

Chapter 2

Alleles at a Single Locus



Figure 2-1

A flower called Camellia showing co-dominance of the red and white alleles of flower colour.

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INTRODUCTION

A mutation is any change in the nucleic acid code for an organism. If the change of “letter” does not alter a gene in a fashion of changing a characteristic, it is called a silent mutation. However, sometimes the change alters a trait. These variations in traits first lead Gregor Mendel to formulate his theories of inheritance. More background about this is available in the prerequisite reading and Chapter 1.

A TERMINOLOGY

A specific position along a chromosome is called a locus. Because each gene occupies a specific locus along a chromosome, the terms locus and gene are often used interchangeably. However, the term “gene” is a much more general term, while “locus” usually is limited to defining the position along a chromosome. Each locus will have an allelic form (allele); a specific DNA sequence. In a population of individuals there will be sequence variation so there will be different alleles. Some may be defined as wild type, some as variants, others as mutant.

The complete set of alleles at all loci in an individual is its genotype. Typically, when writing out a genotype, only the alleles at the locus (or loci) of interest are

considered and written down – all the others are still present and assumed to be wild type. So, typically only the alleles at the few mutant loci appear in the written genotype. All the many, many others that are wild type are not.

The visible or detectable effect of alleles on the structure or function of that individual is called its phenotype – what it looks like. The phenotype studied in any particular genetic experiment may range from simple, visible traits such as hair color, to more complex phenotypes including disease susceptibility or behavior. If two alleles are present in an individual, as is the case with diploid organisms, then various interactions between them may influence their expression in the phenotype.

B SOMATIC VS. GERMLINE MUTATIONS

A mutation occurs in the DNA of a single cell. It can be passed on to the cell's direct descendants through mitosis, and it also may be passed on to the organism's descendants in the process of meiosis. In single-cell organisms a mutation is passed on directly to its descendants. In multicellular organisms, there is a partitioning into somatic cells and germline cells that occurs very early in development of animals. In plants, this separation occurs later, in the cells that form the flower.

B.1 SOMATIC MUTATIONS

Somatic cells form the tissues of the organism and are not passed on in reproduction. Any mutations in somatic cells will only affect the individual in which they occur, not its progeny. If mutations occur in somatic cells, its mutant descendants will exist along side other non-mutant (wild type) cells. If the mutation occurs at a very early stage of development the impact of the mutation will involve

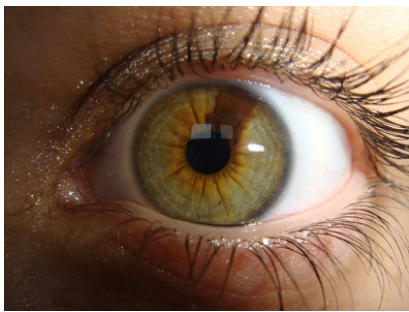


Figure 2-2
Patch of brown eye colour in a green eye. (Wikipedia-Sheila.lorquiana-CC BY-SA 3.0)

more cells. This gives rise to an individual composed of two or more types of cells that differ in their genetic composition. Such an individual is said to be a mosaic. An example is shown in **Figure 2-2** and cancer cells are another example.

B.2 GERMLINE MUTATIONS

Germline cells are those that form the eggs or sperm cells (ovum or pollen in plants), and are passed on to form the next generation. Therefore, mutations in germline cells will be passed on to the next generation but won't affect the individual in which they occur.

In animals, somatic cells are segregated from germline cells. In plants, somatic cells become germline cells; so somatic mutations can become germline mutations.

B.3 HAPLOID VS. DIPLOID ORGANISM

In haploid organisms, there is only one copy of a gene so a mutation will directly affect the organism's phenotype. Therefore, one can infer the genotype of the organism just by looking at its phenotype. However, in diploid organisms, there are two copies of each gene. This can result in an interaction between two alleles of

a gene so that a mutation may not have a direct impact on the organism's phenotype. The mutated allele can demonstrate complete dominance, incomplete dominance, co-dominance, or it can be recessive. Therefore, inferring one's genotype based upon its phenotype is not always simple in diploids.

