Chapter 20 –Biological Change

Objectives

Given the synopsis in this chapter, competence in each objective will be demonstrated by responding to multiple choices or matching questions, completing fill-in questions, or writing short answers, at the level of 75% or greater proficiency for each student.

A. To explain the Hardy-Weinberg equilibrium.
B. To explain the major factors that change allele frequencies.
C. To explain crossover and mutation.
D. To explain the effects of mutations on gene function and protein synthesis.

Hardy-Weinberg equilibrium

Populations show no inherent tendency to change allele or genotype frequencies. The frequency of a given dominant allele is represented by *p*. The frequency of a given recessive allele is represented by *q*. In the absence of forces that can drive biological change, a population with given values of *p* and *q* will settle into a stable set of genotypic proportions. This state is called a Hardy-Weinberg equilibrium (1908). The Hardy-Weinberg equilibrium of a population with allele frequencies *p* and *q* is defined by the set of genotypic frequencies p^2 of *RR*, 2*pq* of *Rr*, and q^2 of *rr*.

We will use as an example a population of pea plants; 25% homozygous for purple flowers, 50% heterozygous for purple flowers, and 25% homozygous for white flowers. We will then allow the plants to randomly cross-pollinate to produce offspring, as shown in table 20.1

Table 20.1. Random cross-pollination of pea plants 25% homozygous for purple, 50% heterozygous for purple flowers, and 25% homozygous for white.

Color of Flower	Purple (RR)		Purple (Rr)		Purple (Rr)		White (rr)	
Purple (RR)	P(RR)	P(RR)	P(RR)	P(Rr)	P(RR)	P(Rr)	P(Rr)	P(Rr)
	P(RR)	P(RR)	P(RR)	P(Rr)	P(RR)	P(Rr)	P(Rr)	P(Rr)
Purple (Rr)	P(RR)	P(RR)	P(RR)	P(Rr)	P(RR)	P(Rr)	P(Rr)	P(Rr)
	P(Rr)	P(Rr)	P(Rr)	W(rr)	P(Rr)	W(rr)	W(rr)	W(rr)
Purple (Rr)	P(RR)	P(RR)	P(RR)	P(Rr)	P(RR)	P(Rr)	P(Rr)	P(Rr)
	P(Rr)	P(Rr)	P(Rr)	W(rr)	P(Rr)	W(rr)	W(rr)	W(rr)
White (rr)	P(Rr)	P(Rr)	P(Rr)	P(Rr)	P(Rr)	P(Rr)	W(rr)	W(rr)
	P(Rr)	P(Rr)	W(rr)	W(rr)	W(rr)	W(rr)	W(rr)	W(rr)

The breeding population, has the following frequency of alleles:

- The frequency of allele "R" is $p = 8/16 = 0.5$;
- The frequency of allele "r" is $q = 8/16 = 0.5$;

And the following frequency of genotypes:

- The frequency of genotype "RR" is $p^2 = 0.5 \times 0.5 = 0.25 = 2/8$;
- The frequency of genotype "Rr" is $2pq = 2(0.5 \times 0.5) = 0.50 = 4/8$;
- The frequency of genotype "rr" is $q^2 = 0.5 \times 0.5 = 0.25 = 2/8$.

The offspring population has the following frequency of alleles:

- The frequency of allele "R" is $p = 64/128 = 0.5$;
- The frequency of allele "r" is $q = 64/128 = 0.5$.

And the following frequency of genotypes:

- The frequency of genotype "RR" is $p^2 = 0.5 \times 0.5 = 0.25 = 16/64$;
- The frequency of genotype "Rr" is $2pq = 2(0.5 \times 0.5) = 0.50 = 32/64$;
- The frequency of genotype "rr" is $q^2 = 0.5 \times 0.5 = 0.25 = 16/64$.

This example demonstrates how a population with given allele frequencies, *and with random mating*, will settle into a stable set of genotypic proportions.

