Sources of variation

The variational theory of evolution has a peculiar self defeating property. If evolution occurs by the differential reproduction of different variants, we expect the variant with the highest rate of reproduction eventually to take over the population and all other genotypes to disappear. But then there is no longer any variation for further evolution. The possibility of continued evolution therefore is critically dependent on renewed variation.

For a given population, there are three sources of variation: mutation, recombination, and immigration of genes. However, recombination by itself does not produce variation unless alleles are segregating already at different loci; otherwise there is nothing to recombine. Similarly, immigration cannot provide variation if the entire species is homozygous for the same allele. Ultimately, the source of all variation must be mutation.

Variation from mutations

Mutations are the *source* of variation, but the *process* of mutation does not itself drive evolution. The rate of change in gene frequency from the mutation process is very low because spontaneous mutation rates are low (Table 24-9). The mutation rate is defined as the probability that a copy of an allele changes to some other allelic form in one generation. Suppose that a population were completely homozygous *A* and mutations to *a* occurred at the rate of 1/100,000 Then, in the next generation, the frequency of *a* 0.00001 and the frequency of = 1/100,000 × alleles would be only 1.0 *A* alleles would be 0.99999. After yet another generation of mutation, the frequency of *a* 0.00009 to a new frequency of 0.000019, whereas the original allele would be reduced in frequency to 0.999981. It is obvious that the rate of increase of the new allele is extremely slow and that = 1/100,000 × would be increased by 0.99999 *it gets slower every generation* because there are fewer copies of the old allele still left to mutate. A general formula for the change in allele frequency under mutation is given in Box 24-3.

Table 24-9 Point-Mutation Rates in Different Organisms

Organism	Gene	Mutation rate per generation
Bacteriophage	Host range	2.5×10^{-9}
Escherichia coli	Phage resistance	2×10^{-8}
Zea mays (corn)	*R* (color factor)	2.9×10^{-4}
	Y (yellow seeds)	2×10^{-6}
Drosophila melanogaster	Average lethal	2.6×10^{-5}

MESSAGE

Mutation rates are so low that mutation alone cannot account for the rapid evolution of populations and species.

If we look at the mutation process from the standpoint of the increase of a particular new allele rather than the decrease of the old form, the process is even slower. Most mutation rates that have been determined are the sum of all mutations of *A* to any mutant form with a detectable effect. Any *specific* base substitution is likely to be at least two orders of magnitude lower in frequency than the sum of all changes.

Box 24-3 Effect of Mutation on Allele Frequency

Let μ be the mutation rate from allele *A* to some other allele *a* (the probability that a gene copy *A* will become *a* in the DNA replication preceding meiosis). If p_t is the frequency of the *A* allele in generation *t*, if $q_t = 1 - p_t$ is the frequency of the *a* allele, and if there are no other causes of gene frequency change (no natural selection, for example), then the change in allelic frequency in one generation is:

$$\Delta p = p_t - p_{t-1} = -\mu p_{t-1}$$

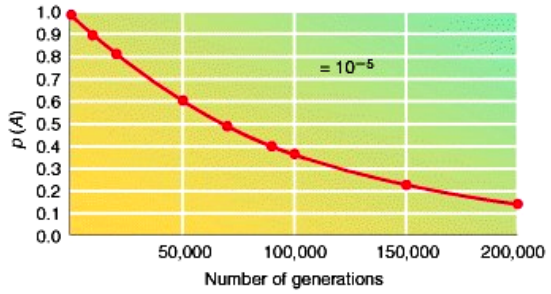
where p_{t-1} is the frequency in the preceding generation. This tells us that the frequency of *A* decreases (and the frequency of *a* increases) by an amount that is proportional to the mutation rate μ and to the proportion *p* of all the genes that are still available to mutate. Thus Δ*p* gets smaller as the frequency of *p* itself decreases, because there are fewer and fewer *A* alleles to mutate into *a* alleles. We can make the approximation that, after *n* generations of mutation,

$$p_n = p_0 e^{-n\mu}$$

where *e* is the base of the natural logarithms. This relation of gene frequency to number of generations is shown in the graph for $\mu = 10^{-5}$. After 10,000 generations of continued mutation of *A* to *a*,

