

## LECTURE 33

### GENETICS OF TRANSLOCATIONS

- A. Translocations are “two-break” events that result in exchanges between non-homologous chromosomes.
1. Translocations were first detected (inferred) from changes in linkage relationships of genes.
  2. Cytologically, must consider pairing in chromosomal homozygotes and heterozygotes.
    - a) Pairing in chromosomal (structural) homozygotes is “normal,” whereas a pachytene cross-like configuration is observed in chromosomal (structural) heterozygotes.
- B. Genetic consequences of translocations (like inversions) arise during meiosis of chromosomal heterozygotes.
1. Consider pairing and crossing over:
    - a) Pairing does occur in the pachytene cross-like configuration, but there is considerable asynapsis in regions proximal to the centromere. Consequently, pairing is generally restricted to distal regions of the chromosomes.
    - b) The rare cross over between non-homologous regions that are proximal to the centromere gives rise to gametes that are duplicated/deficient for genetic material (i.e., genetically aneuploid). Generally, genetically aneuploid chromatids are expected to result in lethality during early zygotic development.
    - c) The net consequence is that regions proximal to the centromere are maintained intact, either because crossing over is restricted or because crossovers generate aneuploid gametes; translocation thus allow the build-up and maintenance of *co-adapted gene complexes*.
  2. Consider segregation at meiosis I:
    - a) Crossovers do (fortunately) occur between homologous regions in the distal wings of the pachytene cross-like configuration. This will generate a “ring-of-four” (quadrivalent ring), where chiasma terminalization during diakinesis produces a “ring-like” multivalent configuration.
    - b) The failure of a crossover to occur in (any of) the distal wings of the “cross” will result in rod-like multivalents and/or univalents, decreasing the probability that segregation will produce euploid (fully haploid) gametes. Note that from the quadrivalent ring, production of euploid gametes requires the alternate segregation pattern (see below).

- c) Segregation from a quadrivalent ring results in three different patterns of 2 x 2 segregation.

Adjacent I: aneuploid gametes that are expected to produce zygotic lethality

Adjacent II: aneuploid gametes that are expected to produce zygotic lethality

Alternate: euploid gametes, 1/2 structurally normal, 1/2 translocation

- d) The expectations are that 2/3 of the gametes stemming from a quadrivalent ring will be genetically aneuploid, and that fertility will be reduced to a *maximum* of 33%. While generally observed, there are several plant species where heterozygosity for translocations leads to only a 50% reduction in fertility. A “figure 8” structure is generally observed in these species, suggesting the non-random “figure 8” structure partially mitigates fertility difficulties.

3. Overall consequences of translocations are essentially the same as for inversions.

- a) Change(s) in linkage relationships of genes;
- b) crossover suppression and generation of gene “complexes” that are generally inseparable by recombination; and
- c) a marked reduction in fertility.

#### D. Translocations in man:

1. Down’s syndrome is caused by trisomy #21, and usually stems from primary or secondary non-disjunction. Thus,

$$2n = 46N \text{ vs } 2n = 47D$$

2. About 5% of Down’s individuals are  $2n = 46D$ , and all  $2n = 46D$  individuals have one parent that is  $2n = 45N$ , i.e.,

$$2n = 46N \text{ vs } 2n = 46D \text{ vs } 2n = 45N$$

3. Chromosome studies indicated involvement of chromosomes #15 and #21, and based on observations of “standard” (normal) karyotypes, a non-reciprocal translocation between chromosomes #15 and #21 was hypothesized to be responsible for the  $2N = 46D$  individuals.

- a) One product of the translocation (the 15/21 chromosome) contained most or all of the euchromatin of both chromosomes; whereas the reciprocal product (the 21/15 chromosome) contained mostly heterochromatin and a chromosomal NOR. Loss of the 21/15 chromosome thus was not expected to have phenotypic consequence.
- b) Matings between a  $2n = 45N$  (translocation heterozygote) and a  $2n = 46N$  normal individual would thus yield...

2/3 aneuploid gametes: zygotic lethality except for the  $2n = 46D$

1/3 euploid gametes: normal zygotes, one of which is a translocation heterozygote

- i) Note that the tendency to have Down's children can be inherited.
- ii) Note also that translocations between D group (#13-#15) and G group (#21, #22) chromosomes in humans occur much more frequently than translocations between all other chromosomes in the human complement.
  - (a) Because both D and G group chromosomes in the human complement carry NORs, exchanges may arise between "homologous regions" of "non-homologous" chromosomes, and may represent a "price" for the existence of multiple NOR-bearing chromosomes.

### OTHER TYPES OF CHROMOSOMAL REARRANGEMENTS

#### A. Robertsonian fusions/dissociations

1. Robertsonian fusions are where non-homologous acrocentric or telocentric chromosomes "fuse" at the centromere to form metacentric chromosomes. Robertsonian dissociations are the reverse.
  - a) There is some controversy as to whether Robertsonian events represent "true" fusions or whether they are simply reciprocal translocations where the "centromere-plus-short-arms element" is lost. Kinetochore staining suggests the rearrangement represent true fusions, but where the "fused" centromeres behave monocentrically.
2. Robertsonian rearrangements are the major mechanism of chromosome number change in animals and plants (although plants have polyploidy and aneuploidy as well).
  - a) There are no apparent fertility problems in fusion/dissociation (structural) heterozygotes. This suggests that orientation and segregation of chromosomes at meiosis I are non-random. This probably represents an example of *meiotic drive*.
3. Robertsonian rearrangements often tend to occur in cascades (repeated times within a lineage). The tendency for similar chromosomal rearrangements to occur repeatedly within a lineage is called *karyotypic orthoselection*.
4. Robertsonian rearrangements are the second most common type of chromosomal change (after heterochromatin additions/deletions).

#### B. Heterochromatin additions/deletions

1. Heterochromatin additions/deletions represent amplification/reduction of constitutive heterochromatin. Recall that heterochromatin is largely satellite DNA, meaning that amplification/reduction represents large blocks of satellite DNA.

2. There are no well-documented effects on fertility of heterochromatin addition/deletion heterozygotes, although as noted previously, heterochromatin appears to affect the frequency and position of crossing over.
3. Heterochromatin additions/deletions appear to be the most common type of chromosomal change (alteration).

C. Duplications: large-scale (cytologically detectable) as opposed to a few base pairs

1. Large (cytologically detectable) deletions are thought to arise from errors during replication, unequal crossing over, and (possibly) transposition.
2. There are three defined types:
  - a) Tandem repeats,
  - b) reverse tandem repeats, and
  - c) displaced tandem (or reverse tandem) repeats.
3. Duplication *per se* appears to be the “rule” rather than the exception in eukaryotic genomes (at virtually all levels).