Lecture 5
Mutation and Genetic Variation

I. Review of DNA structure and function—you should already know this.
   A. Some definitions based on understanding molecular structure of DNA:
      1. **gene** = length of DNA coding for functional RNA product
         a. note definition includes both DNA coding for proteins (mRNA is functional RNA product) and for rRNAs, tRNAs
      2. **locus** (pl. loci) = position of gene on chromosome; often used almost synonymously with gene
      3. **alleles** = versions of a gene that differ in their base sequences.
   2. Coding region of the gene includes stretches of DNA that are transcribed but not translated
      a. pieces that are transcribed and translated = **exons** (because they’re **expressed**)
      b. pieces that are transcribed but not translated = **introns** (because they intervene between exons)
   3. After translation, but before mRNA leaves nucleus, system of enzymes carries out mRNA processing = process of removing introns and splicing exons back together

II. Point mutations create new alleles.
   **Mutation** – An error in the replication of a nucleotide sequence, or any other alteration of the genome that is not manifested as reciprocal recombination.
   **Point mutation** – a single base substitution in DNA. (base mutation).

A. Causes of point mutations.
   1. Two causes, both the result of reactions catalyzed by DNA polymerase:
      a. Uncorrected replication errors
      b. Errors in repair of damaged sites
   2. Point mutations can be classified by the type of change to the DNA sequence
      a. **transitions** = replace purine with purine (A for G), pyrimidine with pyrimidine (T for C).
      b. **transversions** = replace purine with pyrimidine (T for G) and vice-versa
      c. “reading frame” is left intact (beginning and ending point of each codon)
   3. Another point mutation - **frameshift mutation**. All codons after the point of mutation are affected:
      a. additions = extra base inserted
      b. deletions = base is “missed”

B. Fitness effects of point mutations
   1. Overall, the effect of a point mutation can range from highly beneficial to very harmful
      a. **Replacement substitution** (nonsynonymous, or missense) – a base substitution that causes a change in the amino acid.
      b. **Silent site substitution** (synonymous) – a base substitution that does not cause a change in the amino acid due to codon redundancy.
   2. In general, most replacement mutations will have relatively little +/- effect on fitness.
3. However, most frameshift mutations will have large effects – usually negative.
   a. It is fairly common for frameshift to result in premature stop codon (nonsense mutation).

4. Fitness effects of a mutation will also depend on environmental conditions. e.g.: sickle-cell anemia.

5. Extreme end of mutations are homeotic mutations- these mutations redirect the development of one part of the body into another.
   a. Mutations that occur in the genes that determine the basic “body plan” of an organism.
   b. In Drosophila, legs might develop in place of antennae, or wings in the place of halteres (a structure that was derived from the second pair of wings in insects).

C. The Limits of Mutations.
   1. Even the most drastic mutation can only alter one or more pre-existing traits.
   2. Mutations with phenotypic effects alter developmental processes, but they cannot alter developmental foundations that do not exist.

D. Rates of point mutations
   1. Mutation rates based almost exclusively on rare autosomal dominant or X-linked recessive traits. It is virtually impossible to measure autosomal recessive traits accurately.
   2. On your own, read about use of loss-of-function mutations to calculate mutation rates and why rates tend to be underestimated
   3. Mutation rates are generally very low.
      c. An average per-locus mutation rate of $10^{-5}$ (one in 100,000 gametes) is so low that the rate of change in the frequency of an allele, due to mutation alone, is very low.
   4. When whole genome is taken into account (i.e., 30-35,000 genes in humans, 10,000 in Drosophila), with an average mutation rate of $10^{-5}$-$10^{-6}$, then 1 in 3 gametes (or 3 %of gametes) would carry a phenotypically detectable mutation somewhere in its genome.

E. Variation in mutation rates.
   **Germinal mutations** occur in germ cells and can be passed on to future generations.
   **Somatic mutations** occur in somatic cells and cannot be transmitted to offspring.
   1. Mutation rates generally greater in plants
      a. mutation rate correlated with generation time: because of the way plants generate germ cell tissues –they come from somatic tissue, which will differentiate into germ cell tissue.
      d. plants with long generation times accumulate more mutations in future germ cell tissues than do plants with short generation times.
   2. Animal germline cells in undergo far few divisions, so fewer opportunities for mutation.
   3. Rates also variable among individuals because of genetic variation in enzymes used for “proofreading” and repair of DNA
   4. Rates vary among genes within individuals; this is also poorly understood.
      a. mutation rate in coding regions of genes is less than non-coding regions.
      b. Repair systems apparently work on transcriptionally active genes only.
   5. Mutation rates also vary among types of cells, or organisms.
      a. Rates are lower in eukaryotes than prokaryotes.
III. Origins of new genes

A. Alterations of the Karyotype.
   1. **Karyotype** is the description of its complement of chromosomes: their number, size, shape, and internal arrangement.
   2. **Aneuploid** - “unbalanced” chromosome complement. Caused by the loss of a whole chromosome, or a major part of a chromosome, usually reduces the viability of a gamete.
   3. Alterations of the karyotype fall into two major categories:
      a. **Rearrangements** of one or more chromosomes. These are caused by breaks in the chromosome, followed by rejoining of the pieces in new configurations.
      b. **Polyploidy** - changes in the number of whole sets of chromosomes.