$$p = p_0 e^{-(10^4)\times(10^{-5})} = p_0 e^{-0.1} = 0.904 p_0$$

If the population started with only *A* alleles ($p_0 = 1.0$), it would still have only 10 percent *a* alleles after 10,000 generations at this rather high mutation rate and would require 60,000 additional generations to reduce *p* to 0.5. Even if mutation rates were doubled (say, by environmental mutagens), the rate of evolution would be very slow. For example, radiation levels of sufficient intensity to double the mutation rate over the reproductive lifetime of an individual human are at the limit of occupational safety regulations, and a dose of radiation sufficient to increase mutation rates by an order of magnitude would be lethal; so rapid genetic change in the species would not be one of the effects of increased radiation. Although we have many things to fear from environmental radiation pollution, turning into a species of monsters is not one of them.



The change over generations in the frequency of a gene *A* due to mutation from *A* to *a* at a constant mutation rate (μ) of 10^{-5}.

So, precise reverse mutations ("back mutations") to the original allele *A* are unlikely, although many mutations may produce alleles that are *phenotypically* similar to the original.

It is not possible to measure locus-specific mutation rates for continuously varying characters, but the rate of accumulation of genetic variance can be determined. Beginning with a completely homozygous line of *Drosophila* derived from a natural population, 1/1000 to 1/500 of the genetic variance in bristle number in the original population is restored each generation by spontaneous mutation.

Variation from recombination

The creation of genetic variation by recombination can be a much faster process than its creation by mutation. When just two chromosomes with "normal" survival, taken from a natural population of *Drosophila*, are allowed to recombine for a single generation, they produce an array of chromosomes with 25 to 75 percent as much genetic variation in survival as was present in the entire natural population from which the parent chromosomes were sampled. This outcome is simply a consequence of the very large number of different recombinant chromosomes that can be produced even if we take into account only single crossovers. If a pair of homologous chromosomes is heterozygous at *n* loci, then a crossover can take place in any one of the $n - 1$ intervals between them, and, because each recombination produces two recombinant products, there

are $2(n-1)$ new unique gametic types from a single generation of crossing-over, even considering only single crossovers. If the heterozygous loci are well spread out on the chromosomes, these new gametic types will be frequent and considerable variation will be generated. Asexual organisms or organisms, such as bacteria, that very seldom undergo sexual recombination do not have this source of variation, so new mutations are the only way in which a change in gene combinations can be achieved. As a result, asexual organisms may evolve more slowly under natural selection than sexual organisms.

Variation from migration

A further source of variation is migration into a population from other populations with different gene frequencies. The resulting mixed population will have an allele frequency that is somewhere intermediate between its original value and the frequency in the donor population. Suppose a population receives a group of migrants whose number is equal to, say, 10 percent of its native population size. Then the newly formed mixed population will have an allele frequency that is a 0.90:0.10 mixture between its original allele frequency and the allele frequency of the donor population. If its original allele frequency of *A* were, say, 0.70, whereas the donor population had an allele frequency of only, say, 0.40, the new mixed population would have a frequency of $0.70 \times 0.90 + 0.40 \times 0.10 = 0.67$. Box 24-4 derives the general result. The change in gene frequency is proportional to the difference in frequency between the recipient population and the average of the donor populations. Unlike the mutation rate, the migration rate (m) can be large, so the change in frequency may be substantial.

Box 24-4 Effect of Migration on Allele Frequency

If p_t is the frequency of an allele in the recipient population in generation t and P is the allelic frequency in a donor population (or the average over several donor populations) and if m is the proportion of the recipient population that is made up of new migrants from the donor population, then the gene frequency in the recipient population in the next generation, p_{t+1}, is the result of mixing $1-m$ genes from the recipient with m genes from the donor population. Thus:

$$p_{t+1} = (1-m)p_t + mP = p_t + m(P - p_t)$$

and

$$\Delta p = p_{t+1} - p_t = m(P - p_t)$$

We must understand *migration* as meaning any form of the introduction of genes from one population into another. So, for example, genes from Europeans have "migrated" into the population of African origin in North America steadily since the Africans were introduced as slaves. We can determine the amount of this migration by looking at the frequency of an allele that is found only in Europeans and not in Africans and comparing its frequency among blacks in North America.

