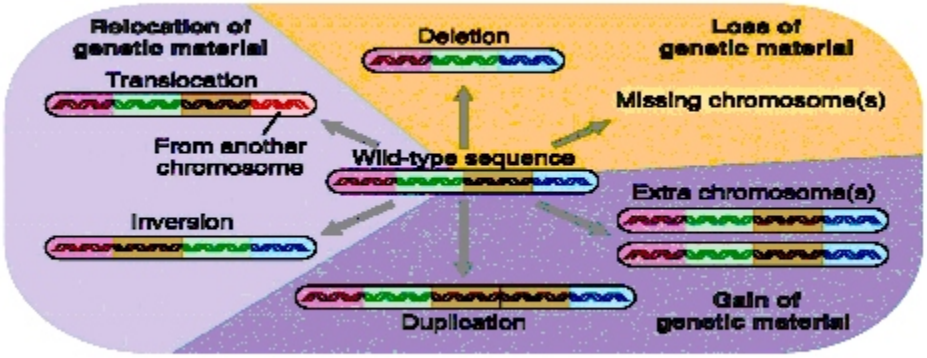
BIO 390 - GENETICS

CHROMOSOME MUTATIONS

OVERVIEW



- Multiples of complete sets of chromosomes are called **polyploidy**.
  - Even numbers are usually fertile.
  - Odd numbers are usually sterile.

- **Aneuploidy** refers to the gain or loss of single chromosomes, usually in meiosis.

- Chromosome aberrations **include translocations, inversion, deletion, duplication**.
  - Each has characteristic meiotic pairing.
  - Crossing-over may result in abnormal gametes, reduced fertility and unmasking of deleterious recessive alleles.
  - Duplication can also provide material for evolutionary divergence.

CHROMOSOME MUTATIONS

- Two major types
  - change in number of copies of chromosomes
  - alteration of chromosome structure

- Reveal features of meiosis

- Provide insight into gene function

- Useful tools for experimental analysis

- Provide insight into evolution

ABERRANT EUPLOIDY

- Changes in *whole* chromosome sets

- **Euploidy**: multiples of basic chromosome set
  - haploid
  - diploid

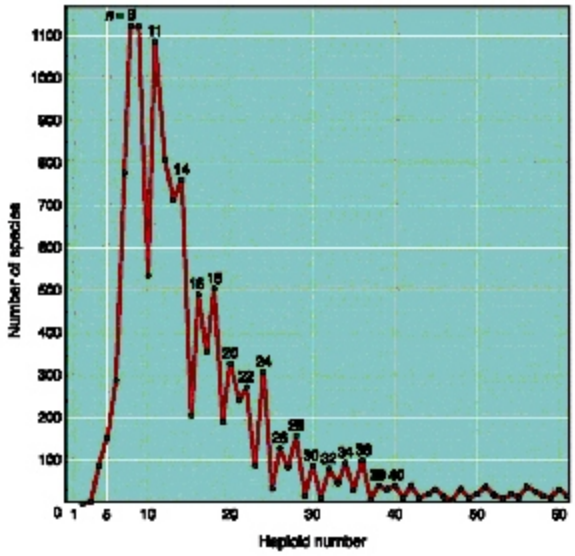
- **Aberrant euploid**: more or less than normal number
  - monoploid (1*n*)
  - triploid (3*n*)
  - tetraploid (4*n*)
  - pentaploid (5*n*)
  - hexaploid (6*n*)

MONOPLOIDY

- Male bees, wasps, ants
  - parthenogenetic development of unfertilized egg
  - single set of chromosomes
  - produce gametes by mitosis

- Usually lethal in other systems
  - unmasks recessive lethals
  - if individual survives to adulthood, no meiosis, sterility

