Population Genetics and Departures from Hardy-Weinberg Equilibrium

Hardy-Weinberg Equilibrium

A population is in **genetic equilibrium** when allele frequencies in the gene pool remain constant across generations. The Hardy-Weinberg tells us that when a population is in equilibrium, the frequencies of genotypes in the population come to an equilibrium that depends entirely on allele frequencies. Consider a trait determined by a single gene with two alleles. Given

- p, the frequency of a dominant allele *A* in the population, and
- q, the frequency of a recessive allele *a* in the population,

if the population is in Hardy-Weinberg equilibrium:

- the frequency of the homozygous dominant genotype (*AA*) = p^2,
- the frequency of the heterozygous genotype (*Aa*) = $2pq$, and
- the frequency of the homozygous recessive genotype (*aa*) = q^2,
- where $p^2 + 2pq + q^2 = 1$.

How then, can any population not be in Hardy-Weinberg equilibrium? A population will tent do depart from Hardy-Weinberg equilibrium if any of the conditions are NOT met:

- the population is very large
- individuals in the population mate randomly
- there is no migration into or out of the population
- natural selection does not act on any specific genotypes
- males and females have the same allele frequencies
- no mutations occur

Departures from Hardy-Weinberg Equilibrium

Determining the allele and genotype frequencies in real populations and investigation of the factors that have pushed these populations out of equilibrium is exciting work for population geneticists. With human populations it often requires investigation into the remote historical past and the migration patterns of the population to find events that can explain unusual genotype frequencies.

Let's consider three of these assumptions concerning Hardy-Weinberg equilibrium, natural selection, allele frequencies, and mating patterns. In each of these sections, we'll consider genes with two alleles, a dominant allele and a recessive allele.

• *Selection Pressure*

Different genotype classes can have different rates of survival and/or reproduction that result from their interaction with the environment – some genotypes are more "fit" than others. When there are such selective pressures that act on one or more genotypes, genotype frequencies will change. Perhaps the best examples are the many human diseases that result when deleterious recessive alleles are homozygous. In this case, we might expect that a significant portion of the homozygous recessives are not reproducing and the recessive alleles they carry are lost to the gene pool of the population. And so, you would expect that this selective pressure would significantly change the allele frequencies. It has been the hope of those who have advocated eugenics that by allowing *no* reproduction by individuals with certain "undesirable" traits, the trait (and the recessive allele) could be eradicated. As you will see, it is not so simple.

Since most copies of rare recessive alleles are found in the heterozygotes, not in the homozygous recessives, even when there is strong selection (fitness = 0) against individuals with the homozygous recessive phenotype, change in the frequency of the deleterious allele is very slow when/because the allele is at very low frequency. You could

say that "selection can't act on nothing!" It has been estimated that it would take 100 generations, or 2,500 years to reduce the frequency of a rare deleterious allele from 1/100 to 1/200 by the eugenic method!

Changes in the allele frequency will occur at higher rates when there is selection against the heterozygotes or even when the selection is against the homozygous recessive portion of the population, if this portion is not rare. In that case, selection effectively reduces the recessive allele frequency until it is "rare" and then further reduction is very very slow.

An interesting stable equilibrium can occur when there are selective pressures against both homozygous classes because of different kinds of interactions with the environment. The persistence of the deleterious recessive allele for sickle cell anemia is an example of such a stable polymorphism: those who are homozygous recessive suffer from sickle cell anemia and those who are homozygous dominant are highly susceptible to one form of malaria. The heterozygotes are more resistant to malaria and do not experience significant anemia. The greater fitness of the heterozygous class results in a stable equilibrium of both alleles even though each allele, when homozygous, has a lower fitness.

• ***Allele Frequencies – Sex-Linked Genes***

The Hardy-Weinberg relationship between allele frequencies and genotype frequencies applies to diploid genes, including autosomal genes in humans, but not to haploid genes, including sex-linked genes in males.

Consider the straightforward case of Y-linked genes with two alleles. Since these alleles are only found in the male population, and each male has one copy, either Y_A or Y_a, of the gene, the two genotype frequencies directly reveal the two allele frequencies; the frequency of the Y_A genotype is *p*, and the frequency of the genotype is *q*.