We can use the formula for the change in gene frequency from migration if we modify it slightly to account for the fact that several generations of admixture have taken place. If the rate of admixture has not been too great, then (to a close order of approximation) the sum of the single-generation migration rates over several generations (let's call this M) will be related to the total change in the recipient population after these several generations by the same expression as the one used for changes due to migration. If, as before, P is the allelic frequency in the donor population and p_0 is the original frequency among the recipients, then

$$\Delta p_{\text{total}} = M(P - p_0)$$

so

$$M = \frac{\Delta p_{\text{total}}}{P - p_0}$$

For example, the Duffy blood group allele Fy^a is absent in Africa but has a frequency of 0.42 in whites from the state of Georgia. Among blacks from Georgia, the Fy^a frequency is 0.046. Therefore, the total migration of genes from whites into the black population since the introduction of slaves in the eighteenth century is

$$M = \frac{\Delta p_{\text{total}}}{P - p} = \frac{0.046 - 0}{0.42 - 0} = 0.1095$$

When the same analysis is carried out on American blacks from Oakland (California) and Detroit, *M* is 0.22 and 0.26, respectively, showing either greater admixture rates in these cities than in Georgia or differential movement into these cities by American blacks who have more European ancestry. In any case, the genetic variation at the *Fy* locus has been increased by this admixture.

Inbreeding and assortative mating

Random mating with respect to a locus is common, but it is not universal. Two kinds of deviation from random mating must be distinguished. First, individuals may mate with each other nonrandomly because of their degree of common ancestry; that is, their degree of genetic relationship. If mating between relatives occurs more commonly than would occur by pure chance, then the population is inbreeding. If mating between relatives is less common than would occur by chance, then the population is said to be undergoing enforced outbreeding, or **negative inbreeding.**

Second, individuals may tend to choose each other as mates, not because of their degree of genetic relationship but because of their degree of resemblance to each other at some locus. Bias toward mating of like with like is called positive assortative mating. Mating with unlike partners is called negative assortative mating. Assortative mating is never complete.

Inbreeding and assortative mating are not the same. Close relatives resemble each other more than unrelated individuals on the average but not necessarily for any particular trait in particular individuals. So inbreeding can result in the mating of quite dissimilar individuals. On the other hand, individuals who resemble each other for some trait may do so because they are relatives, but unrelated individuals also may have specific resemblances. Brothers and sisters do not all have the same eye color, and blue-eyed people are not all related to one another.

Assortative mating for some traits is common. In humans, there is a positive assortative mating bias for skin color and height, for example. An important difference between assortative mating and inbreeding is that the former is specific to a trait, whereas the latter applies to the entire genome. Individuals may mate assortatively with respect to height but at random with respect to blood group. Cousins, on the other hand, resemble each other genetically on the average to the same degree at all loci.

For both positive assortative mating and inbreeding, the consequence to population structure is the same: there is an increase in homozygosity above the level predicted by the Hardy-Weinberg equilibrium. If two individuals are related, they have at least one common ancestor. Thus, there is some chance that an allele carried by one of them and an allele carried by the other are both descended from the identical DNA molecule. The result is that there is an extra chance of **homozygosity by descent,** to be added to the chance of homozygosity ($p^2 + q^2$) that arises from the random mating of unrelated individuals. The probability of homozygosity by descent is called the inbreeding coefficient (*F*). Figure 24-6 and Box 24-5 illustrate the calculation of the probability of homozygosity by descent. Individuals I and II are full sibs because they share both parents. We label each allele in the parents uniquely to keep track of them. Individuals I and II mate to produce individual III. If individual I is A_1/A_3 and the gamete that it contributes to III contains the allele A_1, then we would like to calculate the probability that the gamete produced by II is also A_1. The chance is 1/2 that II will receive A_1 from its father, and, if it does, the chance is 1/2 that II will pass A_1 on to the gamete in question. Thus, the probability that III will receive an A_1 from II is $1/2 \times 1/2 = 1/4$ and this is the chance that III—the product of a full-sib mating—will be homozygous by descent.

