A*-locus is said to be epistatic to the *B*-locus. Furthermore, since the dominant allele *A* is able to express itself in the presence of either *B* or *b*, this is a case of dominant epistasis. Only when the genotype of the individual is homozygous recessive at the epistatic locus (*aa*) can the alleles of the hypostatic locus (*B or b*) be expressed. Thus, the genotype *A_B_* and *A_bb* produce the same phenotype, whereas *aaB_* and *aabb* produce two additional phenotypes. The classical 9:3:3:1 ratio is modified into 12:3:1 ratio.

2. Recessive Epistasis.

    If the recessive genotype at one locus (e.g *aa*) suppresses the expression of alleles at the *B*_locus, the *A*_locus is said to exhibit recessive epistasis over the *B*_locus. Only if the dominant allele is present at the *A*_locus can the alleles of the hypostatic *B*_locus be expressed. The genotypes *A_B_* and *A_bb* produce two additional phenotypes. The classical 9:3:3:1 ratio is modified into 9:3:4 ratio.

3. Duplicate Genes with Cumulative Effect.

    If the dominant condition (either homozygous or heterozygous) at either locus (but not both) produces the same phenotype, the F_2 ratio becomes 9:6:1. For example, where the epistatic genes are involved in producing various amounts of a substance such as pigment, the dominant genotypes of each locus may be considered to produce one unit of pigment independently. Thus genotypes *A_bb* and *aaB_* produce one unit of pigment each and therefore have the same phenotype. The genotype *aabb* produces no pigment, but in the genotype *A_B_* the effect is cumulative and two units of pigment are produced.

4. Duplicate Dominant Genes.

    The classical Mendelian ratio becomes 15:1 ratio if the dominant alleles of both loci each produce the same phenotype without cumulative effect.

5. Duplicate Recessive Genes.

    In the case where identical phenotypes are produced by both homozygous recessive genotypes, the F_2 ratio becomes 9:7. The genotypes *aaB_*, *A_bb* and *aabb* produce one phenotype. Both dominant alleles, when present together, complement each other and produce a different phenotype.

6. Dominant and Recessive Interaction.

    Only two F_2 phenotypes result when a dominant genotype at one locus (e.g. *A_*) and the recessive genotype at the other (*bb*) produce the same phenotypic

effect. Thus, *A_B_, A_bb* and *aabb* produce one phenotype and *aaB_* produces another in the ratio 13:3.

MODIFIER GENES

These are genes that have small quantitative effects on the level of expression of another gene. Instead of masking the effects of another gene, a gene can modify the expression of a second gene. In mice for example, coat colour is controlled by the B gene. The B allele conditions black coat colour and is dominant to the b allele that produces a brown coat. The intensity of the colour, either black or brown is controlled by another gene, the D gene.

The dominant D allele controls full colour whereas the recessive d allele conditions a dilute or faded expression of the colour expression at the B gene. Therefore, if a cross is made among mice that are BdDd, the following phenotypic distribution will be seen.

F2 Genotypic Ratio	Final Phenotypic ratio
9 B-D-	Black
3 B-dd	Dilute Black
3 bbD-	Brown
1 bbdd	Dilute brown

The D gene does not mask the effect of the B gene, rather it modifies its expression.

PENETRANCE AND EXPRESSIVITY

Some mutant genotypes are always expressed as a distinct phenotype, whereas others produce a proportion of individuals whose phenotypes can not be distinguished from normal (wild). The degree of expression of a particular trait

may be studied quantitatively by determining the penetrance and expressivity of the genotype under investigation. The percentage of individuals that show at least some degree of expression of a mutant genotype defines the penetrance of the mutation. For example, the phenotypic expression of many mutant alleles in Drosophilia may overlap with wild type. If 15 percent of mutant flies show wild type appearance, the mutant gene is said to have a penetrance of 85 percent.

By contrast, expressivity reflects the range of expression of the mutant genotype. Flies homozygous for the recessive mutant gene eyeless yield phenotypes that range from the presence of normal eyes to a partial reduction in size to the complete absence of one or both eyes. Although, the average reduction of eye size is one-fourth to one-half, expressivity ranges from complete loss of both eyes to completely normal eyes. Examples such as the expression of eyeless gene have provided the basis for experiments to determine the causes of phenotypic variation.

Penetrance is the extent to which a particular gene or set of genes is expressed in the phenotypes of individuals possessing it, measured by the proportion of carries of the gene showing the characteristic phenotype.

