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 **Multiple Alleles(for M.Sc. II Semester Paper III)**

 It has been observed that a given phenotypic trait (character) of an individual depends on a single pair of genes, each of which occupies a specific position calledthe gene locus, on a homologous chromosome. Moreover, a particular gene has been found to occur in two alternative forms or allelomorphs, one being dominant and other reces- sive; one being wild form and the other mutant form. For example, a gene (L) for length of Drosophila wings may occur in two alternative forms : a allele or gene (L+) for normal development of wings and another allele or gene (Lvg) for vestigial wings. Because, most flies have normally developed wings, so, it can be easily concluded that gene L+ is the original form of gene or allele from which the other form of gene or allele (Lvg) might have originated by certain mutational event at sometime in past. The gene L+ for normal development of wing is called the normal or wild type allele of the gene L and usually symbolized as L+, while the mutated gene Lvgfor vestigial wing is called reduced type or mutant allele of the gene L. A fly with normal wings, thus, has two wild type alleles (L+L+) and the vestigial winged fly has two mutant alleles (Lvg Lvg). Both of these allelic forms (L+ and Lvg) of gene L occur at correspond- ing positions on genetically identical (homologous) chromo- somes of same or different individual.If the mutant allele has developed from the wild form of allele due to mutation, one may expect that the wild form of allele can mutate in more than one way. The mutant form of allele too can mutate once again to give rise to another mutant form of allele. Therefore, it is possible to have more than two allelic forms, i.e., multiple alleles, of one kind of gene. Al-though only two actual alleles of a gene can exist in a diploid cell (and only one in a haploid cell), the total number of possible different allelic forms that might exist in a population of individuals is often quite large. This situation is termed as **multiple allelism**, and the set of alleles itself is called a **multiple allelic series**.

**CHARACTERS OF MULTIPLE ALLELES**

The most important and distinguishing features of multiple alleles are summarized below :

1. Multiple alleles of a series always occupy the same locus in the chromosome.
2. Because, all the alleles of multiple series occupy same locus in chromosome, therefore, no crossing-over occurs within the alleles of a same multiple allele series.
3. Multiple alleles always influence the same character.
4. The wild type allele is nearly always dominant, while the other mutant alleles in the series may show dominance or there may be an intermediate phenotypic effect.
5. When any two of the mutant multiple alleles are crossed, the phenotype is mutant type and not the wild type.

**SYMBOLISM FOR MULTIPLE ALLELES**

The dominance hierarchy is defined at the beginning of each problem involving multiple alleles. A capital letter is commonly used to designate the allele which is dominant to all other alleles in the series.

The corresponding lower case letter designates the allele which is recessive to all others in the series. Other alleles which are intermediate in their degree of dominance between these two extremes, are usually assigned the lower case letter with some suitable superscript.

A Wild type, agouti or full colour

Genotype = c+c+,c+cch

c+ch, c+c.

B Chinchilla Genotype =cchcch,cchch

cchc.

C Himalayan Genotype = chch,chc.

D Albino Genotype = cc.

**Fig. 10.1.** Different coat colours in rabbits (cafter Burns 1969).

**EXAMPLES**

The best examples of multiple allelic sys- tem have been observed in coat colour of rabbits, wings of *Drosophila* and blood groups in man.

1. **The C gene in Rabbit (Coat Colour)**

The coat of rabbit may have following sdifferent colours :

* 1. **Full colour.** The coat of the ordinary (wild type) rabbit is referred to as “**agouti**” or **full colour**, in which individuals have banded hairs, the portion nearest the skin being gray, suc- ceeded by a yellow band, and finally a black or brown tip. The genes for full colour may be represented by capital letter C or c+.
	2. **Chinchilla.** In some individuals, the coat lacking the yellow pigment and due to the optical effect of black and gray hairs, have the appearance of silvery-gray. The gene for chin- chilla is represented as c*ch*.
	3. **Himalayan.** The Himalayan type coat is white except for black extremities (nose, ears, feet and tail). The eyes are pigmented. The gene for Himalayan coat is represented by ch.

**MULTIPLE ALLELES**

**117**

* 1. **Albino.** The albino coat totally lacks in pigmentation and the eyes of an albino also remain pink due to lack of pigment in iris of eye. The gene for albino is represented by c.