Box 24-5 Effect of the Mating of Close Relatives on Homozygosity

The probability of a homozygous *a*/*a* offspring from a brother–sister mating is:

probability that one or the other grandparent is *A*/*a*
× probability that *a* is passed to male sib
× probability that *a* is passed to female sib
× probability of a homozygous *a*/*a* offspring from *A*/*a* × *A*/*a*

$= (2pq + 2pq) \times \frac{1}{2} \times \frac{1}{2} \times \frac{1}{4}$

$= \frac{pq}{4}$

We assume that the chance that both grandparents are *A*/*a* is negligible. If *p* is very small, then *q* is nearly 1.0 and the chance of an affected offspring is close to *p*/4. For $p = 1/1000$, there is 1 chance in 4000 of an affected child, compared with the 1-in-a-million chance from a random mating. In general, for full sibs, the ratio of risks will be:

$$\frac{p/4}{p^2} = \frac{1}{4p}$$

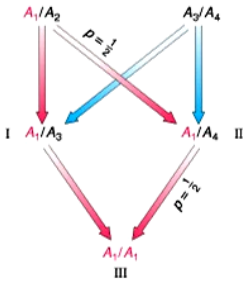


Figure 24-6

Calculation of homozygosity by descent for an offspring (III) of a brother–sister (I–II) mating. The probability that II will receive A_1 from its father is 1/2; if it does, the probability that II will pass A_1 on to the generation producing III is 1/2. Thus, the probability that III will receive an A_1 from II is 1/2 × 1/2 = 1/4.

Such close inbreeding can have deleterious consequences. Let's consider a rare deleterious allele *a* that, when homozygous, causes a metabolic disorder. If the frequency of the allele in the population is *p*, then the probability that a random couple will produce a homozygous offspring is only p^2 (from the Hardy-Weinberg equilibrium). Thus, if *p* is, say, 1/1000, the frequency of homozygotes will be 1 in 1,000,000. Now suppose that the couple are brother and sister. If one of their common parents is a heterozygote for the disease, they may both receive it and may both pass it on to their offspring. As the calculation shows, the rarer the gene, the worse the *relative* risk of a defective offspring from inbreeding. For more-distant relatives, the chance of homozygosity by descent is less but still substantial. For first cousins, for example, the relative risk is 1/16*p* compared with random mating.

Systematic inbreeding between close relatives eventually leads to complete homozygosity of the population but at different rates, depending on the degree of relationship. Which allele is fixed within a line is a matter of chance. If, in the original population from which the inbred lines are taken, allele *A* has frequency *p* and allele *a* has frequency $q = 1 - p$, then a proportion *p* of the homozygous lines established by inbreeding will be homozygous *A*/*A* and a proportion *q* of the lines will be *a*/*a*. Inbreeding takes the genetic variation present *within* the original population and converts it into variation *between* homozygous inbred lines sampled from the population (Figure 24-7).

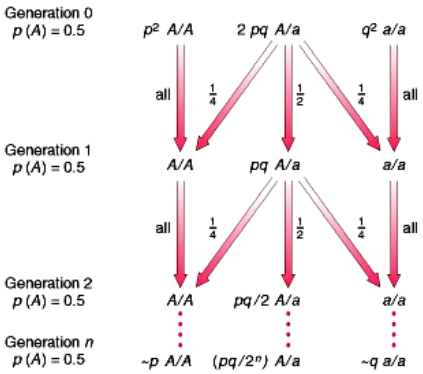


Figure 24-7

Repeated generations of self-fertilization (or inbreeding) will eventually split a heterozygous population into a series of completely homozygous lines. The frequency of *A*/*A* lines among the homozygous lines will be equal to the frequency of allele *A* in the original heterozygous population.

