## LECTURE 8: CHROMOSOMAL REARRANGEMENTS I
**Reading for this and next lecture:** Ch. 14, p. 489-515; Fig. 7.9 (p 215) & associated text; optional reading in the Drosophila portrait (skim section D.3)
**Problems for this and next lecture:** Ch. 14, solved probs I, II; also 6, 8, 11-14, 17, 20, 21, 24
**Announcements**:
*Are you doing the problems? There is no "practice" midterm for this class, and doing the problems is by far the best way to study for the class.
*Due to an unavoidable conflict, I will not hold office hours next week. Instead I will add extra office hours the following Friday, 10/3, from 10-noon. That same week, I will also hold my regular office hours on Thursday, Oct 2 from 1:30-3:30. The GSIs and I plan to cover Friday and half the day on Monday with office hours – we feel that this will be much more helpful to you than a review session.
*Next week, beginning Septmeber 24th, Section 114 (Wed 2-3 pm) moves from 2032 VLSB to 2038 VLSB


So far, we've concentrated mainly on phenotypic changes caused by mutations in single genes. Today and next time, we'll talk about chromosomal rearrangements - reorganizations of chromosome structure that can affect expression of more than one gene and the pattern of gene transmission. Your book describes four types of rearrangements: Deletions, Duplications, Inversions, and Translocations.

### How do mutations arise?
Mutations can arise spontaneously at a very low frequency. The average spontaneous mutation rate is 2-12 x $10^{-6}$ mutations/gene/generation, which means that any given gene mutates to a recessive allele every 2-12 per 1 million gametes. If we assume that there are 30,000 human genes, this means that every 4-20 human gametes will have a mutation affecting phenotype. The spontaneous mutation rate is affected by two mechanisms. First, mutations can arise by errors in DNA replication. It is important to note that the fidelity of DNA replication is amazing, and most errors are corrected by DNA repair systems. Second, mutations can arise from environmental damage. Chemicals, transposable elements, and radiation can cause DNA damage, and in fact, geneticists use these to induce mutations. High energy radiation (ionizing radiation, e.g. X-rays) at low doses induces point mutations, but at high doses, causes double stranded breaks in DNA. Sealing these breaks can cause a variety of mutations -- ionizing radiation is the leading cause of gross chromosomal mutations in humans. UV radiation can covalently link adjacent thymine bases, causing the formation of thymine dimers. Transposable elements, mobile pieces of DNA that can hop around ("transpose") through the genome, also cause mutations.

### Types of mutations
Most mutations fall into 3 classes: (1) point mutations, (2) rearrangements, and (3) transposable element-induced mutations. Point mutations change one base pair and usually alter the function of only one gene. Chromosomal rearrangements, the topic of the next two lectures, change chromosomal structure and can alter the function of one or more genes and can change the pattern of gene transmission. Transposable elements can insert into genes, altering their function and can cause chromosomal rearrangements. Today and next time, we will talk about four types of chromosomal rearrangements: deficiencies, duplications, inversions, and translocations. Each type of rearrangement has distinct cytological and genetic consequences.

**Deletion (Deficiency):** A rearrangement that removes a segment of DNA. *Df* or *Del* is the symbol used. Deletions can be located within a chromosome (interstitial) or can remove the end of a chromosome (terminal).

Deletions can be small (intragenic), affecting only one gene, or can span multiple genes (multigenic). Deletions can arise from DNA damage (X-rays or chemical agents that break chromosomes), or from mistakes during recombination or replication.

If the deleted region does not contain any genes essential for survival, an individual homozygous for a deletion (Del/Del) will live. An example is the original *white* allele in Drosophila which is a small deletion affecting only the *white* gene. However, large deletions that span multiple genes usually result in homozygous lethality because they remove essential genes. What about individuals heterozygous for a normal chromosome and a deficiency chromosome (Del/+)? In some instances, heterozygotes are viable and fertile. There are at least two reasons why heterozygosity for a deletion might be detrimental. (1) Gene dosage problems: a deletion heterozygote will have only half the normal dose of each gene that is missing in the deletion. In general, humans cannot survive (even as heterozygotes) with deletions that remove more than ~3% of the genome. An example of a syndrome caused by a heterozygous deletion is "cri du chat" syndrome, which results from a deletion of all or part of the short arm of Chromosome 5. The diagnostic phenotypic feature of the syndrome is that the cry of an affected infant sounds like a high-pitched cat cry, as well as many other features. Although individuals usually survive, they often don't live past childhood, and those that do are usually profoundly retarded. (2) Somatic mutation of the remaining normal copy of an essential gene may lead to defects (often called "pseudodominance"). Individuals with retinoblastoma (malignant eye cancer) are often heterozygous for deletions on Chromosome 13 in normal tissue; the disease results when a somatic mutation in the remaining copy of the RB tumor suppressor gene occurs in retinal cells.