Crosses of homozygous agouti (c+c+) and albino (cc) individuals produce a uniform agouti F1; interbreeding of the F1 produces an F2 ratio of 3 agouti : 1 albino (Fig. 10.2). Two third of F2 agouti are found to be heterozygous by testcrosses. Thus, it is a case of monohybrid inheritance, with agouti completely dominant to albino. Likewise, crosses between chinchilla and agouti (Fig. 10.3) produce all agouti individuals in the F1 and a 3 agouti : 1 chinchilla ratio in the F2. Such complete dominance of agouti also occurs on Himalayan (Fig. 10.4). Further crosses, reveal that c*ch* allele for chinchilla though is recessive to c+ allele for agouti coat or skin, is incompletely dominant over Himalayan (c*h*) and albino

1. alleles (Fig. 10.5 and Fig. 10.6). Likewise, c*h* allele for Himalayan coat is recessive to c+ (agouti) and c*ch* (chinchilla) but dominates over albino (Fig. 10.7). The results of all these crosses exhibit that c+ (agouti), c*ch* (chinchilla), c*h* (Himalayan) and c (albino) are allelic to each other and the alleles of this multiple allelic series have following dominance hierarchy :

c+ > c*ch* > c*h* > c

The possible phenotypes and their associated genotypes of this multiple allelic series can be summarized in Table 10-1.

|  |
| --- |
| **P1 :** Agouti X Albino **P1 :** Agouti X Chinchilla c+c+  cc c+ c+  cchcchAgouti Agouti**F1 :** c+c **F1 :** c+c*ch***F2 :** 1c+c+ : 2c+c : 1cc **F2 :** 1c+c+ : 2c+ c*ch* : 1 cchc*ch*3 Agouti : 1 Albino 3Agouti : 1 Chinchilla**Fig 10.2.** A monohybrid cross between agouti **Fig. 10.3.** A monohybrid cross between agouti and albino rabbits. and chinchilla rabbits. |

|  |
| --- |
| **P1 :** Agouti X Himalayan **P1 :** Chinchilla X Himalayan c+c+  chc*h* c*ch* c*ch*  c*h*c*h***F1 :** Agouti **F1 :** Light grayc+c*h* c*ch* c*h***F2 :** 1c+c+ : 2 c+c*h* : 1 c*h*c*h* **F2 :** 1 c*ch* c*ch* : 2 c*ch* c*h* : 1 c*h* c*h*3 Agouti : 1 Himalayan 1 Chinchilla : 2 Light gray :1 Himalayan**Fig. 10.4.** A monohybrid cross between agouti **Fig. 10.5.** A monohybrid cross between chinchilla and and Himalayan (or Russian) rabbits. Himalayan rabbits. Showing incompletedominance of chinchilla on Himalayan. |

|  |
| --- |
| **P1 :** Chinchilla X Albino **P1 :** Himalayan X Albino c*ch* c*ch*  c c c*h* c*h*  c c**F1 :** Light gray **F1 :** Himalayan c*ch* c c*h* c**F2 :** 1c*ch* c*ch* : 2 c*ch* c : 1cc **F2 :** 1 c*h* c*h* : 2c*h* c : 1 c c1Chinchilla : 2 Light gray : 1 Albino 3 Himalayan : 1 Albino**Fig. 10.6.**A monohybrid cross between chinchillaand albino rabbits showing incomplete domi- **Fig. 10.7.** A monohybrid cross between nance of chinchilla over albino. Himalayan and albino rabbits. |

**GENETICS, HUMAN GENETICS AND EUGENICS**

**118**

**Table 10-1. The phenotypes and genotypes of multiple allelic series for coat colour in rabbit.**

**Phenotypes**

It should be noted here that in this case four allelic forms of genes may produce at least ten genotypes, whereas in case of single pair of alleles at a given locus only three genotypes were produced where dominance is complete. Thus, as the number of genes in a series of multiple alleles increases, the variety of genotypes rises still more rapidly, such as exemplified on next p\age.