The calculations of the Hardy-Weinberg equilibrium depend on several assumptions. The most critical one, of course, is that there is random mating. In addition, the population must be large, and there can be no other pressures, that can change allele frequencies. In spite of these stringent requirements, many natural populations have been shown to be in a Hardy-Weinberg equilibrium for the genes studied.

If the Hardy-Weinberg principle of population genetics shows that there is no inherent tendency for population change, then how does change occur?

Changes in Gene (Allele) Frequencies

Selection

One assumption behind the calculation of unchanging genotypic frequencies in Hardy-Weinberg equilibrium is that all genotypes have a similar fitness. In genetics, fitness is a measure of the ability to produce fertile offspring. The genotype with the greatest fitness is given the fitness value (w) of 1, and the lesser fitness genotypes are fractions of 1. The proportional difference from the most-fit is called the selection 6coefficient, s. Hence, $s = 1 - w$.

Alleles carried by less-fit individuals will be gradually lost from the population, and the relevant allele frequency will decline. This is the fundamental way in which natural selection operates in a population. Selection against dominant alleles is relatively efficient, because these are by definition expressed in the phenotype. Selection against recessive alleles is less efficient, because these alleles are sheltered in heterozygotes. Heterozygotes are much more common than recessive homozygotes; thus, most of the recessive alleles in a population will escape selection.

Because of the sheltering effect of heterozygotes, selection against recessive phenotypes changes the frequency of the recessive allele slowly.

A different type of natural selection occurs when the fitness of a heterozygote exceeds the fitness of both homozygotes. The maintenance in human populations of the severe hereditary disease sickle cell anemia is owing to this form of selection. The disease allele (Hb^S) produces a specific type of hemoglobin that causes distortion (sickling) of the red blood cells in which the hemoglobin is carried. (Normal hemoglobin is coded by another allele, Hb^A). Accordingly, the possible genotypes are Hb^AHb^A, Hb^AHb^S, and Hb^SHb^S. The latter individuals are homozygous for the sickle cell allele and will develop severe anemia because the oxygen transporting property of their blood is compromised. While the condition is not lethal before birth, such individuals rarely survive long enough to reproduce. On these grounds it might be expected that the disease allele would be selected against, driving the allele frequency to very low levels. However, in tropical areas of the world, the allele and the disease

are common. The explanation is that the Hb^AHb^S heterozygote is fitter and capable of leaving more offspring than is the homozygous normal Hb^AHb^A in an environment containing the falciparum form of malaria. This extra measure of protection is evidently provided by the sickle cell hemoglobin, which is detrimental to the malaria parasite. In malarial environments, therefore, populations that contain the sickle cell gene have advantages over populations free of this gene. The former populations are in less danger from malaria, although they "pay" for this advantage by sacrificing in every generation some individuals who die of anemia.

Nonrandom mating

Many species engage in alternatives to random mating as normal parts of their cycle of sexual reproduction. An important example is sexual selection, in which an individual chooses a mate on the basis of some aspect of the mate's phenotype. The selection can be based on some display feature such as bright feathers, or it may be a simple preference for a phenotype similar to the individual's own (positive assortative mating).

Two other important examples are inbreeding (mating with relatives) and enforced outbreeding. Both can shift the equilibrium proportions expected under Hardy-Weinberg calculations. For example, inbreeding increases the proportions of homozygotes, and the most extreme form of inbreeding, self-fertilization, eventually eliminates all heterozygotes.

Inbreeding and outbreeding are evolutionary strategies adopted by plants and animals living under certain conditions. Outbreeding brings gametes of different genotypes together, and the resulting individual differs from the parents. Increased levels of variation provide more evolutionary flexibility. All the showy colors and shapes of flowers are to promote this kind of exchange. In contrast, inbreeding maintains uniform genotypes, a strategy successful in stable ecological habitats.