C ALLELES: HETERO-, HOMO-, HEMIZYGOSITY

Mendel's First Law (segregation of alleles) is especially remarkable because he made his observations and conclusions (1865) without knowing about the relationships between genes, chromosomes, and DNA. We now know the reason why more than one allele of a gene can be present in an individual: most eukaryotic organisms are diploid and have at least two sets of homologous chromosomes. For organisms that are predominantly diploid, such as humans or Mendel's peas, chromosomes exist as pairs, with one homolog inherited from each parent. Diploid cells therefore can contain two different alleles of each gene, with one allele on each member of a pair of homologous chromosomes. If both alleles of a particular gene are the same (indistinguishable), the individual is said to be homozygous at that gene or locus. On the other hand, if the alleles are different from each other, the genotype is heterozygous.

In cases where there is only one copy of a gene present, for example if there is a deletion of the locus on the homologous chromosome, we use the term hemizygous. Another example is the single X- and Y- chromosomes in X/Y males in which almost all the loci on those chromosomes are hemizygous. (The exception is the pseudo-autosomal region which is an evolutionary holdover before X/Y sex determination – see the chapter on sex chromosomes.)

Although a single diploid individual can have at most two different alleles of a particular gene, many more alleles can exist in a population of individuals. In a natural population the most common allelic form is usually called the wild-type allele. However, in many populations there can be multiple variants at the DNA sequence level that are visibly indistinguishable as all exhibit a normal, wild type appearance. There can also be various mutant alleles (in wild populations and in lab strains) that vary from wild type in their appearance, each with a different change at the DNA sequence level. The many different mutations (alleles) at the same locus are called an allelic series for a locus.

D PLEIOTROPY AND POLYGENIC INHERITANCE

There is usually not a one-to-one correspondence between a gene and a physical characteristic. Often a gene is responsible for several phenotypic traits and it is said to be pleiotropic. For example, mutations in the vestigial gene (*vg*) in *Drosophila* results in an easily visible short wing phenotype. However, mutations in this gene also affect the number of egg strings, position of the bristles on scutellum, and lifespan in *Drosophila*. Therefore, *vg* gene is said to be pleiotropic in that it affects many different phenotypic characteristics.

The opposite is also found. Single characteristics can be affected by mutations in multiple, different genes. This implies that many genes are needed to make each characteristic. For example, if we return to the *Drosophila* wing, there are dozens of genes that when mutant alter the normal shape of the wing, not just the *vg* locus. Thus there are many genes that are needed to make a normal wing; the mutation of any one causes an abnormal, mutant, phenotype. This type of arrangement is called polygenic inheritance.

E COMPLETE DOMINANCE AND RECESSIVE

Let us return to an example of a simple phenotype: flower color in Mendel's peas. We have already said that one allele as a homozygote produces purple flowers, while the other allele as a homozygote produces white flowers (Figure 2). But what about an individual that has one purple allele and one white allele; what is the phenotype of an individual whose genotype is heterozygous? This can only be determined by experiment, such as observation. We know from observation that individuals heterozygous for the purple and white alleles of the flower color gene have purple flowers. Thus, the allele associated with purple color is therefore said to be dominant to the allele that produces the white color. The white allele, whose phenotype is masked by the purple allele in a heterozygote, is recessive to the purple allele. The dominant/recessive character is a relationship between proteins formed by each allele and must be determined by observation of the heterozygote phenotype.

Sometimes, to represent this relationship, a dominant allele will be written as a capital letter (e.g. *A*) while a recessive allele will be written in lower case (e.g. *a*). However, this is not the only system. Many different systems of genetic symbols are in use. The most common are shown in Table 2-1. Also note that genotypes (alleles)

are usually written in italics and chromosomes and proteins are not. For example, the white gene in *Drosophila melanogaster* on the X chromosome encodes a protein called WHITE, which is a pigment precursor transmembrane transporter enzyme.

Table 2-1

Examples of symbols used to represent genes and alleles.