Suppose that a population is founded by some small number of individuals who mate at random to produce the next generation. Assume that no further immigration into the population ever occurs again. (For example, the rabbits now in Australia probably have descended from a single introduction of a few animals in the nineteenth century.) In later generations, then, everyone is related to everyone else, because their family trees have common ancestors here and there in their pedigrees. Such a population is then inbred, in the sense that there is some probability of a gene's being homozygous by descent. Because the population is, of necessity, finite in size, some of the originally introduced family lines will become extinct in every generation, just as family names disappear in a closed human population because, by chance, no male offspring are left. As original family lines disappear, the population comes to be made up of descendants of fewer and fewer of the original founder individuals, and all the members of the population become more and more likely to carry the same alleles by descent. In other words, the inbreeding coefficient *F* increases, and the heterozygosity decreases over time until finally *F* reaches 1.00 and heterozygosity reaches 0.

The rate of loss of heterozygosity per generation in such a closed, finite, randomly breeding population is inversely proportional to the total number ($2N$) of haploid genomes, where N is the number of diploid individuals in the population. In each generation, $1/2N$ of the remaining heterozygosity is lost, so

$$H_t = H_0\left(1 - \frac{1}{2N}\right)^t \cong H_0 e^{-t/2N}$$

where H_t and H_0 are the proportions of heterozygotes in the tth and original generations, respectively. As the number t of generations becomes very large, H_t approaches zero.

Balance between inbreeding and new variation

Any population of any species is finite in size, so all populations should eventually become homozygous and differentiated from one another as a result of inbreeding. In nature, however, new variation is always being introduced into populations by mutation and by some migration between localities. Thus, the actual variation available for natural selection is a balance between the introduction of new variation and its loss through local inbreeding. The rate of loss of heterozygosity in a closed population is $1/2N$, so any effective differentiation between populations will be negated if new variation is introduced at this rate or higher.

Genetic variation

If all members of a species have the same set of genes, how can there be genetic variation? As indicated earlier, the answer is that genes come in different forms called alleles. In a population, for any given gene there can be from one to many different alleles; however, because most organisms carry only one or two chromosome sets per cell, any individual organism can carry only one or two alleles per gene. The alleles of one gene will always be found in one chromosomal position. Allelic variation is the basis for hereditary variation.

Types of variation

Because a great deal of genetics concerns the analysis of variants, it is important to understand the types of variation found in populations. A useful classification is into discontinuous and continuous variation (Figure 1-12). Allelic variation contributes to both.

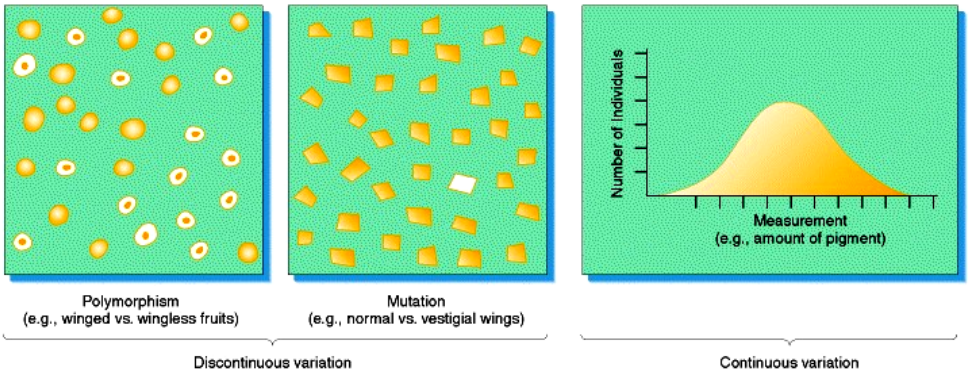


Figure 1-12

Discontinuous and continuous variation in natural populations. In populations showing discontinuous variation for a particular character, each member possesses one of several discrete alternatives. For example, in the left-hand panel, a population of plants manifests two distinct, common fruit types: winged and wingless (see Figure 1-14a). Such variation is called a *polymorphism*. Sometimes most of the population is of one kind, with mutation providing only the occasional alternative, as in the vestigial wing type in the fruit fly, *Drosophila*. Discontinuous variants are often determined by the alleles of a single gene. Continuous variation, on the other hand, does not show such discrete alternatives; a character may be found in phenotypic gradations in a population. There may be no genetic basis – that is, all variation may be environmentally caused – or genes may play a role, often several or many genes.