B. Rearrangements
   1. Some rearrangements change may affect the proportion of viable gametes.
   2. Most chromosome rearrangements seem not to have direct effects on morphological or other phenotypic features.
      a. But, alteration of gene order may bring certain genes under the influence of the control regions (e.g. promoters) of other genes, and so alter their expression.
      b. Such **position effects** have been documented in the lab, but it is unclear that they have contributed to evolutionary change under natural conditions.
   3. Chromosome rearrangements include:
      a. **Deletions** or deficiencies
      b. **Duplications**
      c. **Inversions**
      d. Translocations
      e. Fissions and fusions

C. Gene duplication
   1. **Gene duplications** are either short or long segments of extra chromosome material originating from duplicated sequences within a genome.
   2. This occurs during crossing over, but what happens is **unequal cross-over**.
      a. **Deletion** of a substantial amount of genetic material results in inviable gametes or zygotes.
      b. **Duplication** of genetic material on the other chromosome may be advantageous. The duplicate material is “free” to mutate without fitness consequences.
   3. **Gene family** - genes that have similar DNA sequences, but differ to some degree in sequence and often in function.
   4. The globin gene family = two clusters of loci coding for component subunits of hemoglobin

D. **Inversions** – reversal in chromosomal gene order.
   1. Individual organisms may be homozygous or heterozygous for a rearranged chromosome.
      a. **Homokaryotype** – both chromosomes are affected.
      b. **Heterokaryotype** – only one chromosome is affected.
   2. Inversions affect the degree of linkage among alleles.
      a. **linkage** = tendency of alleles to be inherited together
   4. Inversions generally lower the recombination frequency within the inverted sequence,
a. As a result, the genes in the loop tend to remain together as a nonrecombinant block, called a *supergene* by some workers.

5. In inversion heterokaryotypes,
   a. Fertility may be reduced because many gametes are inviable because the chromosome lacks a centromere and,
   b. Other chromosomes are missing genetic information, and are also inviable.
   c. Unusual to find two or more inversions in a polymorphic state within a population because of the reduced fertility of heterokaryotypes: one of the arrangements is rapidly eliminated from the population by natural selection.

E. Other mechanisms for creating new genes.
1. **Overprinting** – point mutations that produce a new start codon and a new reading frame for translation.
2. One of the best documented examples of how new genes can originate concerns the evolution of the gene that codes for the enzyme alcohol dehydrogenase (*Adh*). = enzyme that breaks down alcohol (found in rotting fruit).

F. Changes in the number of chromosomes.
   **Anueuploid variation** – changes in the number of single chromosomes within a set.
   **Euploid variation** – Change in the number of entire sets of chromosomes - **polyploidy**.
   **Autopolyploidy** - the appearance of extra sets of chromosomes within a species itself.
   **Allopolyplody**- polyploids that originate from crossing between different species.

1. Polyploidy is common among plants.
   a. Majority of polyploidy plants are alloployploids (from closely related species).
2. Polyploidy is much rarer in animals than in plants, because animals show much greater developmental sensitivity to even a small change in chromosome number.
   a. This extends to chromosomal sex-determining mechanisms, so that animal polyploids face difficulties in maintaining the same proportions of X and Y chromosomes present in normal diploids.
3. Polyploidy probably has some advantages in both plants and animals.
   a. Extra chromosomes may act as multiple buffers in various organismic processes.
   b. Additional chromosomes may provide the chance to evolve new functions.
   c. Duplication of genome offers same possibilities for mutations to produce novel traits as does gene duplication (it’s just on a larger scale) Rate of
9. Consequences – polyploid offspring may be reproductively isolated from parents (unable to be reproduce with normal 1n gamete from parent), resulting in new species.

IV. Genetic Variation in Natural Populations.
   A. Source of Genetic Variation in Natural Populations.
   1. **Polymorphism**- the presence of two or more genetic or phenotypic variants in a population. The rarest type is usually of a frequency greater than 1% and is not maintained by mutation alone
   2. Debate on whether genetic variants become fixed in the genome due to genetic drift.
a. According to the **neutral theory**, most of alleles at most polymorphic loci are functionally and selectively equivalent. Genetic diversity is maintained because it is not eliminated by selection (and are neutral in their effect).

b. According to the **balance, or selectionist theory**, genetic diversity is maintained by natural selection:
   - In favor of rare individuals
   - In favor of heterozygotes
   - In favor of different alleles at different times and places

   a. a. Alcohol dehydrogenase locus in Drosophila in Australia.

B. Quantifying genetic variation in natural populations.
   Three measures of genetic variation are commonly important:
   1. **Allele frequency**: what proportion of the alleles in a population are of a specific type?
   2. **Percent polymorphism** = % of loci in the population that have multiple alleles (note that this measures variation within the population as a whole)
      a. Let A = allele #1 for gene A; a = allele #2 for gene A, etc.
      b. Assume sample population of the following genotypes:
         i. AaBbCCDD
         ii. AABBCCDD
         iii. AAbbCCDD
         iv. aabbCCDD
      c. Calculate % polymorphism:
         i. loci total in the population (A, B, C, and D)
         ii. 2 loci are polymorphic (A and B)
         iii. 2/4 = 50% polymorphism
   3. **Mean heterozygosity** = % of heterozygous loci in the average individual (so this measures variation across loci within an individual)
      a. Use same sample population as above
      b. Calculate % heterozygosity for each individual:
         i. AaBbCCDD: 2 heterozygous loci/4 loci total = 50% hetero
         ii. AABBCCDD: 0 heterozygous loci = 0%
         iii. AAbbCCDD: 0 heterozygous loci = 0%
         iv. aabbCCDD: 0 heterozygous loci = 0%
      c. Average individual scores: 50%/4 individuals = 12.5%
   4. How much genetic variation do typical populations have? Tremendous variations among populations, but general findings are that:
      a. Based on studies to date, natural population has between 33 and 50% polymorphism (between 1/3 and ½ of loci have more than one allele)
      b. Mean heterozygosity ranges from 4 to 15% (average individual is heterozygous at 4 - 15% of loci)