Examples	Interpretation
<i>A</i> and <i>a</i>	Uppercase letters represent dominant alleles and lowercase letters indicate recessive alleles. Mendel invented this system but it is not commonly used because not all alleles show complete dominance and many genes have more than two alleles.
<i>a</i> ⁺ and <i>a</i> ¹	Superscripts or subscripts are used to indicate alleles. For wild type alleles the symbol is a superscript +.
<i>AA</i> or <i>A/A</i>	Sometimes a forward slash is used to indicate that the two symbols are alleles of the same gene locus, but on homologous chromosomes.

F INCOMPLETE DOMINANCE

Besides the complete dominant and recessive relationship, other relationships can exist between alleles. In incomplete dominance (also called semi-dominance), both alleles affect the trait additively, and the phenotype of the heterozygote shows a typically intermediate between the homozygotes, which is often referred to as blended phenotype. For example, alleles for color in carnation flowers (and many other species) exhibit incomplete dominance. Plants with an allele for red petals (*A*¹) and an allele for white petals (*A*²) have pink petals. We say that the *A*¹ and the *A*² alleles show incomplete dominance because neither allele is completely dominant over the other (Figure 2-3 on page 13).

G CODOMINANCE

Codominance is another type of allelic relationship in which a heterozygous individual expresses the phenotype of both alleles simultaneously (Figure 2-3).

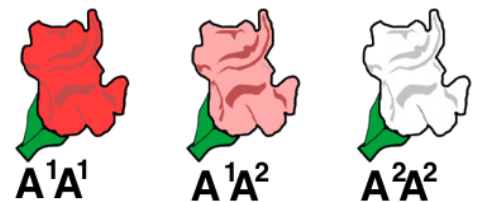


Figure 2-3

Relationship between genotype and phenotype for incompletely dominant alleles affecting petal colour in carnations. (Original-Deyholos- CC BY-NC 3.0)

An example of codominance is found within the ABO blood

group of humans. The ABO gene has three common alleles that were named (for historical reasons) I^A , I^B , and i . People homozygous for I^A or I^B display only A or B type antigens, respectively, on the surface of their blood cells, and therefore have either type A or type B blood (**Figure 2-4**). Heterozygous $I^A I^B$ individuals have both A and B antigens on their cells, and so have type AB blood. Note that the heterozygote expresses both alleles simultaneously, and is not some kind of novel intermediate between A and B. Codominance is therefore distinct from incomplete dominance, although they are sometimes confused.

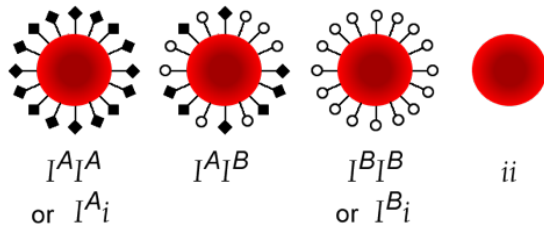


Figure 2-4

Relationship between genotype and phenotype for three alleles of the human ABO gene. The I^A and I^B alleles show co-dominance. The I^A allele is completely dominant to the i allele. The I^B allele is completely dominant to the i allele.

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It is also important to note that the third allele, i , does not make either antigen and thus is recessive to the other alleles. I^A/i or I^B/i individuals display only A or B antigens, respectively. People homozygous for the i allele have type O blood.

This is a useful reminder that different types of dominance relationships can exist, even for alleles of the same gene. Many types of molecular markers, which we will discuss in a later chapter, display a co-dominant relationship among alleles. Another example of co-dominance is shown in the first figure of this chapter – flower colour in *Camellia* sp.

H BIOCHEMICAL BASIS OF DOMINANCE

Given that a heterozygote's phenotype cannot simply be predicted from the phenotype of homozygotes, what does the type of dominance tell us about the biochemical nature of the gene product? How does dominance work at the biochemical level? There are several different biochemical mechanisms that may make one allele dominant to another.

For the majority of genes studied, the normal (i.e. wild-type) alleles are haplosufficient. So in diploids,

even with a mutation that causes a complete loss of function in one allele, the other allele, a wild-type allele, will provide sufficient normal biochemical activity to yield a wild type phenotype and thus be dominant and dictate the heterozygote phenotype.