Most of the research in genetics in the past century has been on discontinuous variation because it is a simpler type of variation, and it is easier to analyze. In discontinuous variation, a character is found in a population in two or more distinct and separate forms called **phenotypes.** Such alternative phenotypes are often found to be encoded by the alleles of one gene. A good example is albinism in humans, which concerns phenotypes of the character of skin pigmentation. In most people, the cells of the skin can make a dark brown or black pigment called melanin, the substance that gives our skin its color ranging from tan color in people of European ancestry to brown or black in those of tropical and subtropical ancestry. Although always rare, albinos are found in all races; they have a totally pigmentless skin and hair (Figure 1-13). The difference between pigmented and unpigmented is caused by two alleles of a gene taking part in melanin synthesis. The alleles of a gene are conventionally designated by letters. The allele that codes for the ability to make melanin is called *A* and the allele that codes for the inability to make melanin (resulting in albinism) is designated *a* to show that they are related. The allelic constitution of an organism is its genotype, which is the hereditary underpinning of the phenotype. Because humans have two sets of chromosomes in each cell, genotypes can be either *A*/*A*, *A*/*a*, or *a*/*a* (the slash shows that they are a pair). The phenotype of *A*/*A* is pigmented, *a*/*a* is albino, and *A*/*a* is pigmented. The *ability* to make pigment is expressed over *inability* (*A* is said to be dominant).

Although allelic differences cause phenotypic differences such as pigmented and albino, this does not mean that only one gene affects skin color. It is known that there are several. However,

the *difference* between pigmented, of whatever shade, and albino is caused by the *difference* at one gene; the state of all the other pigment genes is irrelevant.

In discontinuous variation, there is a predictable one-to-one relation between genotype and phenotype under most conditions. In other words, the two phenotypes (and their underlying genotypes) can almost always be distinguished. In the albinism example, the *A* allele always allows some pigment formation, whereas the white allele always results in albinism when homozygous. For this reason, discontinuous variation has been successfully used by geneticists to identify the underlying alleles and their role in cellular functions.

Geneticists distinguish two categories of discontinuous variation on the basis of simple allelic differences. In a natural population, the existence of two or more *common* discontinuous variants is called polymorphism (Greek; many forms), and an example is shown in Figure 1-14a. The various forms are called **morphs.** It is often found that morphs are determined by the alleles of a single gene. Why do populations show genetic polymorphism? Special types of natural selection can explain a few cases, but, in other cases, the morphs seem to be selectively neutral.

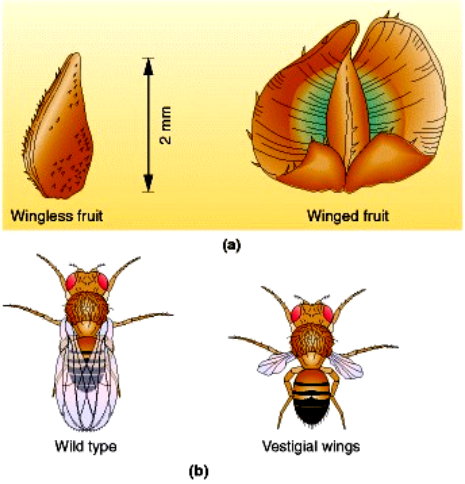


Figure 1-14

A dimorphism. (a) The fruits of two different forms of *Plectritis congesta,* the sea blush. Any one plant has either all wingless or all winged fruits. In every other way, the plants are identical. (b) A *Drosophila* mutant with abnormal wings and a normal fly (wild type) for comparison. In both cases, the two phenotypes are caused by the alleles of one gene.

Rare, exceptional discontinuous variants are called **mutants,** whereas the more common "normal" companion phenotype is called the wild type. Figure 1-14b shows an example of a mutant phenotype. Again, in many cases, the wild-type and mutant phenotypes are determined by the alleles of one gene. Mutants can occur spontaneously in nature (for example, albinos) or they can be obtained after treatment with mutagenic chemicals or radiations. Geneticists regularly induce mutations artificially to carry out genetic analysis because mutations that affect some specific biological function under study identify the various genes that interact in that function. Note that polymorphisms originally arise as mutations, but somehow the mutant allele becomes common.

MESSAGE

In many cases, an allelic difference at a single gene may result in discrete phenotypic forms that make it easy to study the gene and its associated biological function.