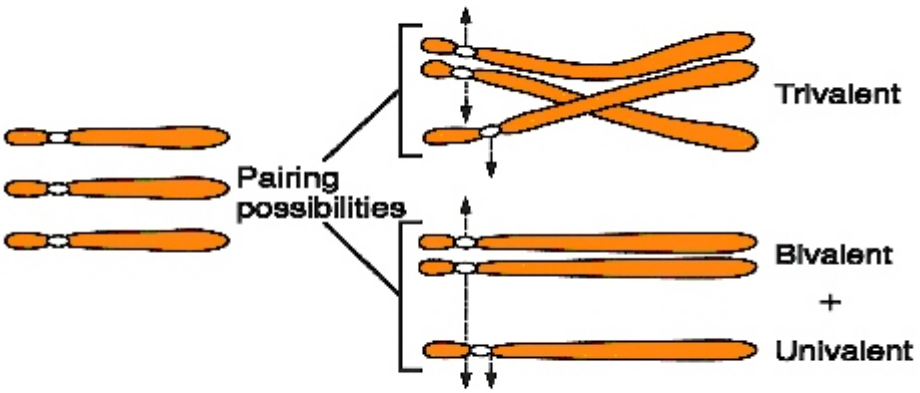
POLYPLOIDY



- Very common in plants
  - associated with origin of new species
    - sympatric speciation
  - may positively correlate to size of individual

POLYPLOIDY

- **Autopolyploids**
  - originate within a species
  - autotriploid ($2n + n$)

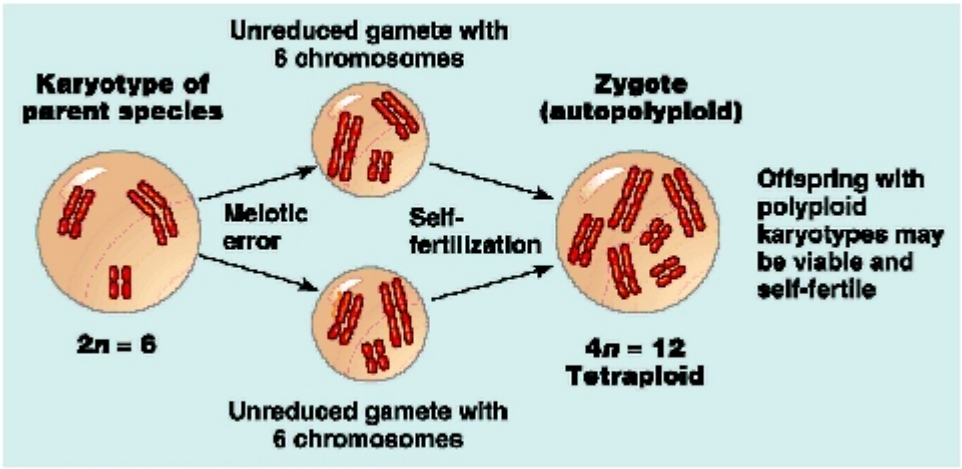


Note: each chromosome is a pair of chromatids

-sterile due to formation of aneuploid gametes

POLYPLOIDY

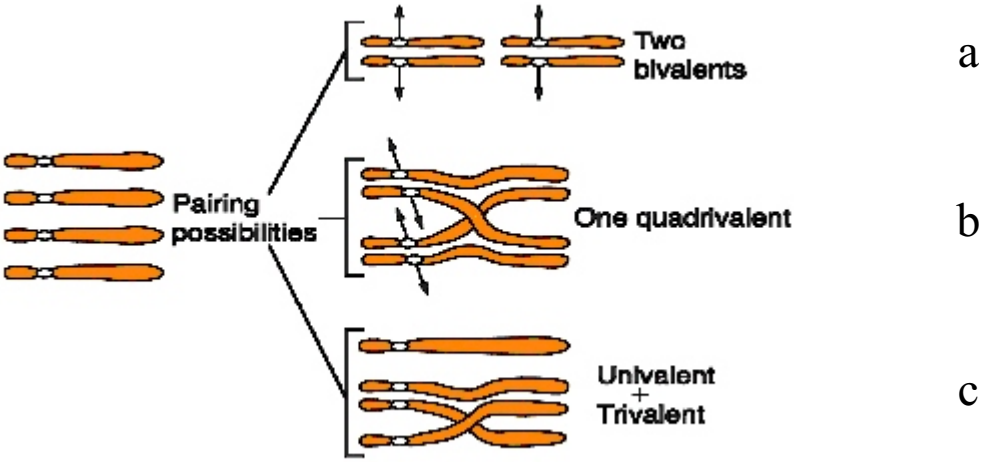
Figure 24.13 Sympatric speciation by autopolyploidy in plants