PLEIOTROPY

A gene that affects more than one phenotype is called pleiotropic gene. This can be illustrated with a cross between a yellow-coated mouse and a mouse with a gray coat. The gray-coated mouse was extensively inbred and therefore was considered to be pure bred.

Parental cross	Yellow	Gray
F_1 distribution	1 (Yellow) :	1 (Gray)

What allelic relationship exists here? The gray mouse is homozygous because it is a pure line. If gray coat was dominant, then all F_1 offspring will be gray mouse. Since yellow and gray mice were obtained, yellow must be dominant to gray.

Gray genotype = yy

Yellow genotype = YY

F_1 genotype= Yy

1YY : 2Yy : 1yy

Expected phenotypic ratio 3 yellow: 1 gray

The result, though, was a ratio of 2 yellow to one gray mice. Therefore all of the yellow mice from the cross of two heterozygous yellow mice are genotypically Yy. Somehow the YY genotype is lethal. Pleiotropy is the effect of a single gene on more than one characteristic.

The 2:1 ratio is the typical ratio for a lethal gene. An important question is how can a gene controlling coat colour cause death in an organism? Possibly in a single dose the allele causes a yellowing of the coat, but when expressed in two doses, the gene product kills the animal. Thus, this gene actually has an effect on two phenotypes. In this example, the gene that causes yellowing of the coat also affects viability and is termed a pleiotropic gene.

Another example is the "frizzle-trait" in chickens. The primary result of this gene is the production of defective feathers i.e. it alters the structure of the feathers. Secondary results are both good and bad. Good include increased adaptation to warm temperatures, while bad include increased metabolic rate, decreased egg-laying, changes in heart, kidney and spleen.

The syndrome called "sickle cell anemia" in humans is due to abnormal hemoglobin. This is the primary effect of the mutant gene. Subsidiary effects of the abnormal hemoglobin include the sickle-shape of the cells and their tendency to clump together and clog blood vessels in various organs of the body. As a result, heart, kidney, spleen and brain damage are common elements of the syndrome. Defective corpuscles are readily destroyed in the body, causing severe anemia.

Self Assessment Exercise

Matings between black rats of identical genotype produced offspring as follows: 14 cream-coloured, 47 black and 19 albino.

(a) What epistatic ratio is approximated by these offspring?

(b) What type of epistasis is in operation?

(c) What are the genotypes of the parents and the offspring (use your own symbols)?

MATERNAL INHERITANCE

The inherited characters can be transferred from sires to progenies through two means, nucleus (chromosomes) and cytoplasm (mitochondrial DNA or chloroplast DNA). Inheritance through the chromosomes means that the chromatic substance of the nucleus is the locus of determiners and since the substance of the nuclear content of egg and sperm is equivalent, this must also mean an equal determinative share by male and female in heredity. Inheritance through the cytoplasm means that the locus of the determiners or representative of a character is the cytoplasm. Since it is the egg alone which contains any significant amount of cytoplasm, this inheritance usually is referred to as maternal inheritance. Maternal inheritance has a great influence on the offspring's gene action, fitness and evolution and it is involved in a wide variety of taxa.

In contrast to nuclear inheritance, cytoplalsmic inheritance in mammals is derived mostly, if not exclusively, from the maternal line. Mitochondria and their DNA molecules (mtDNA) are the genetic units of this method of inheritance. Mitochondrial genes, in contrast to genes in the nucleus, have an exclusively maternal mode of inheritance in mammals. Numerous mechanisms are responsible for maternal inheritance. The Predominance of mitochondria of maternal origin in the offspring can be partially explained by the fact that at

fertilization the spermatozoon contains approximately 75 mitochondria compared with approximately 100,000 mitochondria in the ooplasm in mice and cattle. Thus there is a 1:1000 ratio between paternal and maternal mtDNA molecules.

Maternal inheritance of chloroplast DNA in higher plants is believed to be governed by methylation of specific DNA sites on maternal organelle, which protects it from degradation in the zygote.

An example of interaction between cytoplasm and nucleaus is the soybean which shows as different types of cotyledon colours; green and yellow. The beans with yellow cotyledons have two types of seed-coat colours, namely green and yellow while the beans with green cotyledons always have green seed-coats. The inheritance of these types of cotyledons and seed coats has been proved to be maternal. Moreover the early development of all metazoan embryos involves RNA transcripts and other cytoplasmic factors packaged in the egg by the mother during oogenesis. Embryogenesis, therefore, involves characters that are maternally inherited. Mitochondria, chloroplasts and other cytoplasmic factors that have physiological effects throughout the life of an individual are transmitted directly from one parent to the offspring, often through the mother.