On the other hand, in some biochemical pathways, a single wild-type allele is not enough protein and may be haploinsufficient to produce enough biochemical activity to result in a normal phenotype, when heterozygous with a non-functioning mutant allele. In this case, the non-functional mutant allele will be dominant (or semidominant) to a wild-type allele.

Mutant alleles may also encode products that have new and/or different biochemical activities instead of, or in addition to, the normal ones. These novel activities could cause a new phenotype that would be dominantly expressed.

I MUTANT CLASSIFICATION

I.1 MORPHOLOGICAL

Morphological mutations cause changes in the visible form of the organism. An example could be a change in size, shape, colour, number etc.

I.2 LETHAL

A lethal mutation causes the premature death to an organism. For example, in *Drosophila* lethal mutations can result in the death during the embryonic, larval, or pupal period of development. Lethal mutations are usually recessive, so both copies of a gene have to be lost for the premature death to occur (homozygous lethal alleles will not be viable). Heterozygotes which have one lethal allele and one wild type allele are typically viable..

I.3 BIOCHEMICAL

Biochemical mutations produce auxotrophic mutants from prototrophic parents. This type of mutation blocks a step in a biochemical pathway as discussed for the arg- mutants of Beadle and Tatum in the chapter on biochemical pathways. Biochemical mutations are a specific type of the conditional mutation class (next).

I.4 CONDITIONAL

This type of mutation relies on the concept of: phenotype = genotype + environment + interaction. Organisms with this kind of mutation express mutant phenotype, but only under specific environmental conditions. Under restrictive conditions, they express

the mutant phenotype while under permissive conditions, they show a wild type phenotype. One example of a conditional mutation is the temperature sensitive pigmentation of Siamese cats. Siamese cats have temperature sensitive fur colour; their fur appears white (unpigmented) when grown in a normal, warm temperature environment and appears black (pigmented) when under a cooler temperature, such as the peripheral regions of the feet, snout, and ears (**Figure 2-5**). This is because in warm temperature, the enzyme that is needed for melanin pigment synthesis becomes nonfunctional. However, in cooler temperature, the enzyme needed for melanin synthesis is functional and the deposition of melanin makes the fur look dark.



Figure 2-5
Siamese cats have temperature sensitive pigmentation due to genetic mutation.

(Wikimedia-Telekokopelli-CC BY-SA 3.0)

J MULLER'S MORPHS

Exposure of an organism to a mutagen causes mutations in essentially random positions along the chromosomes. Consequently, most of the mutant phenotypes recovered from a genetic screen are caused by loss-of-function mutations. These alleles are due to random changes in the DNA sequence that cause it to no longer produce the same level of active protein as the wild-type allele (**Figure 2-6**). Loss-of-function alleles tend to be recessive because the wild-type allele is haplosufficient. A loss-of-function allele that produces no active protein is called an amorph, or null. On the other hand, alleles with only a partial loss-of-function are called hypomorphs. More rarely, a mutant allele may have a gain-of-function, producing either more of the active protein (hypermorph) or producing an active protein with a new and different function (neomorph). Finally, antimorph alleles have an activity that is dominant and opposite to the wild-type function; antimorphs are also known as dominant negative mutations.

Thus, mutations (changes in a gene sequence) can result in mutant alleles that no longer produce the same level or type of active product as the wild-type allele (**Figure 2-6**). Any mutant allele can be classified into one of five types: (1) amorph, (2) hypomorph, (3) hypermorph, (4) neomorph, and (5) antimorph.

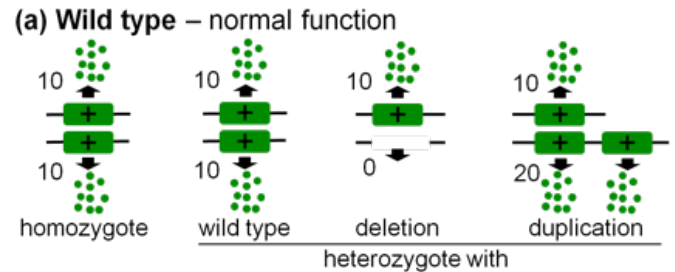


Figure 2-6

"Normal" function of a gene. This is the situation to which Muller's morphs are compared to explain their mechanism of expression.