- autotetraploid (doubling of $2n$)
  - spontaneous doubling

POLYPLOIDY

- induced by drug such as colchicine



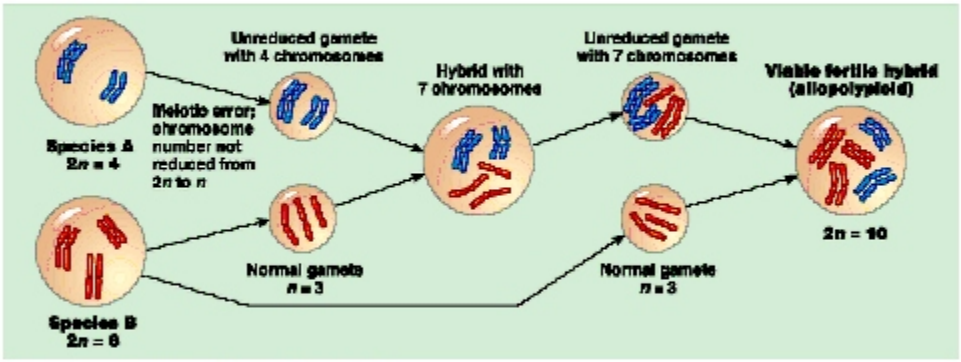
Note: each chromosome is a pair of chromatids

- results in
  - diploid (a,b) gametes which upon fusion will regenerate the tetraploid state
  - nonfunctional aneuploid gametes (c) resulting in sterility

POLYPLOIDY

- **Allopolyploidy**
  - hybrid of two or more closely related species
  - partially homologous chromosomes (homeologous)
  - amphidiploid: doubled diploid
  - *Triticum aestivum* ($2n = 42$)
    - multiple episodes of allopolyploidy

Figure 24.15 One mechanism for allopolyploid speciation in plants



- Agricultural applications
  - plant monoploids grown from $1n$ cells in anther
  - bananas ($3n = 33$)
  - *Triticale*: amphidiploid of wheat and rye

POLYPLOIDY IN ANIMALS

- Rare occurrence
  - species of flatworms, leaches, brine shrimps
  - certain fishes, amphibians, reptiles

- Sometimes artificially induced, e.g., triploid oysters

ANEUPLOIDY

- Chromosome complement differs from normal by part of chromosome set
  - e.g., $2n \pm 1$
  - tolerated in plants
  - usually lethal in animals

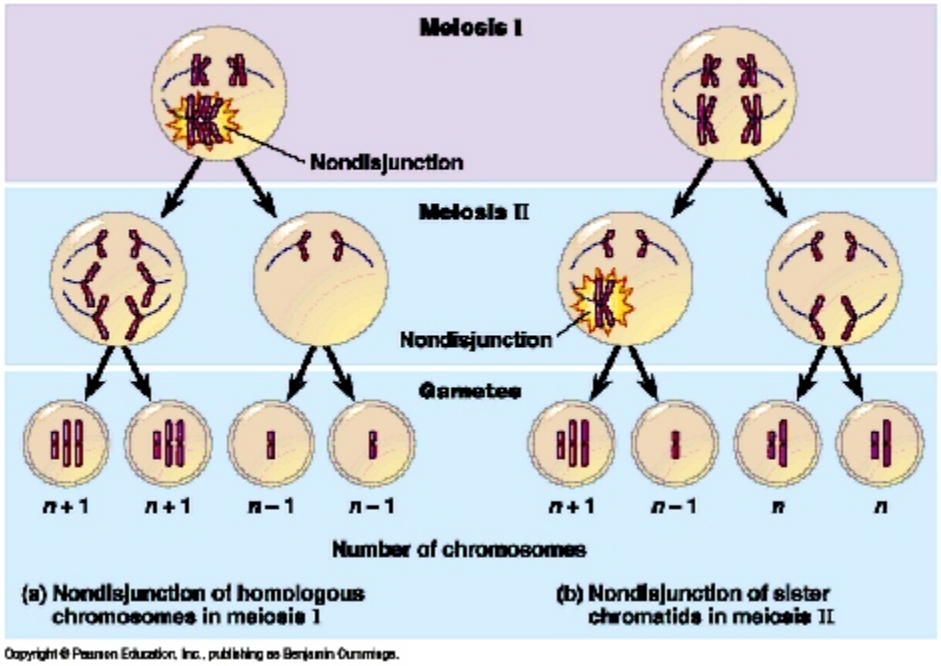
- For autosomes:
  - monosomy: $2n - 1$
  - trisomy: $2n + 1$
  - nullisomy: $2n - 2$
  - disomy: $n + 1$ (in haploids

