LECTURE NO ONE

Basic mendelian genetics

Any inherited trait such *as eye* **color** is referred to as a phenotype. All phenotypes result from the presence **of a** specific gene or combination of genes, the genotype. In hybrids one phenotype may be dominant to another. Pure-breeding lines are strains of a species which have been bred for many generations and have maintained me same phenotype.

Crosses between pure-breeding (homozygous) lines differing in one inherited character yield progeny that all have the same phenotype. This is termed the F_I generation and is composed of heterozygous individuals. When these are inter-crossed, the next generation, the F_2, shows both of the original phenotypes in the ratio 3:1 with the dominant phenotype being the majority class. Each individual carries two copies (alleles) of each gene. Homozygous individuals carry two identical alleles, heterozygous individuals carry two different alleles.

When an individual that is heterozygous for one gene is crossed to a recessive homozygote only two classes of progeny are observed. The dominant and recessive phenotypes arise at equal frequency. This is a test cross.

The 3:1 ratio depends on complete dominance of one phenotype over the other. If the phenotypes under study show partial or codominance, a 1 : 2 :1 ratio will be obtained. If either allele has a negative effect on viability this will also distort the ratio. Alleles that can cause lethality when homozygous are called lethal alleles. Semi-lethal alleles have a quantitative effect on viability.

Most genes exist in several different forms, multiple alleles. This is caused by mutations of bases at different sites within the same gene,

thus effecting different amino adds in the encoded protein. These arise at random within the population.

More Mendelian genetics

B—te concepts

The first clear evidence pointing to what we now call genes came from the work of Gregor Mendel who carried out experiments on inheritance in pea plants in the middle of the nineteenth century. Before we examine his results it is necessary to establish an understanding of some of the basic terms that are used in the study of inheritance in higher organisms.

Phenotype

Any character (trait) which can be shown to be inherited, such as eye color, leaf shape or an inherited disease, such a cystic fibrosis, is referred to as a phenotype. A fly may be described as having a red-eyed phenotype or a child as displaying the cystic fibrosis phenotype. The pattern of genes that are responsible for a particular phenotype in an individual is referred to as the genotype.

Pure-breeding lines

This refers to organisms which have been inbred for many generations in which a certain phenotype remains the same. Pedigree breeds of dogs or cats are commonplace examples of pure-breeding lines.

Dominance

Within a species there may be differences in the phenotype for one inherited character. In hybrids between two individuals displaying different phenotypes only one phenotype may be observed. For instance, in crosses of pure-bred truit flies with short wings with pure-bred long-winged flies the progeny will a0 have long wings. The phenotype expressed in the hybrids is said to be dominant and the other recessive. In the example above long wings are dominant to short wings.

The key ingredients for success in Mendel's experiments were the use of pure-breeding strains of pea plants and the fact that he subjected his results to simple mathematical analysis.

The monohybrid

Mendel studied inheritance of several phenotypes in pea plants, but we will concentrate on only one of these, petal color. He made a cross between two pure-breeding lines of plants, one of which had violet petals and the other white petals. The hybrids produced in this cross were referred to as the F_I (first filial) generation. These all had violet flowers. Thus violet was dominant to white. He then allowed these plants to self-fertilize to produce the F_2 (second filial) generation. Some plants had white flowers and others violet flowers. The ratio of violet to white flowered plants was dose to 3:1. In crosses between plants differing in seed color, pod shape or other phenotypes, the same pattern WAS observed. The recessive phenotype always reappeared in the F_2 generation and made up approximately one quarter of the

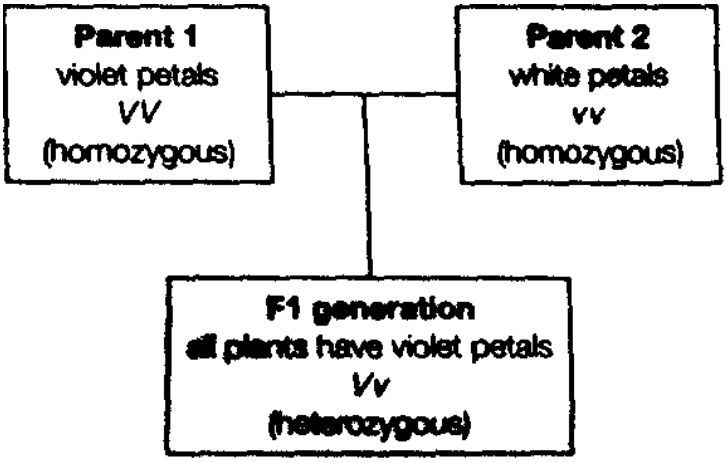
plants.