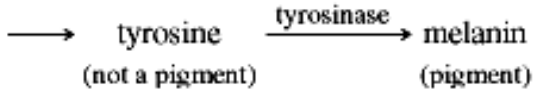
Continuous variation of a character shows an unbroken range of phenotypes in the population (see Figure 1-12). Measurable characters such as height, weight, and color intensity are good examples of such variation. Intermediate phenotypes are generally more common than extreme phenotypes and, when phenotypic

frequencies are plotted as a graph, a bell-shaped distribution is observed. In some such distributions, all the variation is environmental and has no genetic basis at all. In other cases, there is a genetic component caused by allelic variation of one or many genes. In most cases, there is both genetic and environmental variation. In continuous distributions, there is no one-to-one correspondence of genotype and phenotype. For this reason, little is known about the types of genes underlying continuous variation, and only recently have techniques become available for identifying and characterizing them.

Continuous variation is encountered more commonly than discontinuous variation in everyday life. We can all identify examples of continuous variation in plant or animal populations that we have observed – many examples exist in human populations. One area of genetics in which continuous variation is important is in plant and animal breeding. Many of the characters that are under selection in breeding programs, such as seed weight or milk production, have complex determination, and the phenotypes show continuous variation in populations. Animals or plants from one extreme end of the range are chosen and selectively bred. Before such selection is undertaken, the sizes of the genetic and environmental components of the variation must be known. We shall return to these specialized techniques in Chapter 20, but, for the greater part of the book, we shall be dealing with the genes underlying discontinuous variation.

Molecular basis of allelic variation

Consider the difference between the pigmented and the albino phenotypes in humans. The dark pigment melanin has a complex structure that is the end product of a biochemical synthetic pathway. Each step in the pathway is a conversion of one molecule into another, with the progressive formation of melanin in a step-by-step manner. Each step is catalyzed by a separate eenzyme protein encoded by a specific gene. Most cases of albinism result from changes in one of these enzymes – tyrosinase. The enzyme tyrosinase catalyzes the last step of the pathway, the conversion of tyrosine into melanin.



To perform this task, tyrosinase binds to its substrate, a molecule of tyrosine, and facilitates the molecular changes necessary to produce the pigment melanin. There is a specific "lock-and-key" fit between tyrosine and the active site of the enzyme. The active site is a pocket formed by several crucial amino acids in the polypeptide. If the DNA of the tyrosinase-encoding gene changes in such a way that one of these crucial amino acids is replaced by another amino acid or lost, then there are several possible consequences. First, the enzyme might still be able to perform its functions but in a less efficient manner. Such a change may have only a small effect at the phenotypic level, so small as to be difficult to observe, but it might lead to a reduction in the amount of melanin formed and, consequently, a lighter skin coloration. Note that the protein is still present more or less intact, but its ability to convert tyrosine into melanin has been compromised. Second, the enzyme might be incapable of any function, in which case the mutational event in the DNA of the gene would have produced an albinism allele, referred to earlier as an *a* allele. Hence a person of genotype *a*/*a* is an albino. The genotype *A*/*a* is interesting. It results in normal pigmentation because transcription of one copy of the wild-type allele (*A*) can provide enough tyrosinase for synthesis of normal amounts of melanin. Alleles are termed *haplosufficient* if roughly normal function is obtained when there is only a single copy of the normal gene. Alleles commonly appear to be haplosufficient, in part because small reductions in function are not vital to the organism. Alleles that fail to code for a functional protein are called **null** ("nothing") **alleles** and are generally not expressed in combination with functional alleles (in individuals of genotype *A*/*a*). The molecular basis of albinism is represented in Figure 1-15.