- For sex chromosomes, notation lists copies of each chromosome. Examples: XXY, XXX, XO

NONDISJUNCTION

- Cause of most aneuploidy
- Failure of chromosomes or chromatids to segregate at meiosis or mitosis
  - **mitotic nondisjunction**
    - zygotic: all cells aneuploid
    - later in development: aneuploid sectors
  - **meiotic nondisjunction**
    - aneuploid haploid organisms ($n \pm 1$)
    - aneuploid gametes ($n \pm 1$) leading to aneuploid zygotes
    - increased frequency if crossing-over fails

Figure 15.11 Meiotic nondisjunction



MONOSOMY

- **2*n* – 1**
- Usually deleterious owing to unmasking of recessive lethals in animals
  - lethal in utero in humans

- **XO: Turner syndrome** in humans
  - only *viable* monosomy in humans
  - phenotypic female
  - sex organs fail to mature
  - secondary sex characteristics fail to develop (breasts)
  - normal intelligence
    - some impairment in cognitive functions

- Used to map genes in plants

TRISOMY

- **$2n + 1$**

- Often lethal in animals owing to chromosome imbalance
  - in euploids the ratio of genes on any one chromosome to the different genes on other chromosomes is 1:1 regardless of the ploidy
  - in aneupolids the ratio of genes on the aneuploid chromosome to genes on the other chromosomes differs from the wild type by 50%
    - 50% for monosomics
    - 150% for trisomics
  - **gene-dosage**
    - relationship between the number of copies of a gene and the amount of the gene's product
    - amount of transcript produced by a gene directly proportional to the number of copies of the gene
    - compensated for with respect to sex chromosomes
      - in mammals X chromosome inactivation
      - in *Drosophila* X chromosome in males is transcribed at twice the rate of either X chromosome in females

- If viable, may be fertile (meiotic trivalent)

TRISOMY

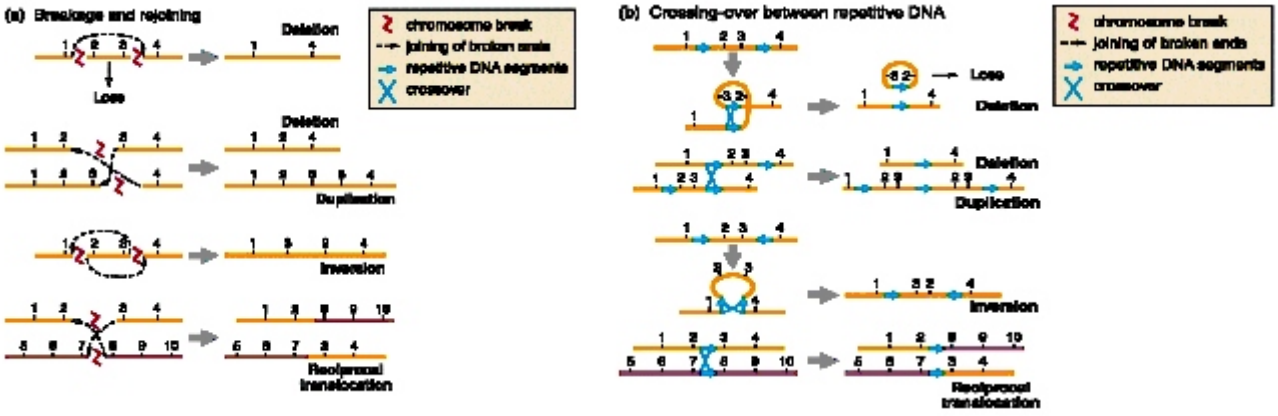
- **XXY: Klinefelter syndrome**
  - male
  - sterile
  - mentally retarded