ABCDEF - cen - G   normal chromosome
ABF - cen - G       deficiency chromosome (lacks CDE)

When homologous chromosomes pair during meiosis in a deletion heterozygote, one can observe a deletion loop representing the unpaired region of the normal chromosome that corresponds to the area deleted from the mutated homologous chromosome. You can see that recombination cannot occur in this region, thus the genes within the deletion loop cannot be separated by recombination and will always be inherited as a unit. This distorts map distances! The distance between C, D, and E will be zero, and the distance between B and F will be shorter than expected (fewer crossovers occur in the now "shorter" region).

Deletion heterozygotes can "uncover" mutations in the non-deleted chromosome. Think of the deletion chromosome as hemizygous for the genes in the deleted interval - we can use the deletion chromosome in complementation tests, screens for new alleles, or to do fine scale mapping (see Fig. 14.8).

Thus, the cytological and genetic consequences of deletions are (1) formation of deletion loops, (2) recessive lethality (often), (3) lack of reversion (deletion chromosomes never revert to normal), (4) reduced RF in heterozygotes (recombination frequency between genes flanking the deficiency is lower than in control crosses), and (5) pseudodominance (sometimes a deficiency will unmask recessive alleles on the non-deleted chromosome).

Interestingly, deletions show different transmission in plants than in animals. A male animal heterozygous for a deletions produces equal numbers of sperm carrying one of the two chromosomes (the deleted vs. non-deleted chromosome). In contrast, the pollen produced by a male deletion heterozygote plant is either functional (carrying the non-deleted chromosome) or nonfunctional (aborted, carrying the deleted chromosome). Pollen, at least in non-polyploid plants, seems sensitive to changes in the amount of chromosomal material -- this might act to weed out deletions.

**Duplication**: A rearrangement that results in an increase in copy number of a particular chromosomal region. Symbol used is *Dp*.

In **tandem** duplications, the duplicated regions lie right next to one another, either in the same order or in reverse order. In **non-tandem** duplications, the repeated regions lie far apart on the same chromosome or on different chromosomes. Duplications can occur due to unequal crossing-over, chromosome breaks and faulty repair, or replication errors.

The dominant *Bar* mutation (we talked about this mutation earlier) is a tandem duplication of the 16A region of the Drosophila X chromosome. One model for how tandem duplications like *Bar* arise is by an unequal crossing-over during meiosis that lead to a chromosome with the *Bar* tandem duplication and a chromosome deleted for this region. In support of this idea, unequal pairing and crossing-over during meiosis in females homozygous for the *Bar* tandem duplication occasionally leads to production of chromosomes bearing three copies of the region (which causes more extreme double-bar eye phenotype) and chromosomes bearing one copy (conferring normal eyes). See Figure 14.13. Another example in humans is red-green colorblindness (Fig. 7.29d) – in this example, unequal crossing over between the closely related red and green photoreceptor genes can cause different combinations of the genes on a chromosome or even hybrid receptors!

ABCDE - cen - FGH      normal chromosome
ABCBCDE - cen - FGH   duplicated chromosome

When homologous chromosomes pair during meiosis in a duplication heterozygote, one can observe a duplication loop representing the unpaired duplicated region of the *Dp* chromosome. This contrasts to the pairing situation in a deletion heterozygote, where the looped out DNA is that of the normal chromosome.

You might imagine that a duplication would be less likely to affect phenotype than a deletion of comparable size, since the duplicated genes are still present. This is true. However, duplications in heterozygotes can have phenotypic consequences if gene copy number is important (three copies of each gene in the duplicated region are now expressed!), or if genes in the duplicated

segment are now put into a new chromosomal environment that alters their expression level or pattern (position effect).

Duplications have been important in the evolution of genomes, because extra gene copies can drift and assume new functions. Your book discusses the duplication events that led to the evolution of the color receptor gene (Chapter 7) and hemoglobin gene (Chapter 9) families.

We will cover inversions and translocations, next time.