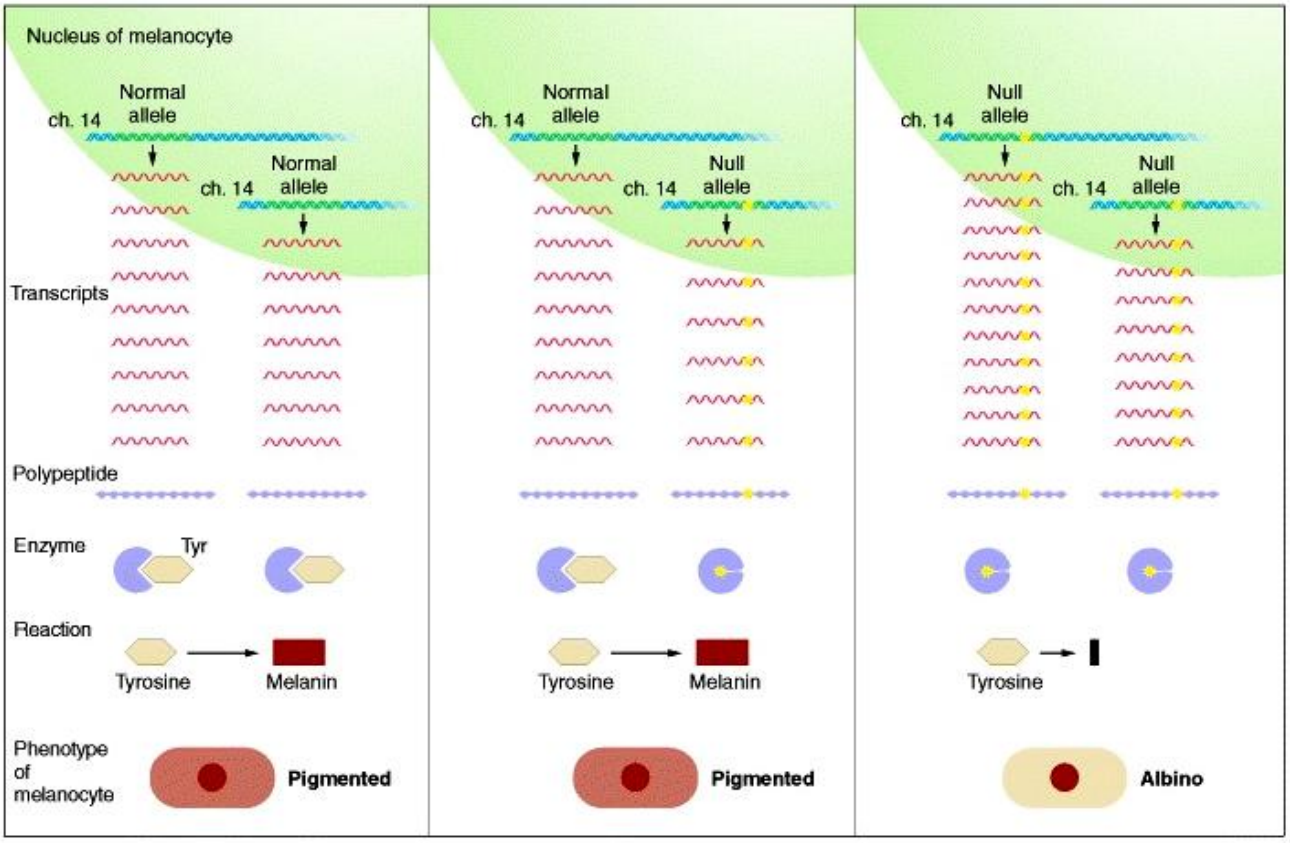


Figure 1-15

Molecular basis of albinism. Expression in cells containing 2, 1, and 0 copies of the normal tyrosinase allele on chromosome 14. Melanocytes are specialized melanin-producing cells.

The mutational site in the DNA can be of a number of types. The simplest and most common type is nucleotide-pair substitution, which can lead to amino acid substitution or to premature stop codons. Small **deletions** and duplication also are common. Even a single base deletion or insertion produces widespread damage at the protein level; because mRNA is read from one end "in frame" in groups of three, a loss or gain of one nucleotide pair shifts the reading frame, and all the amino acids translationally downstream will be incorrect. Such mutations are called **frameshift mutations.**

At the protein level, mutation changes the amino acid composition of the protein. The most important outcomes are change in shape and size. Such change in shape or size can result in no biological function (which would be the basis of a null allele), or reduced function. More rarely, mutation can lead to new function of the protein product.

MESSAGE

New alleles formed by mutation can result in no function, less function, or new function at the protein level.