Lecture 28

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:

$$\mathbf{A} \xrightarrow{\mu} \mathbf{a}$$

μ =mutation rate (probability of a mutation/generation)

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

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 a recessive human disease that arises in a human population at mutation frequency $\mu = 10^{-6}$. Because the disease is recessive, there is no selection against the newly arising heterozygotes and the number of alleles will increase by a fraction $\mu = 10^{-6}$ 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:

$f(\mathbf{A/A}) = p^2$, $f(\mathbf{A/a}) = 2pq$, $f(\mathbf{a/a}) = q^2$

Genotype	frequency	after selection	Δ 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 a serious recessive disease S = 1 and thus during human evolution the allele frequency will reach a steady state $q = \sqrt{\mu} = 10^{-3}$. If one now imagines that in modern time a cure for the disease is found such that S < 1, the allele frequency will begin to rise. But the increase will be at rate $\mu = 10^{-6}$ which means that Δq will increase by a factor of about 10^{-3} per generation, and it will take a very long time to observe an apreciable effect on q.

Now let's determine the steady state allele frequency for a **dominant** disease with allele frequency $q = f(\mathbf{A})$. 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. $q = f(\mathbf{A/A}) + {}^1/_2 f(\mathbf{A/a}) \approx {}^1/_2 f(\mathbf{A/a})$

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

$$\Delta q_{sel} = {}^1/_2 [\Delta f(\mathbf{A/a})] = {}^1/_2 (-2Sq)$$
$$= -Sq$$

(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: $\Delta q_{sel} + \Delta q_{mut} = 0$, $-Sq + \mu = 0$, $\mu = Sq$

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

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 $q = f(\mathbf{a})$. 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.

Therefore,

$$\Delta q_{sel} = {}^1/_3\,[\Delta f(X^a\ y)] = {}^1/_3\,(-Sq)$$
$$= -Sq/3$$

In the steady state: $\Delta q_{sel} + \Delta q_{mut} = 0$, $-Sq/3 + \mu = 0$, $\mu = Sq/3$

$$q = 3\mu/S \qquad \text{For } S = 1,\ q = 3\mu$$

For X-linked recessive mutations with fitness = 0, exactly one third of the alleles in a population will be new mutations. This relationship has been demonstrated for the debilitating X-linked diseases hemophilia A and Duchenne muscular dystrophy.

Balanced Polymorphism

Now we will consider a situation in which an allele is deleterious in the homozygous state but is beneficial in the heterozygous state. The steady state value of q will be set by a balance between selection for the heterozygote and selection against the homozygote.

We will need a new parameter that represents the increased reproductive fitness of heterozygote over an average individual.
h = heterozygote advantage

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

$$\Delta q = \Delta f(\mathbf{a/a}) + {}^1/_2\, \Delta f(\mathbf{A/a}) = -Sq^2 + {}^1/_2(2hq)$$

$$= -Sq^2 + hq$$

Say $S = 1$, then $\Delta q = 0$ when $q^2 = hq$ i.e. $h = q$

The possibility of a subtle selection for (or against) the heterozygote for an allele that appears to be recessive means that in practice the estimates of μ from allele frequencies are quite unreliable.

For example, $q = 10^{-2}$. This could mean $\mu = 10^{-4}$ and $h = 0$ or $\mu < 10^{-4}$ and $h = 10^{-2}$. Since a 1% increase in heterozygote advantage would be extremely difficult to measure, we wouldn't be able to distinguish these possibilities.

The best understood case of balanced polymorphism is **sickle-cell anemia**

The allele of hemoglobin known as Hb^S is recessive for the disease but is dominant for malarial resistance. Hb^S is most prevalent in a number of different equatorial populations where malaria is common: sub-Saharan Africa, the Mediterranean, and Southeast Asia.

In parts of Africa the frequency of the disease can be as high as ~ 2.6 %, which means that in these populations $q = 0.16$.

During human history sickle cell disease would almost certainly be fatal thus $S \approx 1$ and therefore h must have been about 0.16. This indicates that during evolution the reproductive advantage for an Hb^S heterozygote is 16%.

Many of the most prevalent genetic diseases are suspected to be at a relatively high frequency because of balanced polymorphism.

Cystic Fibrosis: Autosomal recessive mutations in CFTR (Cystic fibrosis transmembrane conductance regulator). Mutants disrupt Cl^- transport leading to disturbed osmotic balance across in epithelial cell layers of the lungs and intestine.

Incidence in European populations ≈ 1/2000. Thus, $q = 0.022$

This high frequency is probably not due to either high mutation frequency or founder effect (many different alleles have been found although 70% are ΔF508).

The hypothesis is that heterozygotes may be more resistant to bacterial infections that cause diarrhea such as typhoid or cholera and that this selection was imposed in densely populated European cities.