LECTURE 9: CHROMOSOMAL REARRANGEMENTS II

Reading for this and last 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 last lecture: Ch. 14, solved probs I, II; also 6, 8, 11-14, 17, 20, 21, 24

Announcements:

*Are you doing the problems? Doing the problems is by far the best way to study for the class.

*No office hours this week. Next week, office hours are Thursday 10/2 1:30-3:30 and Friday 10/3 from 10-noon.

*This week, beginning September 24th, Section 114 (Wed 2-3 pm) moves from 2032 VLSB to 2038 VLSB

Today we'll continue talking about rearrangements, focusing on inversions and translocations.

Inversion: A rearrangement in which a chromosomal segment is rotated 180 degrees. The symbol used is *In*. Inversions in which the rotated segment includes the centromere are called pericentric inversions; those in which the rotated segment is located completely on one chromosomal arm and do not include the centromere are called paracentric inversions. Inversions can occur when two double-strand breaks release a chromosomal region that inverts before religating to flanking DNA, or by intrachromosomal recombination.

Pericentric (includes centromere; "peri" means "around, about")
ABC - cen - DEFGH
A**D - cen - CB**EFGH

Paracentric (does not include centromere; "para" means "beside, beyond")
cen - A**BCD**EFGH
cen - A**DCB**EFGH

Even though gene order is changed in an inversion, many inversions do not cause abnormal phenotypes. Many inversions can be made homozgous, and inversions can be detected in haploid organisms. However, if the breakpoint of an inversion is within an essential gene, individuals homozygous for the inversion will not survive. Unusual phenotypes can also be observed if the inversion places a gene or group of genes in a new regulatory environment.
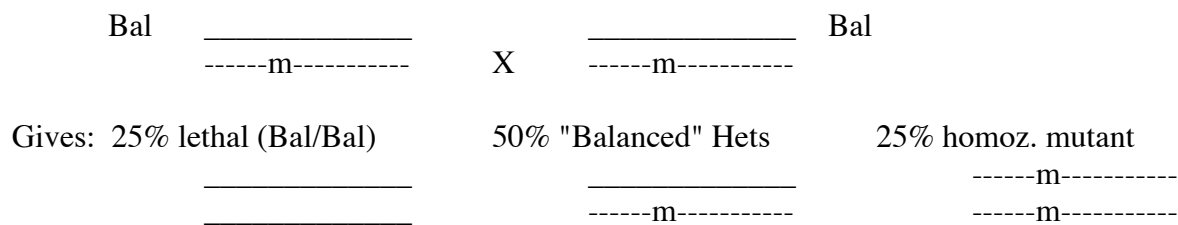
In inversion heterozygotes, the observed number of recombinant progeny is reduced. Why? During meiosis, the homologous chromosomes in inversion heterozygotes form an inversion loop to maximize pairing. Recombination within the inversion loop leads to abnormal chromatids (whether the inversion is pericentric or paracentric). Thus, even though crossovers occur, the abnormal recombinant gametes can rarely give rise to viable progeny upon fertilization. We see a preponderance of nonrecombinant progeny.

Let's look in in more detail at crossovers in the two inversion types. In pericentric inversion heterozygotes, a cross-over in the inversion loop will lead to recombinant gametes bearing a duplicated region and a deleted region. Zygotes that form from these gametes will probably not survive because of the abnormal dosage of some of the genes within the inversion. In paracentric inversion heterozygotes, a crossover in the inversion loop will lead to recombinant chromosomes that have altered gene dosage and centromere number (one acentric and one dicentric). The acentric chromosome is lost and the dicentric chromosome breaks randomly during meiosis.

Upon fertilization, the recombinant gametes cannot support survival of the zygote. Only nonrecombinant progeny survive. SEE FIGURE 14.18.

Thus the diagnostic features of inversions are (1) inversion loops, (2) reduction of RF, (3) reduced fertility, and (4) inverted arrangement of chromosomal landmarks.

Inversions are of extreme importance in diploid genetics. Geneticists are often interested in studying genes that are essential for development and mutations in such genes lead to recessive lethality. Geneticists use special inversion chromosomes, called **balancer chromosomes**, to maintain these mutations in a population. Balancer chromosomes have multiple inversions, thus recombinant chromosomes are not recovered. Many balancers also carry a dominant marker mutation and a recessive lethal mutation. A strain heterozygous for a balancer chromosome carrying a lethal mutation and a chromosome carrying a second lethal mutation of interest is a stable strain. The inversions suppress the formation of wild-type recombinant chromosomes, thus the strain can be easily maintained by crossing heterozygous individuals.

Bal   _____   _____   Bal
       ------m----------   X   ------m----------

Gives: 25% lethal (Bal/Bal)   50% "Balanced" Hets   25% homoz. mutant
      _____   _____   ------m----------
      _____   ------m----------   ------m----------

m = recessive lethal mutation of interest

Balancer chromosomes can also be used in genetic screens to find mutations. See Fig. 7.9.

Translocation: A chromosomal rearrangement in which part of one chromosome becomes attached to a non-homologous chromosome (**non-reciprocal**), or in which parts of two non-homologous chromosomes trade places (**reciprocal**).

Most individuals bearing reciprocal translocations are viable and fertile. However, just like with inversions, abnormal phenotypes can be observed if the translocation breakpoint lies within a critical gene, or if the translocation places a gene or group of genes in a new regulatory environment.

N1   A - cen - BCDEF
T1   A - cen - BC**JKL**

N2   G - cen - HIJKL
T2   G - cen - HI**DEF**

During meiosis in reciprocal translocation heterozygotes, the translocated chromosomes and the normal homologous chromosomes maximize pairing by forming a cross-like structure among all four chromosomes (instead of the usual two). Reciprocal translocations can segregate in three ways: alternate, adjacent-1, and infrequently, adjacent-2. **Alternate** segregation leads to gametes

with either normal chromosomes (N1 and N2) or translocation chromosomes (T1 and T2); these gametes have a balanced set of chromosomes and will give rise to viable progeny. **Adjacent-1** segregation leads to unbalanced gametes (N1; T2 and N2;T1), since each gamete contains a large duplication and a large deletion. The gametes derived from adjacent-1 segregation lead to zygotic lethality in animals and to sterility in plants. In rare **adjacent-2** segregation, non-disjunction of homologous centromeres occurs, leading to unbalanced gametes (N1;T1 and N2;T2) and zygotic lethality. SEE FIGURE 14.21. Translocation chromosomes obey Mendel's laws - we see the alternate and adjacent-1 segregation patterns with equal frequency (about 50%). Since adjacent-1 and the rare adjacent-2 gametes lead to zygotic lethality, markers will appear linked in a test cross, if the normal chromosomes are marked.

Cytological and genetic consequences of reciprocal translocations: (1) semisterility (in plants, ~50% of the gametes are inviable; in animals, ~50% of the zygotes are inviable), (2) apparent linkage of genes known to be on different chromosomes, and (3) alterations in chromosome size.

******We will cover Robertsonian translocations next time*********

A special kind of translocation, called a **Robertsonian translocation** (Fig 14.19) is one in which a reciprocal exchange between two acrocentric chromosomes leads to a large metacentric chromosome and a very small chromosome (that may even carry so few genes that it does not cause genetic imbalance and is lost). In fact, a less common form of Down's Syndrome (<5% of cases) is caused by a Robertsonian translocation between Chromosome 21 and Chromosome 14. This form of Down's Syndrome can recur in families. Please review the formation of the "Down's" translocation chromosome and the segregation of the normal and translocation chromosomes during meiosis (Fig. 14.22).