**Alleles in series**

2

3

4

5

n

**Genotypes**

3

6

10

15

n/2 (n+1)

Karl Landsteiner (1868-1943).

c+c+, c+c*ch*, c+c*h*, c+c c*ch* c*ch*

c*ch*c*h*, c*ch* c c*h*c*h*, c*h*c cc

Full colour (Agouti) Chinchilla

Light gray Himalayan Albino

**Genotypes**

1. **A, B, AB and O Blood Groups in Humans Landsteiner** in 1900 and 1902 discovered two kinds of **agglutinogens** or **antigens**, called **A** and **B antigens** from the surface of red blood cells of human blood. He found that out of A and B anti-

gens, a person may contain either one (*i.e.,* A or B antigen) or neither of them. Accordingly, he recognised three kinds of **blood types** or **blood groups** : **type A**, **type B**, and **type O**. The fourth and most rare, the **A B blood group** or type, was discovered in 1902 by two of **Landsteiner’s** students, **Von Decastello** and **Sturli**. For A and B antigens, there occur two **agglutinins** or **antibodies**

CH2OH

CH2OH

HO

O

H

HO

O H

OH

OH

OH OH

HN CCH3

OH

O

-D-galactose (type B)

N-acetyl-D-galactosamine

(type A)

**Fig. 10-8.** Sugars associated with the surface of erythrocytes in blood type A and type B persons (after Goodenough and Levine, 1974).

: anti-A (or ) and anti-B (or ).

Recent, chemical investigations have shown that A and B antigens are not proteins but, are mucopoly-

**MULTIPLE ALLELES**

Type A serum

Type B serum

O

A

B

AB

**Fig. 10.9.** Agglutination tests for A, B, AB and O human blood groups (after Gardner, 1968).

**119**

saccharides (sugars + aminoacids) of 300,000 molecular weights.

The four blood types have different

agglutinizing properties. To determine the blood group types of different persons, an **agglutination test** is performed. On a glass slide is placed a drop of type A serum (containing anti-B antibodies) and a separate drop of type B serum (containing anti-A antibodies). When a drop of type O blood is added to each drop there is no agglutination or clumping of red blood cells in either drop takes place. This shows that O blood group has neither A nor B antigen. If a drop of type B blood is added agglutination occurs with type A serum; type A red blood cells are agglutinated by type B serum and type AB red blood cells are agglutinated by both sera. The agglutination tests for four types of human blood has been illus- trated in Figure 10.9.

Each person, therefore, can use the blood of its own blood group in emergency, otherwise, clumping of red blood cells may take place, if blood group of different type is transfused in him. The clumped red blood cells occlude capillaries and, thus, deprive vital organs of normal blood supply and may lead to death. The characteristics of blood groups and the types of transfusions can be summarized in following table 10-2.

**Table 10-2 Human blood groups.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Blood groups (phenotype)** | **Antigen in red blood cells** | **Antibodies in plasma** | **Can give blood to groups** | **Can receive blood from group** | **Genotype** |
| OA BAB | NoneA BA and B | Anti-A, Anti-B, Anti-B Anti-ANone | O, A, B, ABA, AB B, ABAB | OO, AO, BO, A, B, AB | iiIAIA or IAiIB IB or IB i IA IB |

**Multiple Allelic Inheritance of A, B, AB and O Blood Types**

**Bernstein** (1925) proposed that inheritance of A, B, AB and O blood types of man is determined by a series of three allelomorphic genes. The gene controlling blood types has been labelled as **L** (after the name of discoverer, **Landsteiner**) or **I** (from **isoagglutination**, the technical term for the **agglutinogen** (antigen) or clumping of the red blood cells by an agglutinin or antibody. The prefix **iso** is derived from the greek *isos,* meaning equal and indicates that the agglutinations caused by a serum from the same species, man). The I gene exists in three different allelic forms : **IA**, **IB** and **i**. The first two alleles produce characteristic antigens on the surface of erythrocytes. Thus, IA allele specifies A antigen, IB allele determines B antigen and allele specifies no antigen.

The pedigree analysis has shown that alleles IA and IB have dominance over i allele. Likewise the pedigree analysis of A and B parents revealed that their children have both A and B antigens on the

**GENETICS, HUMAN GENETICS AND EUGENICS**

Arctic Circle

Tropic of Cancer

Equator

Tropic of Capricorn

Percentage range of

*B* allele frequency :

The frequency with which the IB allele of the ABO blood group occurs throughout the world.