These experimental data led Mendel to suggest that heredity was due to die action of specific factors, which we now call genes. This apparently simple conclusion was, however, in complete opposition to the conventional view that heredity was due to blending of fluids from both parents. Clearly no blending had occurred in Mendel's experiments, neither in the F_I where only one phenotype was expressed nor in the F_2 where both were expressed separately.

From our modem knowledge of genes and gene structure it is easy for us to appreciate how Mendel explained what was happening in his experiment This is set out diagrammatically in Fig. 1. He suggested that the pure-breeding violet flowered plants carried two copies of a gene for violet pigment, V. The white flowered plants carried two copies of a variant of this gene that code • for white flowers, *v.* We refer to individuals with two identical copies of a gene as being homozygous. The Fl hybrids inherited two different copies of fte pigment gene, *V v* and are referred to as heterozygous. As violet is dominant to white these plants had violet flowers. When Fl plants self-fertilize three different classes of genotype, *V V, V v* and *v v* are possible. These arise in the ratio 1:2:1 *{Table 1).* This is how the 3 :1 phenotypic ratio is established fLe. 3 violet : 1 white).

The validity of this hypothesis was strengthened when individual plants from each of the F_2 classes were self-fertilized. All white-flowered plants were found

(a)



(b)

VV	*Vv*
^y	*vv*

Fig. 1. (a) Gametes produced by the F1 plants carry V or v alleles these fuse at random to give offspring with the genotypes VV, Vv or vv was shown in (b). (b) Each of the four fusions arise with equal frequency. Hence the phenotype ratio in the F_2 generation is 3 purple: 1 white and the genotype ratio is 1VV: 2Vv: vv.

Table 1. Products of Fl self-fertilization in pea plants

Genotype	Phenotype (petal color)	Ratio
VV	Violet	1
Vv	Violet	2
vv	White	1

Table 2. Examples of inheritance is controlled by a single gene

Species	Character (phenotype)
Mice	Albino/normal coat, pale/normal ears

Red clover	Red/white flowers
Fruit flies	Normal/vestigial wings
Humans	Blue/brown eyes, cystic fibrosis, sickle cell anaemia, phenyl ketone urea

to be pure-breeding. One-third or the violet-flowered plants were pure-breeding and two-thuds give purple- and white-flowered plants in the ratio 3:1. There have subsequently been many examples of the 3:1 ratio for the inheritance of characters controlled by a single gene in many different species. A few of these are listed in Table 2.

One new term needs to be denned at this stage. Genes become altered through the process of mutation. The different variants of a gene are referred to as alleles. Students often are confused between the terms genes and alleles. In the previous example it is better to refer to V and f as two alleles of a petal color gene. It is conventional to denote dominant alleles with upper case and recessive alleles with lower case letters. The 3:1 ratio is referred to as the monohybrid ratio, and is the basis for all patterns of inheritance in higher organisms.

Detection of heterozygotes:

One simple extension of the 3 :1 phenotype ratio is a 1:1 ratio produced when an Fl individual is crossed to the homozygous recessive parent. As shown in Fig. 2 Ac heterozygous Fl can produce only two classes of gamete, carrying either the dominant or the recessive allele.

The parent with the recessive phenotype can only produce gametes with recessive alleles, and so the progeny of the cross have the dominant and recessive phenotypes in equal numbers, a 1: i phenotype ratio. This type of cross is termed a testcross, and is useful in any situation where it is necessary to determine if an individual is heterozygous. It is also the expected phenotype ratio in families where one parent carries a rare dominant allele, such as Huntington's disease. Because the dominant allele is rare, the affected individual is unlikely to be homozygous.