J.1 AMORPH

Amorphic alleles have a complete loss-of-function. They make no active product – zero function. They are known as a “Null” mutation or a “loss-of-function” mutation (**Figure 2-7**).

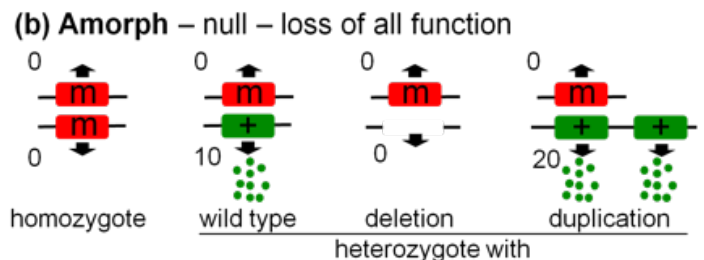


Figure 2-7

A mutant allele that produces no product or a functional product is considered an amorph.

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Molecular explanation - Changes in the DNA base pair sequence of an amorphic allele may cause one or more of the following:

- (1) Gene deletion - The DNA sequence is removed from the chromosome.
- (2) Gene is present, but is not transcribed due to gene regulation mutation, such as mutation in the promoter or enhancer/regulatory elements.
- (3) Gene is present but the transcript is not processed properly. There is normal transcription but base pair changes cause the mature mRNA to incorrectly splice introns, therefore the translated amino acid se-

quence would be altered and nonfunctional.

(4) Gene is present and a transcript is produced but no translation occurs – changes in the base pair sequences would preclude the mRNA from binding to the ribosome for translation.

(5) Gene is present and a transcript is produced and translated but a nonfunctional protein product is produced – the mutation alters a key amino acid in the polypeptide sequence producing a completely non-functional polypeptide.

Genetic/phenotypic explanation - Amorphic mutations of most genes usually act as recessive to wild type (Figure 2-8). However, with some genes the amorphic mutations are dominant to wild type (Table 2-2). For the *Minute* gene, we concluded that the organism needs both copies to have a wild type phenotype. Loss of one copy (an amorphic mutation) produces a dominant visible mutant phenotype. Deletion of the gene is an example of classical amorphic mutation.

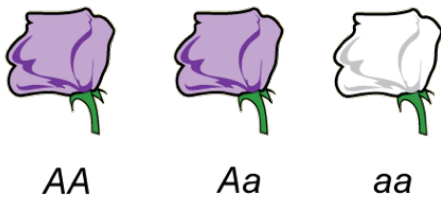


Figure 2-8

An amorph lacking the gene to produce pigment results in an allele that is expressed as a recessive pattern.

Table 2-2

Phenotypes that arise from cases #1 and #2 in the text.

case #1: <i>white</i> gene in <i>Drosophila</i>	
w^+/w^+	wildtype (red eyed phenotype)
w^+/w^-	wildtype (red eyed phenotype)
w^-/w^-	mutant (white eyed phenotype)
case #2: <i>Minute</i> locus in <i>Drosophila</i>	
M^+/M^+	wildtype (long bristled phenotype)
M^+/M^-	Mutant (short bristled phenotype)
M^-/M^-	Phenotype = dead; recessive lethal

J.2 HYPOMORPH

Hypomorphic alleles are only a partial loss-of-function. These alleles are sometimes referred to as “leaky” mutations, because they provide some function, but not complete, normal function (Figure 2-9).

Molecular explanation - Changes in the DNA base pair sequence of the hypomorphic allele may cause one or more of the following, with gene still being present:

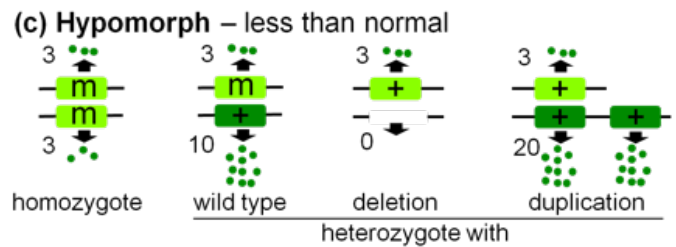


Figure 2-9

A mutant allele that produces fewer proteins or proteins that have lower effectivity than wild-type is considered a hypomorph.