In humans, various degrees of inbreeding have been practiced in different cultures. In most cultures today, mating of first cousins is the maximal form of inbreeding tolerated by society. Apart from ethical considerations, a negative outcome of inbreeding is that it increases the likelihood of homozygous recessive alleles originating from common ancestors. The inbreeding coefficient F is a measure of the likelihood of homozygous recessive alleles; for example, in first-cousin marriages, $F = {}^1/_{16}$. A large proportion of recessive hereditary diseases can be traced to first-cousin marriages and other types of inbreeding.

Random genetic drift

In populations of finite size, the genetic structure of a new generation is not necessarily that of the previous one. The explanation lies in a sampling effect, based on the fact that a subsample from any large set is not always representative of the larger set. The gametes that form any generation can be thought of as a sample of the alleles from the parental one. If sampling is skewed in the same direction from generation to

generation, the allele frequency can change radically. This process is known as random genetic drift. As might be expected, the smaller the population, the greater chance of sampling error and hence significant levels of drift in any one generation. In extreme cases, drift over the generations can result in the complete loss of one allele.

Other cases of sampling error occur when new colonies of plants or animals are founded by small numbers of migrants (founder effect) and when there is radical reduction in population size because of a natural catastrophe (population bottleneck). One inevitable effect of these processes is a reduction in the amount of variation in the population after the size reduction.

Mutation

Genetics has shown that mutation is the ultimate source of all hereditary variation. At the level of a single gene whose normal functional allele is "*A"*, it is known that mutation can change it to a nonfunctional recessive form, "*a"*. Such "forward mutation" is more frequent than "back mutation" (reversion), which converts "*a"* into "*A"*. Molecular analysis of specific examples of mutant recessive alleles has shown that they are generally a heterogeneous set of small structural changes in the DNA of a gene. For example, the disease phenylketonuria is inherited as a recessive phenotype and is ascribed to a causative allele. However, sequencing alleles of many independent cases of phenylketonuria has shown that this allele is in fact a set of many different kinds of mutational changes, which can be in any of the protein-coding regions of that gene.

Mechanisms of Crossover and Mutation

Crossover often causes recombination of genes. Mutations arise from changes to the DNA of a gene. These changes can be quite small, affecting only one nucleotide pair, or they can be relatively large, affecting hundreds or thousands of nucleotides.

Chromosome (DNA) Crossover

Crossover occurs during prophase of Meiosis part 1, when two homologous chromosomes break and then exchange some distal portions of their DNA.

If the chromosomes break at the same locus in the sequence of DNA base pairs, the result is an exchange of genes. This process is the normal way for crossover to occur, and is called **genetic recombination**.

If the chromosomes break at slightly different loci, the result can be a **duplication** (addition) of genes on one chromosome and a **deletion** of genes on the other chromosome. This process is less common, and is called unequal crossover.

If chromosomes break on both sides of the same centromere and rejoin to exclude the centromere, the result can be one chromosome being lost during cell division

Point Mutations

Mutations in which one base is changed are called **point mutations**—for example, substitution of the nucleotide pair AT by GC, CG, or TA. Base **substitutions** can have different consequences at the protein level. Some base substitutions are "silent," meaning that they result in a new codon that codes for the same amino acid as the wild type codon at that position or a codon that codes for a different amino acid that happens to have the same properties as those in the wild type.

Substitutions that result in a functionally different amino acid are called "**missense**" mutations; these can lead to alteration or loss of protein function. A more severe type of base substitution, called a "**nonsense**" mutation, results in a stop codon in a position where there was not one before, which causes the premature termination of **protein synthesis** and, more than likely, a complete loss of function in the finished protein.