- **XYY**:
  - fertile, no extra Y in gametes
    - X pairs with one of the Ys
    - other Y does not pair and is not transmitted to the gametes

- **XXX**:
  - fertile, no extra X in gametes
    - two Xs pair
    - third X does not pair and is not transmitted to the gametes

- **Trisomy 21: Down syndrome**
  - characteristic facial features, short stature, heart defects, susceptibility to respiratory infection and mental retardation
  - trisomy of chromosome 21(due to nondisjunction)
  - frequency correlates with age of the mother

CHANGES IN CHROMOSOME STRUCTURE

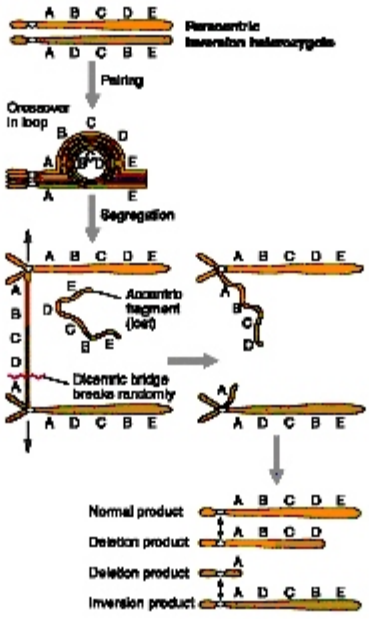


- Also called chromosome rearrangements
  - deletion: loss of segment
  - duplication: gain of segment
  - inversion: reversal of region
  - translocation: movement of segment to another chromosome

- Origin in double-stranded breaks where product has centromere and two telomeres
  - acentric fragments lost at anaphase
  - dicentric fragments dragged to both poles, lost

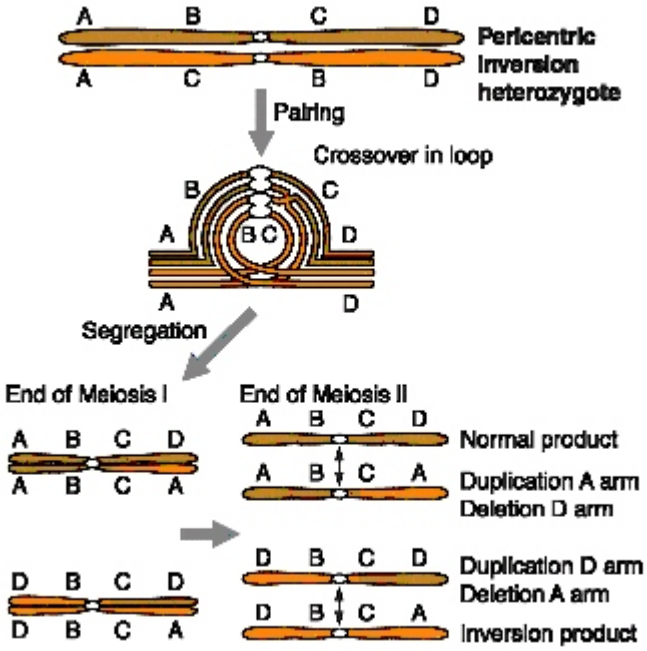
BALANCED REARRANGEMENT: INVERSION

- Change in gene order, but no gain or loss of DNA
- Inversion loop formed at meiosis I
- **Paracentric**: centromere outside inversion
  - crossing-over in inversion heterozygote results in one dicentric chromatid and one acentric fragment
  - reduced number of viable gametes
  - drastically lower RF
    - close to zero for genes within the inversion
    - reduced in proportion to the size of the inversion for genes flanking the inversion
      - longer the inversion the greater the probability of a crossover occurring within producing an inviable meiotic product
    - crossover products are not recovered



