4 Mutation and selection


Mutation

- A mutation is the result of an error in DNA replication
  - A change in a single nucleotide is called a point mutation. In higher plants and animals, the probability of a point mutation (i.e., the mutation rate) is very low, roughly 2/1,000,000,000 or 2x10^{-9} per nucleotide per generation. Rates of point mutations are higher in bacteria and higher still in viruses.
  - Other types of mutations occur: small or large pieces of chromosomes can be deleted or duplicated. A duplications can create a second copy of a gene.
  - Whole chromosomes can be duplicated. In humans, individuals with 3 copies of chromosome 21 (trisomy 21) have Down’s syndrome. The risk of trisomy 21 in the US population is between 1/650 and 1/1000; the risk increases with maternal age\(^1\).
  - Whole genomes can be duplicated. If there is no reduction division during meiosis, diploid gametes are produced. A diploid gamete combined with a haploid gamete creates a triploid zygote. Bananas and many other domesticated plants are triploid.

Forces causing gene frequency change

- Random mating does not cause allele frequencies to change, but other forces do. Mutation creates new alleles but mutation rates are so that mutation has little effect on the frequencies of alleles already present in a population. Alleles frequencies change because of the combined effects of natural selection, genetic drift, gene flow and recombination.

Natural selection

- Fitness
  - If individuals with different genotypes differ in their chances of survival and reproduction, then there are differences in fitness that cause allele frequencies to change.
  - Average fitnesses of different genotypes may depend on the environment. For example, individuals with defective alleles of the PAH gene who eat a normal diet die at an early age because of the accumulation of phenylalanine. They suffer from phenylketonuria (PKU). If phenylalanine is removed from the diet, there is almost no reduction in survival rate.

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\(^1\) Information about trisomy 21 and other inherited diseases and conditions in humans can be found from OMIM (Online Mendelian Inheritance in Man), http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM.
Lecture 4

- **Directional selection**
  - Directional selection occurs when one allele is always favored. For example, if there are two alleles $A$ and $a$, and $AA$ individuals have a higher fitness than $Aa$ individuals who have a higher fitness than $aa$ individuals, then $A$ is the advantageous allele and $a$ is the deleterious allele.
  - If a population initially contains only $aa$ individuals, and an advantageous allele $A$ is created by mutation, then the frequency of $A$ will increase every generation because of natural selection. Eventually $A$ will be substituted for $a$.
  - Population geneticists showed early in the 1900s that natural selection can cause the substitution of an advantageous allele quickly even if fitness differences are small. They concluded that even very weak natural selection acting of Mendelian alleles could cause changes in allele frequencies in a relatively short time, meaning hundreds of thousands of generations. Although that is a long time from a human perspective, it is a short time from a geological perspective.
  - An example of directional selection in humans is on alleles conferring lactose tolerance in adults. Most adults of European ancestry and some adults of east African ancestry can digest lactose because the gene coding for the enzyme lactase-phlorizin hydrolase (LPH) is expressed in adults. One mutation that enhances production of LPH is responsible in Europeans and three different mutations are responsible in east Africans. All four mutations have reached high frequency in these populations because of directional selection in roughly the last 7000 years.²
  - Past episodes of directional selection in humans may contribute to current health problems. Native Americans are at a relatively high risk for type II diabetes (non-insulin-dependent diabetes) as adults. One explanation for this pattern is the “thrifty gene” hypothesis: ancestors of Native Americans experienced repeated famines that selected for efficient metabolism which leads to type II diabetes under modern conditions. Some kinds of hypertension (high blood pressure) are caused by a tendency to retain too much salt, which possibly resulted from selection for salt retention during periods of low salt abundance. Although the thrifty gene and salt retention theories are plausible, they are not proved.

- **Purifying selection**
  - If $A$ is an advantageous allele and the population contains only $AA$ individuals, and then a deleterious allele $a$ is created by mutation, natural selection will tend to eliminate it. This is purifying selection.
  - Although mutation rates are very low, there are so many genes (more than 30,000 in humans) that deleterious alleles are created by mutation every generation.
  - A balance between mutation creating deleterious mutations and purifying selection will be reached.
  - Many genetic diseases in humans, including PKU, have frequencies determined by the balance reached between mutation and purifying selection.

- **Balancing selection**
  - If heterozygous individuals have a higher fitness than either homozygote, selection will maintain both alleles in the population. The high frequency of the $S$

² See http://www.nature.com/ng/journal/v39/n1/full/ng1946.html for details.
allele of the β-globin gene in populations with a high incidence of malaria. AA individuals are more likely to die of malaria as children than are AS individuals. As a consequence, S is maintained in frequencies as high as 12% in malarial regions even though SS individuals suffer from a severe disease, sickle cell anemia which results in early death in many cases.

- In non-malarial regions, S is deleterious and A is advantageous. S alleles are very rare in non-malarial regions except as the result of immigration from malarial regions.
- Malaria has been a particularly important selective force in human populations. In addition to the S allele of β-globin, alleles of the α-globin gene which cause thalassemia provide partial protection against malaria. A defective allele (called A–) of the G6PD gene has a frequency of between 4 and 20% in malarial regions. Individuals homozygous for A– suffer from favism, a type of anemia induced when fava beans are eaten.
- Do not confuse balancing selection with mutation-selection balance.

- Rapid evolution occurs in response to changes imposed by humans.
- Resistance to antibiotics, insecticides, herbicides, and poisons intended to control parasites, pests and pathogens, evolves quickly in virtually all species. Rapid evolution of resistance tells us that resistance alleles are already present.

Sample questions (correct answer is underlined).

- Assume you determine the genotypes of 1,000 adults at the locus that codes for β-globin? In which one of the following data sets is there evidence for selection in favor of heterozygous individuals?
  a. AA 200, AS 600, SS 200.
  b. AA 640, AS 320, SS 40.
  c. AA 600, AS 300, SS 100.
  d. AA 1000, AS 0, SS 0.
  e. None of the above.

- Assume you are studying the fitnesses of individuals with different genotypes at the β-globin locus in a population. The following are lists of the fractions of newborn individuals with each genotype that survive to adulthood. Which one of the following indicates that there is directional selection in favor of A in this population?
  a. AA 0.9, AS 0.95, SS 0.2.
  b. AA 0.9, AS 0.9, SS 0.9.
  c. AA 0.9, AS 0.85, SS 0.2.
  d. AA 0.9, AS 0.85, SS 0.9.
  e. AA 0.9, AS 0.95, SS 0.95.

- Which pair of words best fills the blanks in the following sentence? In areas with a high incidence of malaria, the S allele of the β-globin gene is maintained in high frequency by ________ selection; in regions where malaria is not present, S will be eliminated by ________ selection.
  a. adaptive, maladaptive.
  b. directional, purifying.
c. purifying, directional.

d. balancing, purifying.

e. directional, balancing.

Which one of the following is **not** a mutation?

a. A change in a single nucleotide.

b. The loss of a chromosome.

c. The duplication of a chromosome.

d. A change in allele frequency.

e. The duplication of a gene.