Maternal inheritance is known from a wide variety of taxa. Body size in mammals, for example, typically shows effects from the uterine environment and maternal lactation performance. In addition to mammals, maternal influences can be strong during the rearing of offspring. Additionally, large maternal effects have been found in many natural populations of animals. Significant maternal effects have also been reported for a range of life-history traits in red deer including total fitness.

Evolution by natural selection pervades all aspects of Biology, but an evolutionary response to selection can occur only if the trait under selection has a genetic basis. Most studies of natural populations have estimated only direct genetic effects (heritability). Some of theoretical and laboratory work suggest that heritable maternal effects can have important indirect influences on the

potential for evolution. Maternal effects arise when the phenotype of a mother or environment she experiences has a phenotypic effect on her offspring.

In conclusion, maternal inheritance has a great influence on the offspring's, growth, gene action, fitness and evolution and it is involved in a wide variety of taxa. Maternal inheritance may be used as a useful tool to create "new" breeds of livestock carrying the best of both nuclear and mitochondrial genes. The study will have important implication not only for our understanding of mitochondrial genetics and diseases in humans but for the increased productivity of animals and plants.

EXTRANUCLEAR/EXTRA CHROMOSOMAL INHERITANCE

In eukaryotes, there are many examples of traits showing extra chromosomal inheritance and many of these have their basis in the genetic material found in the cell organelles, namely the mitochondria and chloroplasts. Throughout the history of genetics, occasional reports have challenged the basic tenet of Mendelian transmission genetics-that the phenotype is transmitted by nuclear genes located on chromosomes of both parents. Observations have revealed inheritance patterns that reflect neither Mendelian nor neo-Mendelian principles and some indicate an apparent extranuclear or extrachromosomal influence on the phenotype. Such observations were commonly regarded with skepticism, but, with the increasing knowledge of molecular genetics and the discovery of DNA in mitochondria and chloroplast, extranuclear inheritance is now recognized as an important aspect of genetics.

There are several varieties of extranuclear inheritance. One major type is described as maternal inheritance, whereby DNA contained in mitochondria or chloroplasts determine the phenotype of the offspring. Examples are recognized on the basis of the uni-parental transmission of these organelles to progeny. A second type involves infectious hereditary: resulting from the symbiotic or parasitic association of a microorganism. In such cases, an inherited phenotype

is affected by the presence of the microorganism in the cytoplasm of the host cells. The third variety involves the maternal effect on the phenotype whereby nuclear gene products are stored and then transmitted through the cytoplasm to offspring.

Mitochondria and chloroplasts

Mitochondria are essential constituents of all aerobic animal and plant cells. They are relative complex organelles with a double membrane and they contain the enzymes of the electron transport chain (the cytochromes) which are involved with the generation of ATP by oxidative phosphorylation.

Chloroplasts are found only in plant cells and they are the site of photosynthesis. Within the chloroplast is a series of flattened sacs called thylakoids whose membranes contain chlorophyll and the other pigments involved in the photosynthetic process. An average leaf cell of a higher plant contains 40-50 chloroplasts.

Both mitochondria and chloroplasts contain genetic material in the form of circular, naked, double-stranded DNA. In this regard, then, the organelle genomes resemble those of the bacteria. Often this DNA has a different buoyant density from that of nuclear DNA. Furthermore, these organelles contain ribosomes and carry out protein synthesis, although not all of the proteins found in the organelles are made *in situ*.

The mitochondrial genetic system

Protein synthesis in mitochondria requires the initiation codon AUG. The RNAs of the mitochondrial ribosomes are coded for by single-copy genes in the mitochondrial genome. Protein synthesis by mitochondrial ribosomes can be inhibited by the antibiotic chloramphenicol (to which cytoplasmic ribosomes are resistant) but not by the antibiotic cycle hezimide (to which cytoplasmic ribosomes are sensititve). By using these inhibitors, it has been shown that most of the ribosomal proteins of mitochondrial ribosomes are made on the cytoplasmic ribosmmes and thus these must be encoded by nuclear genes. Assembly of the ribosomes occurs within the mitochondria and thus the completed ribosomal proteins must be transported across the mitochondrial

membranes. The mitochondria contain several important respiratory enzymes called cytochromes. The cytochromes are proteins, each of which has an atom of iron held within a *haem* group.

