Chapter 16
Variations in Chromosome Structure and Number

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Variations in Chromosome Structure

- Mutations involving changes in chromosome structure occur in four common types:
  - Deletions
  - Duplications
  - Inversions (changing orientation of a DNA segment)
  - Translocations (moving a DNA segment)
- All chromosome structure mutations begin with a break in the DNA, leaving ends that are not protected by telomeres but are “sticky” and may adhere to other broken ends.

Deletion

- In a deletion, part of a chromosome is missing
  - Deletions start with chromosomal breaks induced by:
    - Heat or radiation (especially ionizing)
    - Viruses
    - Chemicals
    - Transposable elements
    - Errors in recombination
  - Deletions do not revert, because the DNA is missing.

Types of Chromosomal Mutations

- Variations in chromosome structure or number can arise spontaneously or be induced by chemicals or radiation. Chromosomal mutation can be detected by:
  - Genetic analysis (observing changes in linkage)
  - Microscopic examination of eukaryotic chromosomes at mitosis and meiosis (karyotype analysis)
- Chromosomal aberrations contribute significantly to human miscarriages, stillbirths, and genetic disorders.
  - About 1⁄2 of spontaneous abortions result from major chromosomal mutations.
  - Visible chromosomal mutations occur in about 6/1,000 live births.
  - About 11% of men with fertility problems and 6% of people institutionalized with mental deficiencies have chromosomal mutations.

Variations in Chromosome Structure

Polytene chromosomes

- Polytene chromosomes (bundles of chromatids produced by DNA synthesis without mitosis or meiosis) are useful for studying chromosome structure mutations.
  - Polytenes are easily detectable microscopically.
  - Homologs are tightly paired, joined at the centromeres by a proteinaceous chromocenter.
  - Detailed banding patterns are characterized for the four polytene chromosomes, with each band averaging 30 kb of DNA, enough to encode several genes.

Effects of Deletion

- The effect of a deletion depends on what was deleted.
  - A deletion in one allele of a homozygous wild-type organism may give a normal phenotype, while the same deletion in the wild-type allele of a heterozygote would produce a mutant phenotype.
  - Deletion of the centromere results in an acentric chromosome that is lost, usually with serious or lethal consequences. (No known living human has an entire autosome deleted from the genome.)
  - Large deletions can be detected by unpaired loops seen in karyotype analysis.
Deletion mapping

- Deletion mapping can indicate the physical location of a gene on the chromosome, because deletion of the dominant allele in a heterozygote results in the recessive phenotype.
  - a. Expression of the recessive trait caused by the absence of a dominant allele is called pseudodominance.
  - b. Deletion experiments correlate the deleted DNA with loss of dominant alleles and the appearance of pseudodominance.
  - c. This technique was used to produce the detailed physical map of Drosophila polytene chromosomes.

Deletions and humans

- Human disorders caused by large chromosomal deletions are generally seen in heterozygotes, since homozygotes usually die.
  - a. The number of gene copies is important.
  - b. Syndromes result from the loss of several to many genes.

Duplications

- Duplications result from doubling of chromosomal segments and occur in a range of sizes and locations.
  - a. Tandem duplications are adjacent to each other.
  - b. Reverse tandem duplications result in genes arranged in the opposite order of the original.
  - c. Tandem duplication at the end of a chromosome is a terminal tandem duplication.
  - d. Heterozygous duplications result in unpaired loops, and may be detected cytologically.

Cri–du–chat (“cry of the cat”) syndrome (OMIM 123450) results from deletion of part of the short arm of chromosome 5. The deletion results in severe mental retardation and physical abnormalities.

Drosophila eye shape allele, Bar, reduces the number of eye facets, giving the eye a slit–like rather than oval appearance.

- a. The Bar allele resembles an incompletely dominant mutation:
  - i. Females heterozygous for Bar have a kidney-shaped eye that is larger and more faceted than that in a female homozygous for Bar.
  - ii. Males hemizygous for Bar have slit-like eyes like those of a Bar/Bar female.
- b. Cytological examination of polytene chromosomes showed that the Bar allele results from duplication of a small segment (16A) of the X chromosome.

