Lecture 13 Maintenance of genetic variability
Reading 765-768

- Darwin based his theory of natural selection on the observation that all characteristics in all species exhibit variability that is inherited. A major problem in genetics is explaining what maintains observed levels of heritable variability. Ultimately, mutation is the source of all new alleles. It is less clear what the role of natural selection is.
- If an allele is advantageous allele it will eventually be fixed because of selection. The species will be better adapted to its environment, but there is a loss in genetic variability.
- There are 3 major explanations for the maintenance of genetic polymorphism and phenotypic variability. They all are true for some loci, but it is not yet possible to say which is the most important.
- On explanation is **balancing selection**, i. e. selection which is some way prevents the loss of genetic variability.
- In a very few cases, individuals with a particular heterozygous genotype have a higher fitness. S**ickle-cell anemia** in malarial regions is a well-documented example of **heterozygous advantage** of this type. In this case the mechanism and the ecological conditions are well understood. However, there are few other examples of this type and most of them are associated with malaria, so it is difficult to know whether heterozygous advantage is important for many genes.
- There are two other cases of balancing selection that maintain extensive polymorphism but only at a few loci.
- Many plants have loci that prevent self fertilization. Such loci are called **self-incompatibility** (SI) loci. One type of SI locus is illustrated in Fig. 3.8 on p. 52). Genetic self-incompatibility ensures that rare alleles are at an advantage and common alleles are at a disadvantage. The result is that SI loci have many alleles, usually 30-50, all in low frequency.
- All jawed vertebrates have loci called **major histocompatibility (MHC) loci** that are an important part of the immune system. Their gene products are involved in presenting foreign antigens to T-cells. In humans the MHC loci are on chromosome 6 and are called **Human leukocyte antigen (HLA)** loci. There are two major groups of loci, class I (HLA-A, HLA-B and HLA-C) and class II (HLA-DR, HLA-DQ, and HLA-DP, plus others). They are the most polymorphic loci know, HLA-B has at least 921 alleles, DR has at least 577 alleles. HLA alleles are associated with higher risk of genetic diseases, including autoimmune diseases such as multiple sclerosis and lupus, and with the course of infectious diseases. A specific haplotype, B*35-Cw*04, is associated with rapid progress of HIV in Caucasians. Other HLA alleles are associated with increased risk of leprosy and tuberculosis. The high level of polymorphism at MHC loci is thought to be caused by balancing selection. Although the idea that greater genetic diversity in the components of the immune system makes intuitive sense, the exact mechanism of balancing selection is unknown.
- Mutation opposed by selection against deleterious alleles **(mutation-selection balance)** can also maintain genetic variation. Although mutation rates are small

selection may be weak. Rare genetic diseases in humans are almost certainly maintained by mutation-selection balance. Mutation is much more effective in maintaining recessive alleles in a population because only homozygotes suffer the fitness loss. Although mutation-selection balance accounts for the presences of deleterious alleles, including alleles that cause genetic diseases, it is not clear whether most phenotypic variation is accounted for by deleterious alleles.

- A third possibility is that some of the genetic variability we see is neutral, meaning that different genotypes have roughly the fitness on average. In that case, variation in maintained by a balance between mutation and **genetic drift**.

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Additional problems

35.1 Self-incompatibility systems in plants, of the kind described in Figure 3.8 in the text, result in fertility selection similar to heterozygous advantage. Why does a new S allele created by mutation have an advantage over S alleles already in the population?

Answer: A new S allele has an immediate advantage because pollen carrying that allele will be able to fertilize all the other plants in the population. In contrast, pollen bearing an S allele already in the population cannot fertilize those plants that are heterozygous for that allele.

35.2 Selection on genotypes that cause the early death of an infant is not as strong as might be supposed, because reproductive compensation occurs. A family in which an infant dies often decides to have an additional child or have another child sooner than it would have otherwise. The effect of reproductive compensation can be approximated by assuming that the viability of the disease-associated genotype is not zero but some larger number, say 0.5. The major allele causing cystic fibrosis in Europeans is ΔF508, a 3-base deletion that results in the loss of the 508^{th} amino acid of the CFTR protein.

a. If there is reproductive compensation, what would the equilibrium frequency of ΔF508 be if it were recessive in its effect and at equilibrium under a mutation-selection balance with a mutation rate 10^{-6} per generation?
b. What would the relative fitness of normal homozygotes have to be if the frequency is 0.02 under heterozygous advantage? [Hint: assume the heterozygous fitness is 1 and the mutant homozygote fitness is 0.5.]

Answer
a. Because ΔF508 is recessive, the frequency under mutation-selection balance is $q=\sqrt{(\mu/s)}$. Because of reproductive compensation, s=0.5, so $q=\sqrt{(10^{-6}/0.5)} = 1.41x10^{-3}=0.00141$. This frequency is much smaller than the observed frequency of ΔF508 in Europeans, 0.02, a result that causes many people to assume that there is or was heterozygous advantage.

b. The equilibrium frequency is p=t/(s+t), when the relative fitnesses are written 1–t, 1, 1–s. You are told that s=0.5 and p=0.02, and you have to solve for t: t≈0.01, which means that carriers of ΔF508 would have to have a 1% better chance of surviving than individuals homozygous for the normal allele of CFTR. At present, there is no agreement about why ΔF508 is so common in European populations. Many people think that carriers are or were somewhat protected against an infectious disease, possibly typhus.

Carrington M et al. (1999) HLA and HIV-1: heterozygote advantage and B*35-Cw*04 disadvantage. Science 283:1748-1752.
http://www.sciencemag.org/cgi/content/abstract/283/5408/1748