**120**

erythrocytes, showing codominance between IA allele and IB allele. The dominance hierarchy of this allelic series can be depicted as follows : IA = IB > i. Additional studies that take into account the subgroups of the A antigen indicate that IA allele may occur in at least four allelic forms. These are

|  |  |
| --- | --- |
| 25-30 | 10-15 |
| 20-25 | 5-10 |
| 15-20 | 0-15 |

symbolized IA1, IA2, IA3, and IA4. IA1 is dominant to all other IA alleles, IA2 is recessive to IA1 but dominant to the other two and so on. Considering all the six alleles of gene I, *i.e.,* four forms of IA, one of IB and one of i, dominance within the multiple allelic series can be shown in the following way :

[(IA1> IA2>IA3>IA4)=IB] > i

Neglecting the very rare IA4 allele, this series of multiple alleles produces 15 genotypes and 8 phenotypes (see Table 10-3).

**Summary of genotype and phenotypes of A, B, AB and O blood group (after Burns**

**Table 10-3**

|  |
| --- |
| **and Bottino, 1989).** |
|  | **Genotype** | **Phenotype** | **Genotype** | **Phenotype** |
| IA1 IA1 |  | IA1 IB | A1B |
| IA1 IA2 | A1 |
| IA2 IB | A2 B |
| IA1 IA3 |  |
| IA i |  | IA3 IB | A3 B |
| IA2 IA2IA2 IA3 IA2 i | A2 | IB IBIB i | B |
| ii | O |
| IA3 IA3 IA3 i | A3 |

**The H Antigen and Bombay Phenotype**

Antigens A and B of A, B and O blood phenotype are synthesized from a precursor muco- polysaccharide in the presence of the dominant allele of another pair designated as H and h. With

**MULTIPLE ALLELES**

*ii Hh*

*IB iHh*

*2*

*IBiH–*

*IBihh*

*IA1iHH*

*IBihh*

*IBiH–*

Unaffected male

Unaffected female

*IA1iBHh*

*iiHh*

Bombay phenotype

(female)

2 2 (two) unaffected children, sex unspecified

**Fig. 10.10.** Pathways leading to production of antigens on the red blood cells or erythrocytes showing how the Bombay phenotype is caused (after Burns and Bottino, 1989).

**121**

genotypes HH or Hh the precursor is converted to an H antigen which, in turn, in the presence of IA and/or IB allele is partly converted to antigen A and/or antigen B. Gene h is termed amorph because it is producing no demon- strable product. So long as persons are of geno- type H–(i.e., HH or Hh), A persons of group A produce antigens A and H, group B persons produce antigens B and H, and group AB persons produce antigens A, B and H. However, group O persons produce only antigen H if they are of the genotype ii H– (Fig. 10.10). On the other hand, blood of person of

genotype- -hh does not react with anti-A, anti-B, or anti-H. This is very rare Bombay phenotype (i.e., one case in 13,000 persons; it is so named because it was first described in a family from the Bombay metropolitan. The allele h is found to be epistatic to the multiple alleles at the A-B-O locus. Erythro- cytes of person having- -hh genotype give no reaction with anti-A or anti-B sera (even though they possess IA or IB genes); in fact, they contain no antigen of this multiple allelic series.

1. **Rh Factor**

The surface of erythrocytes (RBC) of some individuals contain one more type of antigen called Rh factor besides the A and B antigens. It is named after the Macaca rhesus monkey in which Rh factor was first discovered by Landsteiner and Wiener in 1940. Human beings are found to contain eight different types of Rh antigens.

The production of Rh antigen (Rh blood phenotype) depends on three closely set autosomal genes (pseudoallels). If any one of them is dominant, a Rh antigen is produced, but if all of them are recessive, no Rh antigen is formed. The individuals possessing the Rh antigen are called Rh-positive (Rh+) and those lacking it are Rh-negative (Rh–). Both of these types of persons are normal and none has natural anti-Rh antibodies in their blood plasma. However, a Rh-negative person can develop these antibodies on receiving Rh antigens through transfusion of Rh-positive blood. Such a blood transfusion will be safe only when the recipient had never been exposed to Rh-positive blood earlier. If already exposed, the previously developed anti-Rh antibodies will agglutinate the donor’s RBC. In fact, the degree of RBC agglutination depends upon the amount of anti-Rh antibodies present. The high concentration of anti-Rh causes severe agglutination of RBC which sometimes proves fatal.