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(1) reduced transcription – changed DNA sequence in the promoter or enhancer/regulatory elements can reduce the level of transcription.

(2) aberrant processing of the transcript – normal transcription but base pair changes cause the mature mRNA to incorrectly splice introns, therefore the translated protein sequence would be altered and function at a reduced level.

(3) reduced translation – changes in the base pair sequences would reduce the efficiency of the mRNA binding to the ribosome for translation.

(4) reduced-function protein product – normal transcription, processing, and translation but mutation changes certain amino acid in the polypeptide sequence so its function is reduced.

Genetic/phenotypic explanation - Hypomorphic mutations of most genes usually act as recessive to wild type, though hypomorphic mutations theoretically could be dominant to wildtype.

Both amorphs and hypomorphs tend to be recessive to wild type in diploids because the wild type allele is usually able to supply sufficient product to produce a wild type phenotype (called haplo-sufficient). If the mutant allele is not able to produce a wild type phenotype, then it is haplo-insufficient, and it will be dominant to the wild type allele. Here -/+ heterozygotes produce a mutant phenotype.

While the first two classes involve a loss-of-function, the next two involve a gain-of-function – quantity or quality. Gain-of-function alleles are almost always dominant to the wild type allele.

J.3 HYPERMORPH

Hypermorphic alleles produce quantitatively more of the same, active product (**Figure 2-10**).

Molecular explanation - Changes in the DNA base pair sequence of the hypermorphic allele may cause one or more of the following, with gene still being present:

- (1) increased transcription – changed DNA sequence in the promoter or enhancer/regulatory elements that increase the level of transcription.
- (2) increased translation – changes in the base pair sequences would increase the efficiency of the mRNA binding to the ribosome for translation.
- (3) increased function protein product – normal transcription, processing, translation but base pair changes alter certain amino acid in the polypeptide sequence so its function is normal but increased in amount.

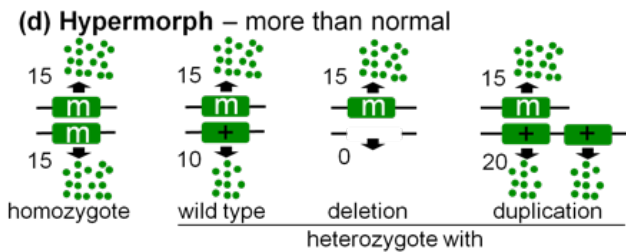


Figure 2-10

A mutant allele that produces more proteins or proteins that have increased effectivity than wild-type is considered a hypermorph.

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Genetic/phenotypic explanation - Hypermorphic mutations of most genes usually act as dominant to wild type since they are a gain of function, The classic hypermorph is a gene duplication.

J.4 NEOMORPH

Neomorphic alleles produce a product with a new, different function, something that the wild type allele doesn't do (**Figure 2-11**).

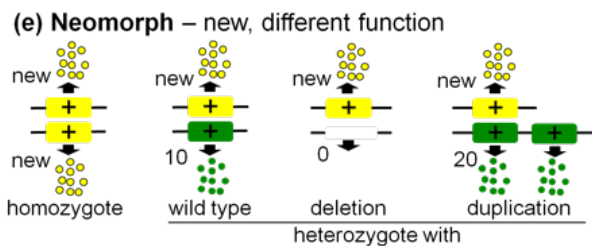


Figure 2-11

Neomorphic alleles encode proteins that have a function very different from those from the wild-type allele.

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Molecular explanation - Changes in the nucleotide sequence of the neomorphic allele may cause one or more of the following (gene is still present):

- (1) transcription – new DNA sequence in the regulatory elements alters transcription either temporally or in a tissue specific manner.
- (2) protein product with new function – normal transcription, processing, translation, but encode a different amino acid(s) so the protein acquires a new function (e.g. additional substrate or new binding site).