Mitochondria DNA contain genes for a number of mitochondrial components including mRNAs, possibly a few ribosomal proteins, some tRNAs, some cytochrome components and a few other constituents. The other essential components are encoded by nuclear genes. Clearly, then, mutations in the organellar genes (among other things) would lead to phenotypes that would show extra chromosomal inheritance.

Characteristics of extrachromosomal inheritance

(1) Differences should be observed in the progeny of reciprocal crosses. A characteristic form of this is maternal inheritance where progeny shows the phenotypes of the female parent. This is the case since in many organisms the female gamete provides vastly more cytoplasm to the zygote than does the male gamete and thus there is transmission through the cytoplasm. With the exception of sex-linked genes, the results of reciprocal crosses are identical for nuclear gene mutations.

(2) A second prediction is that the extrachromosomal mutation should be non-mappable specifically, in organisms that have well-mapped linkage groups, it should not be possible to find linkage of the mutation to any of the chromosomal genes.

(3) A third prediction is that the presumed extra-chromosomally-coded characteristics should persist when the nuclei in the cells are substituted with nuclei of a different genetic constitution.

Examples of extrachromosomal inheritance

Mutations in mitochondria DNA causes human disorders. The DNA found in mitochondria (mtDNA) has been extensively characterized in a variety of organisms, including humans. Human mtDNA, which is circular contains 16, 569 base pairs and is inherited strictly maternally. The mitochondrial gene products encoded include:

a. 13 protein, required for oxidative phosphorylation

b. 22 transfer RNAs (tRNAs), required for translation

c. 2 rRNAs, required for translation

Because cellular respiration is such an intricate metabolic process, disruption of any mitochondrial gene by mutation is likely to have a severe impact on that organism.

A zygote receives a large number of organelles through the egg, so if only one of them contains a mutation, its impact is greatly diluted because there will be many more mitochondria that will function normally. During early development, cell division disperses the initial population of mitochondria present in the zygote, and in newly formed cells of these organelles reproduce autonomously. Therefore, if a deleterious mutation arises or is present in the initial population of organelles, adults will have cells with a variable mixture of both normal and abnormal organelles. This condition is called heteroplasmy.

In order for a human disorder to be attributable to genetically altered mitochondria, several criteria must be met:

i. Inheritance must exhibit a maternal rather than a Mendellian pattern

ii. The disorder must reflect a deficiency in the bio-energetic function of the organelle

iii. There must be a specific genetic mutation in one of the mitochondrial genes

Several cases are known to demonstrate these characteristics. For example, myoclonic epilepsy and ragged red fiber disease demonstrates a pattern of inheritance consistent with maternal inheritance. Only offspring of the affected fathers are all normal. Individuals with this rare disorder express deafness, dementia and seizures. Both muscle fibers and mitochondria are affected; the aberrant mitochondria characterize what are described as a ragged red fiber (RRFs) of skeletal muscle.

Analysis of mtDNA has revealed a mutation in one of the mitochondrial genes encoding a tRNA. This genetic alteration apparently interferes with translation with the organelle, which in turn leads to the various manifestations of the disorder.

Leber's hereditary optic neuropathy (LHON) is another disorder which shows maternal inheritance as well as mtDNA lesions. The disorder is characterized by sudden bilateral blindness. The average age of vision loss is 27 but onset is quite variable. Four mutations have been identified, all of which disrupt normal oxidative phosphorylation. Over 50% of cases are due to a mutation at a specific position in the mitochondrial gene encoding a subunit of NADH dehydrogenase so that the amino acid arginine is converted to histidine. This mutation is transmitted to all maternal off-spring. It is interesting to note that in many instances of this disorder, there is no family history; a significant number of cases appear to result from new mutations.

A third disorder is called Kearns Sayre Syndrome (KSS). Affected individual lose vision, undergo hearing loss and display heart conditions. The genetic basis of KSS involves deletions at various positions within mtDNA. Many KSS patients are symptom-free as children but display progressive symptoms as adults. The proportion of mtDNAs that reveal deletions increases as the severity of symptoms increases.

The study of hereditary mitochondrial-based disorders provides insights into the importance and genetic basis of this organelle during normal development, as well as the relationship between mitochondrial function and neuromuscular disorders. Such study has also suggested a hypothesis for aging based on the progressive accumulation of mtDNA mutations and the accompany loss of mitochondrial function.