Frame-Shift Mutation

Another type of point mutation that can lead to drastic loss of function is a **frame-shift mutation**, the addition or deletion of one or more DNA bases. In a protein-coding gene, the sequence of codons starting with AUG and ending with a termination codon is called the reading frame. If a nucleotide pair is added to or subtracted from this sequence, the reading frame from that point will be shifted by one nucleotide pair, and all of the codons downstream will be altered. The result will be a protein whose first section (before the mutational site) is that of the wild type amino acid sequence, followed by a tail of functionally meaningless amino acids. Large **deletions** of many codons will not only remove amino acids from a protein but may also result in a frame-shift mutation if the number of nucleotides deleted is not a multiple of three. Likewise, an **insertion** of a block of nucleotides will add amino acids to a protein and perhaps also have a frame-shift effect.

A number of human diseases are caused by the expansion of a triplet nucleotide repeat. For example, **fragile-X syndrome**, the most common type of inherited mental retardation in humans, is caused by the repetition of up to 1,000 copies of a CGG repeat in a gene on the X chromosome.

Consequences of Mutations

The impact of a mutation depends upon the type of cell involved. In a gamete cell, any mutant allele will most likely be expressed in the **phenotype** of that cell. In a diploid cell, a **dominant** mutation will be expressed over the wild type allele, but a **recessive** mutation will remain masked by the wild type. If recessive mutations occur in both members of one gene pair in the same cell, the mutant phenotype will be expressed. Mutations in germinal cells (i.e., reproductive cells) may be passed on to successive generations. However, mutations in somatic (body) cells will exert their effect only on that individual and will not be passed on to progeny.

The impact of an expressed somatic mutation depends upon which gene has been mutated. In most cases, the somatic cell with the mutation will die, an event that is generally of little consequence in a multicellular organism. However, mutations in a special class of genes called proto-oncogenes can cause uncontrolled division of that cell, resulting in a group of cells that constitutes a cancerous tumor.

Effects of mutations on gene function

Mutations can affect gene function in several different ways.

First, the structure and function of the protein coded by that gene can be affected. For example, enzymes are particularly susceptible to mutations that affect the amino acid sequence at their active site (i.e., the region that allows the enzyme to bind with its specific substrate). This may lead to enzyme inactivity; a protein is made, but it has no enzymatic function.

Second, some nonsense or frame-shift mutations can lead to the complete absence of a protein.

Third, changes to the promoter region of the gene can result in gene malfunction by interfering with transcription. In this situation, protein production is either inhibited or it occurs at an inappropriate time because of alterations somewhere in the regulatory region.

Fourth, mutations within introns that affect the specific nucleotide sequences that direct intron **splicing** may result in an mRNA that still contains an intron. When translated, this extra RNA will almost certainly be meaningless at the protein level, and its extra length will lead to a functionless protein. Any mutation that results in a lack of function for a particular gene is called a “null” mutation. Less-severe mutations are called “leaky” mutations because some normal function still “leaks through” into the phenotype.

Causes of Mutations

Most mutations occur spontaneously and have no known cause. The synthesis of DNA is a cooperative venture of many different interacting cellular processes, and occasionally mistakes occur that result in mutations. Like many chemical structures, the bases of DNA are able to exist in several conformations called isomers. The keto-form of a DNA base is the normal form that gives the molecule its standard base-pairing properties. However, the keto-form occasionally changes spontaneously to the enol-form, which has different base-pairing properties. For example, the keto form of **cytosine** pairs with **guanine** (its normal pairing partner), but the enol-form of cytosine pairs with **adenine**. During DNA replication, this adenine base will act as the template for **thymine** in the newly synthesized strand. Therefore, a CG base pair will have mutated to a TA base pair. If this change results in a functionally different amino acid, then a missense mutation may result. Another spontaneous event that can lead to mutation is the complete loss of a purine base (adenine or guanine) at some location in the DNA. The resulting gap can be filled by any base during subsequent replications.

Numerous studies have demonstrated that ionizing radiation, some chemicals, and certain viruses are capable of acting as **mutagens**—agents that can increase the rate at which mutations occur. Some mutagens have been implicated as a cause of **cancer**. For example, ultraviolet (UV) radiation from the sun is known to cause skin cancer, and cigarette smoke is a primary cause of lung cancer.