Gene Families as result of duplication

- Hemoglobin (Hb) is an example:
  - a. Each Hb contains two copies of two subunits (e.g., 2 α-globins and 2 β-globins), and the identity of the subunits changes with the organism’s developmental stage.
  - b. Genes for the α-type polypeptides are clustered together on one chromosome, and those for β-type polypeptides are clustered on another.
  - c. α-type genes have similar sequences, as do β-type. They probably result from duplication and subsequent sequence divergence.
Inversions

- Inversion results when a chromosome segment excises and reintegrates oriented 180° from the original orientation. There are two types:
  a. Pericentric inversions include the centromere.
  b. Paracentric inversions do not include the centromere.

Inversions generally do not result in lost DNA, but phenotypes can arise if the breakpoints are in genes or regulatory regions.

Linked genes and inversion

- Linked genes are often inverted together. The meiotic consequence depends on whether the inversion occurs in a homozygote or a heterozygote.
  a. A homozygote will have normal meiosis.
  b. The effect in a heterozygote depends on whether crossing-over occurs.
    i. If there is no crossing-over, no meiotic problems occur.
    ii. If crossing-over occurs in the inversion, unequal crossover may produce serious genetic consequences.

Recombination events—heterozygotes

- Paracentric inversions (no centromere) result in visible inversion loops between homologous chromosomes.
  i. Crossover in the inversion region results in unbalanced sets of genes, and gametes or zygotes derived from recombined chromatids may be inviable due to abnormal gene dose.
  ii. Without crossover in the looped region, gametes receive complete sets of genes (two gametes with normal and two with inversions) and are viable.

Effects of a single crossover within an inverted segment in a heterozygote include:

1. Joining of homologous regions of two chromatids to produce a dicentric bridge, and corresponding loss of an acentric fragment.
2. During anaphase the two centromeres of the dicentric chromosome migrate toward opposite poles, causing the bridge to break and producing two chromatids with deletions.
3. The second meiotic division distributes one chromatid to each gamete:
   a. Two gametes carry normal sets of genes (one in the normal order and the other in inverted order).
   b. Two gametes are missing many genes, and are inviable.

Translocations

- No DNA is lost or gained. Simple translocations are of two types:
  a. Intrachromosomal, with a change of position within the same chromosome
  b. Interchromosomal, with transfer of the segment to a nonhomo-logous chromosome
    i. If a segment is transferred from one chromosome to another, it is nonreciprocal.
    ii. If segments are exchanged, it is reciprocal

Gametes after translocation

- Gamete formation is affected by translocations.
  a. In homozygotes with the same translocation on both chromosomes, altered gene linkage is seen.
  b. Gametes produced with chromosomal translocations often have unbalanced duplications and/or deletions and are inviable or produce disorders such as familial Down syndrome.
  c. Strains that are homozygous for a reciprocal translocation form normal gametes.
Strains that are heterozygous for a reciprocal translocation must pair a set of normal chromosomes (N) with a set of translocated ones (T).

◦ i. Result is a crosslike configuration in meiotic prophase I of four associated chromosomes, each partially homologous to two others in the group.

◦ ii. Anaphase I segregation may occur in three different ways (crossover will not be considered).

1. Alternate segregation moves alternate centromeres to the same poles (e.g., N₁ and N₂ one direction, T₁ and T₂ the other). Gametes are viable, with either normal or translocated chromosomes.

2. Adjacent-1 segregation moves adjacent nonhomologous centromeres to the same pole (e.g., N₁ and T₂ one direction, N₂ and T₁ the other). Gametes are inviable due to gene duplications and deletions.

3. Adjacent-2 segregation is rare, moving different pairs of adjacent homologous centromeres to the same pole (N₁ and T₁ one direction, N₂ and T₂ the other). These gametes are usually inviable.