Parent 1 **Aa**		**Parent 2** ***aa***
Aa dominant phenotype		*Aa* dominant phenotype
aa recessive phenotype		aa recessive phenotype

Fig. 2. The genotype and phenotype ratios are both 1:1 because the alleles contributed by the doubly recessive parent do not affect the phenotype.

The simple 3 :1 monohybrid ratio is not always observed in instances when-only one gene is responsible for a particular phenotype. This may be due to a number of factors.

Variations of the 3:1

The simple 3:1 monohybrid ratio is not always observed in instances where only one gene is responsible for a particular phenotype. This may be due to a number of factors.

Partial or incomplete dominance

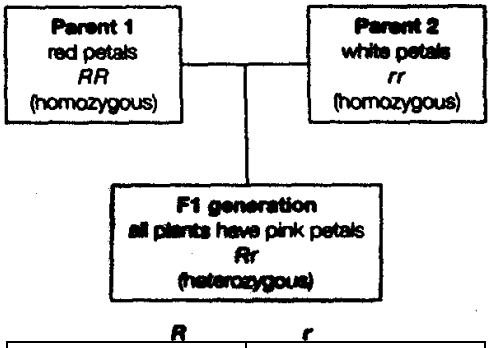
In the preceding section the example used showed complete dominance, h other words the phenotype of the F_1 generation was identical to that of one of me parents (the dominant phenotype). This is not always the case. Often the Fl is clearly intermediate between two parents. A simple example of Ada K we inheritance of petal color in snapdragons. When pure-bred white and purebred red-flowered plants are crossed the F_1 generation has pink rather dun white or red petals. The F_2 comprises three classes of plants (Table 3). This 1:2:1 ratio of three phenotypes is dearly different from the 3:1 but it is easy to see how the two relate. The cross is set out in Fig. 3. The genotype of the

Table 3. Inheritance of petal color in the snapdragon

Genotype	Phenotype	Ratio
rr	White petals	1
Rr	Pink petals	2
RR	Red petals	1

(a)

(b) Prof Dr Makhlouf M. M. Bekhit , Head of Genetic Department



R	r
RR **red**	**Rr** **pink**
Rr **pink**	**rr** **white**

Fig. 3. (a) Gametes produced by the F1 plants carry R or r and these fuse at random to give offspring with the genotypes RR, Rr or rr as shown in (b). (b) The genotype ratios are the same as in fig. 1 but the phenotype ratio is 1 red: 2 pink: 1 white.

red-flowered plants is RR and that of the white-flowered plants is rr. The Fl generation consists of Rr heterozygotes. In the F2 generation the ratio of genotypes is the same as that described previously. The difference here is that the Rr heterozygotes are pink thus altering the ratio of phenotypes.

The red- and white-flowered F_2 classes are homozygous and are therefore pure-breeding, whilst the pink heterozygotes when self-fertilized will always produce a 1:2:1 ratio of white-, pink- and red-flowered plants.

Co-dominance is similar to incomplete dominance, but here the heterozygote displays both alleles. Examples of this are found frequently in the inheritance of blood groups. In humans the MN blood

group is controlled by « single gene. Only two alleles exist, M and N. Children whose father is an NN homozygote with group N blood and whose mother is a MM homozygote with group M blood are MN heterozygotes and have group MN blood. Both phenotypes are identifiable in the hybrid. Codominance also modifies 3:1 ratios to 1:2:1 ratios. Alleles mat are differentiated by molecular methods such as polymerase chain reaction (PCR), or Southern blotting are also codominant.

Lethal alleles

Some alleles affect the viability of individuals mat carry them. In most cases the homozygous recessive does not survive but the heterozygotes may have a normal life-span. To be detected the heterozygotes need some observable phonotype. The best known example of this is the inheritance of yellow coat color in mice. Yellow varieties can arise in strains of mice with different coat colors, for instance, black mice. Yellow coat color is dominant to black coat color; BB mice are black, BBi mice are yellow. When two yellow mice are mated the progeny would be expected to be in the proportion shown in Table 4. However, BB> is lethal and any mice with mis genotype die in utero. Hence livebom progeny from this cross are in me ratio given in Table 5. The 3:1 phenotypic ratio has been distorted to a 2:1 ratio.

