

Lecture 27

In this lecture we will consider how allele frequencies can change under the influence of mutation and selection.

The first consider the conversion of a wild type gene to an altered allele by mutation:

μ
A \rightarrow **a** μ =mutation rate (probability of a mutation/generation)

$$\Delta q_{\text{mut}} = \mu f(\mathbf{A}) = \mu p \approx \mu$$

Typical mutation rates vary from $\mu = 10^{-4} - 10^{-8}$

Thus, in the absence of any other effects, such as selection, for any given gene the frequency of mutant alleles will increase a little each generation because of new mutations

Consider the disease phenylketonuria (PKU), which is an autosomal recessive defect in the enzyme phenylalanine hydroxylase. The absence of the enzyme prevents phenylalanine from being metabolized causing unusually high levels of phenylalanine in the body leading to severe mental retardation.

Say, that for PKU, $\mu = 10^{-4}$. The frequency of PKU will then slowly increase each generation.

When the allele frequency gets high enough selection against homozygotes will counterbalance new mutations and q will stay constant. In order to treat selection quantitatively we need an additional concept.

S = selective disadvantage; and fitness = **1-S**

If a genotype has $S = 0.75$ then fitness = 0.25, meaning that individuals with this genotype will reproduce at a rate of only 25% relative to an average individual. Fitness can be thought of as a combination of survival and fertility.

Recall that for alleles in H-W equilibrium (random mating) the genotype frequencies will be:

$$f(A/A) = p^2, f(A/a) = 2pq, f(a/a) = q^2$$

Genotype	frequency	after selection	Δf frequency
A/A	p^2	p^2	0
A/a	$2pq$	$2pq$	0
a/a	q^2	$q^2(1 - S)$	$-Sq^2$

$$\Delta q_{sel} = -Sq^2$$

In the steady state: $\Delta q_{sel} + \Delta q_{mut} = 0$, $-Sq^2 + \mu = 0$, $\mu = Sq^2$

$$q = \sqrt{\mu/S}$$

For PKU, q is $10^{-2} S$ and during human evolution $S \approx 1$. Therefore, the estimated value of μ is about 10^{-4} . The actual mutation frequency is probably not this high - and the relatively high q for PKU is probably due to a founder effect in the European population or a balanced polymorphism (see below).

In modern times PKU can be treated by a low-phenylalanine diet so $S < 1$. So the frequency of PKU should start to rise at a rate $\Delta q_{mut} = 10^{-4}$.

Thus, q will only increase by a factor of 1% per generation and it will take a long time for this change in environment to have a significant effect on disease frequency.

Now let's determine the steady state allele frequency for a **dominant** disease with allele frequency $q = f(A)$. In contrast to the situation for recessive alleles, for dominant alleles selection will operate against heterozygotes.

Note that for a rare dominant trait almost all affected individuals are heterozygotes. $q = f(A/A) + 1/2 f(A/a) \approx 1/2 f(A/a)$

Genotype	frequency	after selection	Δ frequency
A/A	-	-	-
A/a	$2pq \approx 2q$	$(1 - S) 2q$	$-2Sq$
a/a	p^2	p^2	0

$$\begin{aligned}\Delta q_{sel} &= 1/2 [\Delta f(A/A)] = 1/2 (-2Sq) \\ &= -Sq\end{aligned}$$

(After selection, $2Sq$ heterozygotes are lost each generation but only 1/2 of their alleles are A. So the net reduction in $f(A)$ is $-Sq$.)

In the steady state: $\Delta q_{sel} + \Delta q_{mut} = 0$, $-Sq + \mu = 0$, $\mu = Sq$

$$q = \mu/S$$

$$\text{For } S = 1, q = \mu$$

In other words, for dominant mutations with fitness = 0, the only instances of the disease will be due to new mutations. This makes sense because mutant alleles cannot be passed from one generation to the next. In this case, the number of affected individuals will be 2μ .

When $S < 1$ the frequency can get quite high. A good example of this is Huntington's disease which has a late onset of degeneration of neuromuscular system at > 35 yrs. This disease is bad personally but doesn't decrease reproductive fitness much.

For the final example of a balance between mutation and selection, consider an **X-linked recessive** allele with frequency $q = f(a)$. For rare alleles the vast majority of affected individuals who are operated on by selection are males, and new mutations will increase the allele frequency $\Delta q_{mut} \approx \mu$

Genotype	frequency	after selection	Δ frequency
$X^A Y$	p	p	0
$X^a Y$	q	$(1 - S)q$	$-Sq$

Note that in a population of equal numbers of males and females, 1/3 of the X chromosomes will be in males.