The situation for X-linked genes is not as immediately clear, since females are diploid while males are haploid. However, we can refer to the overall allele frequencies, *p* and *q*, across males and females and it can be shown that, when the other Hardy-Weinberg assumptions hold,

- for females, the Hardy-Weinberg principle applies to X-linked genes; and
- for males, the two hemizygous genotype frequencies, X_A abd X_a, are equal to the corresponding allele frequencies, p and q.

• ***Mating Patterns***

Hardy-Weinberg equilibrium assumes that mate selection is essentially random. There are a variety of ways in which mating patterns can depart from random.

• ***Self-fertilization*.** Some plants are capable of self-fertilization and it can be shown readily that pure self-fertilization disrupts the Hardy-Weinberg relationship between allele frequency and genotype frequency. Assume we start with a plant population which happens to be in Hardy-Weinberg equilibrium, with $p = q = 0.5$, as shown in the first column below:

Parental Frequencies		F1 Offspring Frequencies AA	Aa	aa
AA = 0.25	===>	0.25	0	0
Aa = 0.50	===>	0.125	0.25	0.125
aa = 0.25	===>	0	0	0.25
	Total:	0.375	0.25	0.375

When these plants self-fertilize, the 25% of the population that is homozygous dominant (*AA*) will reproduce itself, as will the 25% that is homozygous recessive (*aa*). However, when the 50% of the population that is heterozygous (Aa) self-fertilizes, only 50% the resulting offspring (25% of the entire F1 generation) is heterozygous, while the other half is homozygous. If follows that each time a generation reproduces through pure self-fertilization, the

remaining percentage of heterozygotes is cut in half, and eventually, heterozygotes will effectively disappear from the population. Note however, that the allele frequencies remain unchanged, in this case, $p = q = 0.5$.

• ***Assortative Mating*.** Mating patterns are assortative to the extent that individuals with the same phenotype mate with each other. With two alleles, simple dominance and assortative mating, homozygous dominant (AA) individuals and heterozygous (Aa) individuals, who share the same phenotype tend to interbreed, while homozygous recessive (aa) individuals tend to interbreed. If we again start with a population which happens to be in Hardy-Weinberg equilibrium, with $p = q = 0.5$, the table below shows the results of complete assortative mating. There will be four types of parental genotype pairings, with the frequencies shown below.

Parental Frequencies		F1 Offspring Frequencies AA	Aa	aa
AA x AA = 0.083	===>	0.083	0	0
Aa x AA = 0.333	===>	0.167	0.167	0
Aa x Aa = 0.333	===>	0.083	0.167	0.083
aa x aa = 0.250		0	0	0.25
	Total	0.333	0.333	0.333

As can be seen under F1 offspring frequencies to the right, assortative mating again decreases the heterozygote frequency, although not as much as self-fertilization. Under pure assortative mating, heterozygotes frequency will again dwindle away to essentially 0, although not as quickly as with self-fertilization. Note again, however, that the allele frequencies remain unchanged, in this case, $p = q = 0.5$.

• ***Inbreeding*.** Inbreeding refers to mating between relatives, i.e. between individuals who share relatively recent ancestors (as a rule of thumb, ancestors no more distant than great-great grandparents). Self-fertilization is the most extreme form of inbreeding, and like self-fertilization, inbreeding more results in a decreased heterozygote frequency in the population. In fact, the common measure of inbreeding in a population, *F*, called the *inbreeding coefficient*, compares the actual heterozygote frequency in a population to the expected frequency under Hardy-Weinberg equilibrium. *2pq*. If we let *f(Aa)* represent the actual heterozygote frequency:

$$F = (2pq - f(Aa)) / 2pq$$

As seen in this equation, F equals proportionate decrease in heterozygote frequency from the expected frequency (the expected frequency of heterozygotes, minus the actual frequency of heterozygotes, divided by the expected frequency). The larger the value of F, i.e., the greater the reduction in heterozygote frequency, the more inbreeding has been occurringin the population.

• **A Generalization: Mating patterns related to common genotypes lead to reduced heterozygote frequency.** By definition, self-fertilization and inbreeding both involve systematic mating based on common genotypes. Assortative mating involves systematic mating based on shared phenotypes, but of course this is closely correlated with shared genotypes. None of these forms of non-random mating affect *p* and *q*, the allele frequencies in the population. Non-random mating does not affect the overall allele frequencies that are transmitted from one generation to the next, but it does affect the distribution of alleles into genotypes. And non-random mating patterns related to common genotypes all have the same impact on genotype frequencies, of reducing the frequency of heterozygotes.