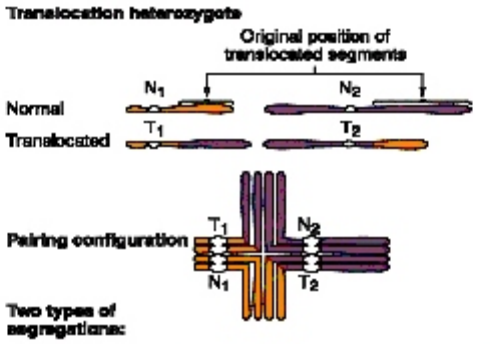
BALANCED REARRANGEMENT: INVERSION

- **Pericentric**: inversion spans centromere
  - crossing over in inversion results in gene imbalance
    - crossover produces chromatids that contain a duplication and a deletion for different parts of the chromosome
  - crossover products are not recovered
  - reduced number of viable gametes



BALANCED REARRANGEMENT: TRANSLOCATION

- Change in gene order, but no gain or loss of DNA
- **Reciprocal translocations**: exchange between two nonhomologous chromosomes
- Cross-shaped configuration at meiosis I
- Two types of segregations
  - **adjacent-1**: segregation of each structurally normal chromosome with one of the translocated ones ($T_1 + N_2$ and $T_2 + N_1$)
  - **alternate segregation**: segregation of the two normal and two translocated chromosomes ($N_1 + N_2$ and $T_1 + T_2$)
- Crossing-over results in gene imbalance, **semisterility**
  - equal numbers of adjacent-1 and alternate segregations
    - half of the overall population of gametes (plants) or zygotes (animals)will be nonfunctional
  - diagnostic tool for identifying translocation
    - heterozygotes



Adjacent-1		Products	
Up	$T_1 + N_2$	Duplication of purple, deletion of orange translocated segment	Often inviable
Down	$T_2 + N_1$	Duplication of orange, deletion of purple translocated segment	
Alternate			
Up	$T_1 + T_2$	Translocation genotype	Both complete and viable
Down	$N_1 + N_2$	Normal	

APPLICATIONS OF INVERSIONS & TRANSLOCATIONS

- Gene mapping
  - assign gene to specific chromosome region
  - correlation of translocations with a phenotype
    - breakpoints (disruptions) define the gene locus

- Synthesizing specific duplications and deletions
  - useful in mapping and study of gene regulation
  - varying gene dosage

- Position-effect variegation
  - gene action can be affected by location near heterochromatin

POSITION-EFFECT VARIEGATION

(b) 

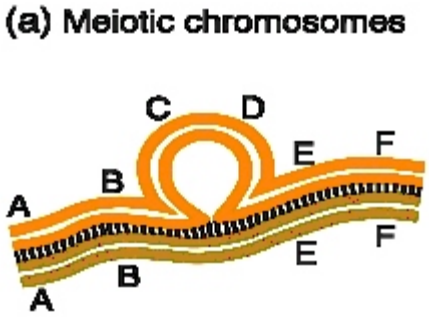
IMBALANCED REARRANGEMENT: DELETION

- Loss of segment of DNA
- Intragenic deletion: small deletion within gene
  - inactivates gene and has the same effect as a other null mutations fo that gene
- Multigene deletion
  - many genes deleted
  - often severe consequences
- gene imbalance
- expression of deleterious recessive mutation
  - **pseudodominance** seems as if the recessive alleles are showing dominance