There is a concept here which sometimes causes problems to students. The allele fir is recessive in relation to its effect on viability, but dominant in relation to coat color. It is important that you recognize this difference. It is quite common.

Table 4. Expected inheritance of yellow coat color in a cross of BBy x BBy mice

Genotype	Phenotype	Ratio
BB	Hack fur	1
BBy	Yellow	2
ByBy	Yellow	1

Table 5. Actual Inheritance of yellow coat color in a cross of BBy x BBy mice

Genotype	Phenotype	Ratio
BB	Hack fur	1
BB»	Yellow fur	2

dominant for one phenotype may be recessive for another. Other examples when alleles are lethal when homozygous, but which have a dominant effect when heterozygous include tailless Manx cats and short-legged Creeper chickens. Genes (hat are involved in developmental processes are often found to have lethal alleles. The presence of one mutant allele alters development so as to produce characteristic changes to the animal, but when two are present development is so aberrant as to cause death. This may occur in utero as described above or result in shortened life expectancy as found in several examples in humans, suck as Tay-Sach's disease, Huntmgton's syndrome or sickle cell anemia.

In other instances a homozygote may not be absent from a cross, but

appear in reduced numbers. An example of mis is vestigial wings in fruit flies, a condition that is caused by a recessive allele (vg). Alleles with this effect are referred to as •enu4ethab.

These examples of alteration to me 3:1 ratio may at first appear complicated. It is essential mat you realize, that in these cases, the behavior of the genes remains the same as in me 3:1 monohybrid ratio but me phenotypic ratio may change. Phenotypes depend on how genes act through protein synthesis and how specific proteins interact in the cells and tissues of an organism. You know a great deal about mis from Section A. You will see further examples of interaction between gene products in the following sections. However, if you concentrate on genotypes and me inheritance of alleles it will be much easier to understand how specific genes are influencing die inheritance of phenotypes.

Multiple alleles:

All the examples used so far have employed genes with only two alternative alleles. For some genes only two alleles have been identified, but for the majority of genes, a large number of alleles have been found. Examples of this include me human P-giobin gene where a specific mutation at codon 6 results in an allele responsible for me hereditary syndrome sickle cell anaemia, whilst mutations at several other sites in me gene cause a different syndrome, p-thalassemia. Although they are alterations of the same gene, me changes are to different codons. The resulting proteins have variant p-globins with discrete differences in ammo add sequence and so behave differently.

In rabbits, multiple alleles of one gene are responsible for a number of different coat color phenotypes. There are four members of this allelic series

agouti, chinchilla, Himalayan and albino. When homozygous each produces a distinct coat pattern. In heterozygotes there is a clear pattern of dominance. Agouti is dominant over all the other alleles, chinchilla is dominant over Himalayan and albino, while Himalayan is dominant only over albino, which fails to produce any pigment and hence is recessive to all the others.

Another well known example of multiple alleles is the human ABO blood group system. Here a single gene codes for an enzyme that is responsible for the addition of sugar residues to a specific glycoprotein on the membrane of red blood cells. Three different alleles of the gene are known. One form of the enzyme adds a molecule of N-acetyl-galactosamine to the glycoprotein resulting in blood group A. A second allele codes for a variant enzyme that adds galactose instead of N-acetyl galactosamine resulting in blood group B. A third allele codes for a nonfunctional enzyme that cannot add any sugar to the glycoprotein, resulting in blood group 0. All three alleles have arisen by mutation from a single ancestor.

The major histocompatability complex which determines the suitability of donor organs for transplantation is an example of a complex multiple allele system. Many other examples of multiple alleles are known and in some cases it is possible to differentiate between the alleles directly using molecular technology. Such approaches are discussed in Topics F_6 (Forensic genetics) and Topic F_5 (The human genome project).