**Erythroblastosis fetalis.** The incompatibility of Rh-positive and Rh-negative bloods may also be noticed in death of the child before or soon after birth. If a Rh-negative women marries a Rh- positive man and bears a Rh-positive foetus, sometime due to some placental defect, some of the foetal RBC carrying Rh antigens may pass into her own blood stream and cause the production of anti-Rh antibodies. The concentration of anti-Rh antibodies is gradually built up in the mother and

**GENETICS, HUMAN GENETICS AND EUGENICS**

**122**

Erythroblastosis fetalis, photomicrograph : This photo- graph shows normal RBC's, damaged RBC's and immature RBCs that still contain nuclei.

she, thus, becomes sensitized only at or just before birth of her first Rh-positive child. In a second or subsequent pregnancy involving a Rh- positive child, these anti-Rh antibodies may return to the foetus through the placenta and destroy the Rh antigen carrying RBC of foetus. The child may then suffer from a disease called erythroblastosis fetalis which is a haemolytic anaemia often accompanied by jaundice, as liver

capillaries become clogged with the remains of red blood cells and bile is being absorbed by the blood. Death of the foetus may occur before birth or soon after birth.

Jaundice infant-major symptom of *erythroblastosis fetalis*.

**Genetics of Rh+ blood type.** There are ample evidences which show the genetic basis of Rh+

and Rh– phenotypes. A single pair of genes, R and r was postulated for Rh+ and Rh– blood types respectively. The Rh+ blood type, later on, is found to be composed of several antigens such as C, c, D, d, E and e, all of which indicate towards the possibility of multiple allelism of gene R. Following two hypotheses have been forwarded to explain nature of inheritance of R gene:

 **Wiener’s hypothesis.** Wiener postulated a number of (at least eight) multiple alleles at a single locus. According to him, gene R contains eight alleles such as r, Ro, R´ R´´, R1 , R2 Rx or Rz and Ry.

1. **Fisher’s hypothesis.** Fisher rejected the Wiener’s concept of multiple allelism for R gene, instead of it, he proposed that a series of at least three pairs of pseudoalleles remain so closely linked with each other that they are usually inherited as a block. According to him, gene R is composed of three pairs of pseudoalleles or separate gene such as Cc, Dd and Ee. Recent genetical investigations have confirmed the Fisher’s concept of pseudoallelism.

The concepts of Wiener and Fisher has been compared in Table 10-4.

**Table 10-4 Comparison of Wiener’s and Fisher’s hypotheses about the genetics of Rh+ blood phenotype.**

**Gene symbol**

**Antigen produced**

**Phenotypes**

|  |  |  |
| --- | --- | --- |
| **Wiener** | **Fisher** |  |
| r | cde | None | Rh– |
| Ro | cDe | Ro | Rh+ |
| R´ | Cde | R´ | Rh+ |
| R´´ | cdE | R´´ | Rh+ |
| R1 | CDe | Ro and R´´ | Rh+ |
| R2 | cDE | Ro and R´´ | Rh+ |
| Rx or Rz | CDE | R´ and R´´ | Rh+ |
| Ry | CdE | R´and R´´ | Rh+ |

**MULTIPLE ALLELES**

**123**

1. **Eye Colour in *Drosophila***

In *Drosophila*, normal red eye colour is determined by a X-linked wild type gene. White eyed Drosophila was one of the first mutants known in the fruit flies. The traits of red eye and white eye exhibited simple dominant recessive relationship. Subsequently, different shades between red and white were recovered. About a dozen different alleles are now known to occur at this locus; they are red or wild type (w+) through coral (w*co*), blood (b*bl*), eosin (w*e*), cherry (w*ch*), appricot (w*a*), honey (w*h*), buff (w*bf*), tinged

The photographs show white eye and the brick-red wild-type eye colour in *Drosophila*.