a b c d e f g

\+ + + + +

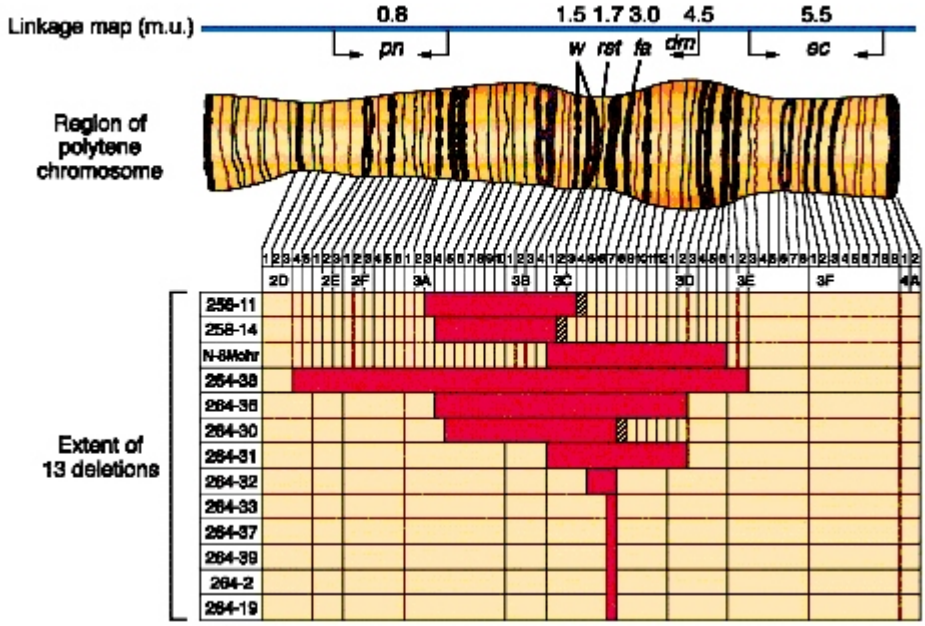
- Visible as deletion loop



- May be used in deletion mapping

IMBALANCED REARRANGEMENT: DELETION

red bars



- prune (*pn*) mutation shows pseudodominance only with deletions 264-38
  - gene located in the 2D-4 to 3A-2 region
- *fa* shows pseudodominance with all but two deletions (258-11 and 258-14)
  - so the locus is located in band 3C-7, the region that all the other deletions have in common

IMBALANCED REARRANGEMENT: DUPLICATION

- Gain of segment of DNA
- Source of new genes and gene families
- Tandem duplication: adjacent duplications
- Insertional duplication: duplicate gene inserted elsewhere in genome
- May be consequence of unequal crossing-over

EVOLUTIONARY ASPECTS

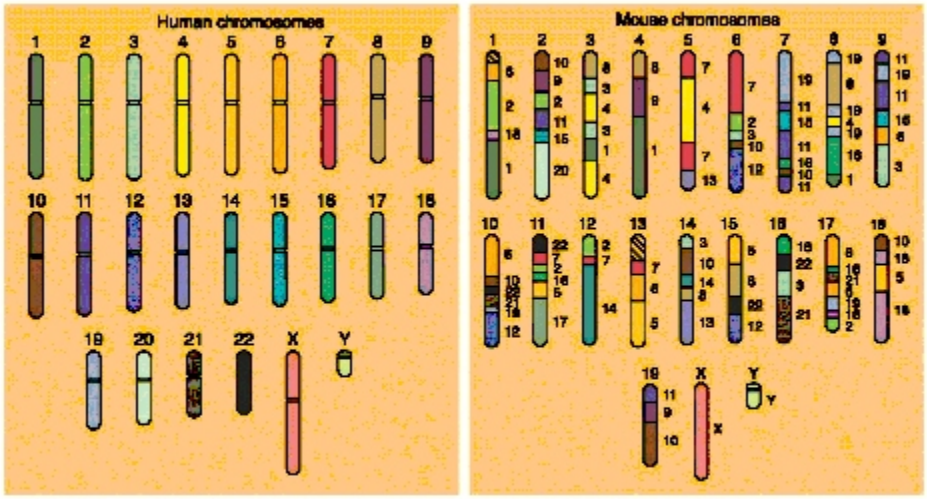
- ~7.5% spontaneous human abortions have chromosomal abnormality

- Chromosomal changes occur in association with speciation
  - fusion of two chromosomes (translocation) to form single chromosome in human evolution
  - duplication and divergence
    - human globin genes

- Chromosomal polymorphism: two or more forms of chromosome in population
  - inversion common
    - paracentric inversions in *Drosophila*
      - because of the strong reduction in RF caused by inversions genes in inverted region segregate as a unit called a supergene
  - commonness due to peculiarities of meiosis
    - no crossing over in *Drosophila* males
    - in *Drosophila* females only the two end nuclei (noncrossovers) are included in the egg

- Chromosomal **synteny**: inheritance of blocks of genes through inversions and translocations

EVOLUTIONARY ASPECTS



- Synteny of mouse (2*n* =40) and human (2*n*= 46) chromosomes
- Since evolutionary divergence multiple rearrangements have placed homologous blocks of genes in different combinations