Genetic/phenotypic explanation - Neomorphic mutations of most genes usually act as a dominant to wild type since they are a gain-of-function. The classical neomorphic mutation is usually a translocation that moves a new regulatory element next to a gene promoter so it is expressed in a new tissue or at a new time during development. Such mutations are often produced when chromosome breaks are rejoined and the regulatory sequences of one gene are put adjacent to the transcriptional unit of another, creating a novel, chimeric gene.

J.5 ANTIMORPH

Antimorphic alleles are relatively rare, and have a new activity that is dominant and opposes the wild-type function. These alleles usually have lost their normal function and they interfere with the function from the wild type allele (**Figure 2-12**). This can happen at the transcriptional, translational, or later level of expression. Thus, when an antimorph allele is heterozygous with wild type, the wild type allele function is reduced or prevented. While at the molecular level there are many ways this can happen, the simplest model to explain an antimorph effect is that the product acts as a dimer (or any multimer) and the inclusion of one mutant subunit poisons the whole complex, thereby preventing it from functioning. Antimorphs are also known as dominant negative mutations because they are usually dominant and act negatively against the wild type function.

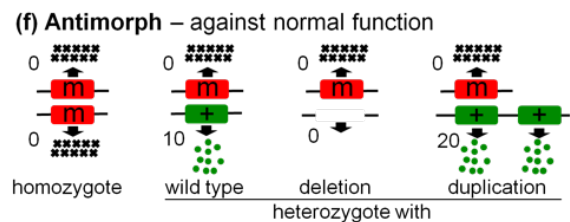


Figure 2-12

In an antimorph, the protein from the mutant allele binds the wild-type protein, inactivating it.

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J.6 IDENTIFYING MULLER'S MORPHS

All mutations can be sorted into one of the five morphs base on how they behave when heterozygous with three other standard alleles (**Figure 7**): (1) null

alleles (zero function), (2) wild type alleles (normal function), and (3) duplication alleles (double normal function).

SUMMARY:

- ◆ Symbols are used to denote the alleles, or genotype, of a locus. See Appendix 1 for rules about symbols.
- ◆ Phenotype depends on the alleles that are present, their dominance relationships, and sometimes also interactions with the environment and other factors.
- ◆ In a diploid organism, the alleles can be homozygous, heterozygous or hemizygous.
- ◆ Somatic mutations affect the individual but not the progeny, whereas germline mutation affect the progeny in the next generation but not the individual in which they occur.
- ◆ Allelic interactions at a locus can be described as dominant vs. recessive, incomplete dominance, or co-dominance.
- ◆ Muller's morphs classify all types of mutations including: amorph, hypomorph, hypermorph, neomorph, and antimorph.

KEY TERMS:

silent mutation	phenotype	haploinsufficiency
homozygous	dominant	loss-of-function
heterozygous	recessive	gain-of-function
hemizygous	complete dominance	amorph
wild-type	incomplete (semi) dominance	null
variant	co-dominance	hypomorph
locus	ABO blood group	hypermorph
genotype	haplosufficiency	neomorph

STUDY QUESTIONS:

1. If your blood type is B, what are the possible genotypes of your parents at the locus that controls the ABO blood types?
2. In **Table 2-3**, match the mouse hair color phenotypes with the term from the list that best explains the observed phenotype, given the genotypes shown. In this case, the allele symbols do not imply anything about the dominance relationships between the alleles. List of terms: haplosufficiency, haploinsufficiency, pleiotropy, incomplete dominance, co-dominance, incomplete penetrance, broad (variable) expressivity.

Table 2-3
Data for Question 2.

	A_1A_1	A_1A_2	A_2A_2
1	all hairs black	on the same individual: 50% of hairs are all black and 50% of hairs are all white	all hairs white
2	all hairs black	all hairs are the same shade of grey	all hairs white
3	all hairs black	all hairs black	50% of individuals have all white hairs and 50% of individuals have all black hairs
4	all hairs black	all hairs black	mice have no hair
5	all hairs black	all hairs white	all hairs white
6	all hairs black	all hairs black	all hairs white
7	all hairs black	all hairs black	hairs are a wide range of shades of grey