(w*t*), pearl (w*p*) and ivory (w*i*), to white (w). All of these were considered, on the basis of F2 ratios, to form a multiple series, wild being dominant to all others and white recessive to all– w+ > w*co* > w*bl* > w*e* > w*ch* > w*a* > w*bf* > w*t* > w*p* > w*i* > w. When any two recessive alleles were brought together, intermediate types, called compound, is obtained. However, some of the members of this multiple allelic series have been found to be pseudoalleles by Lewis (1951) (see Chapter 11: Fine structure of Gene).

1. **Self-sterility Alleles**

A series of self-sterility alleles insures cross pollination in many plants. In fact, it is well known for long that some plants just will not self-pollinate in contrast to selfing in pea plant by Mendel.

Thus, a single plant may produce both male and female gametes but pollen grains of this plant fail to fertilize the ovules of the same plant; so as a result no seed will ever be produced. The same plants, however, will cross with certain other plants, so evidently they are not sterile. This phenomenon is called self- incompatibility or self-sterility. Kolreuter (1764) described self-sterility in tobacco plant (Nicotiana). Later on, the phenomenon of self-sterility is found to be common in many other dicot and monocot plants such as sweet cherries, petunias and evening primroses.

Eye colour in *Drosophila*.

**East and Mangelsdrof** (1925) proposed a series of self-sterility alleles, labelled S1, S2, S3, S4 ..... Sn. A Nicotiana plant could have any two of these, but no more, since they are alleles located opposite each other in a pair of chromo-

somes. Fertilization could be accomplished only by a pollen grain with one of the alleles not present. For example, S1/S2 plants if pollinated by S1/S2 pollen would set no seed because neither S1 nor S2 could affect fertilization. Apparently pollen tubes will not grow down a style of the same genotype

(Fig.10.11). Various combinations of crosses with their progenies have been tabulated in Table 10-5.

**GENETICS, HUMAN GENETICS AND EUGENICS**

**124**

**Pollen**

Self-fertilization or crosses between parents of same genotype S1/S2×S1/S2

S1 S1 S2 S2

Cross-fertilization

**Parents**

S1/S2×S2/S3

S1/S2×S3/S4

S2 S2 S3

S3

S3 S3 S

4

S4

**Egg cell**

S1 S1

S1 S2

S1 S2 S1 S2

**Progeny**

None

S1/S3

S2/S3

S1/S3 S2/S4

S2/S3 S1/S4

Fully incompatible Semicompatible Fully compatible

**Fig.10.11.** Diagram showing how multiple alleles control self-sterility in certain plants. A pollen tube will not grow if the S allele that it contains is present in the female parent (after Suzuki *et al.*, 1986).

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Genotype of parent** | **Functional pollen** | **Progeny** |
| 1. S1 /S2 × self | None | 0 seed |
| 2. S1/S2 × S1/S3 | S3 | S1 / S3 S2 / S3 |
| 3. S1/S2 × S2/S3 | S3 | S1 / S3 S2 / S3 |
| 4. S1/S3 × S1/S2 | S2 | S1 / S2 S2 / S3 |
| 5. S1/S3 × S2/S3 | S2 | S1 / S2 S2 / S3 |
| 6. S2/S3 × S1/S2 | S1 | S1 / S3 S1 / S2 |
| 7. S2/S3 × S1/S3 | S1 | S1 / S2 S1 / S3 |

We are not limited to three alleles for self-sterility. Several more have been found in Nicotiana. In evening primrose (Oenothera), 37 different self-sterility alleles have been observed. Red clover contains more than 200 alleles for the self-sterility (Bateman,1949).

**Table 10-5 Functional pollen produced and progeny resulting from crosses of different geno- types of self-sterility alleles (Source: Singleton, 1967).**

Molecular biology of self-sterility. Recently some biologists have tried to understand the mechanism of self-sterility at the molecular level. For example, Nasrallah et al., (1985) cloned DNA from S6 allele of Brassica oleracea and showed that the S6 allele causes the production of a S-specific glycoprotein which can be detected by an antibody. It is also shown that different S alleles may have different sequences.

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