Chromosome mutations

are variations in:

1. Chromosome structure (chromosomal rearrangements)
   - deletions
   - duplications
   - translocations
   - inversions
   - transpositions

2. Chromosome number
   - aneuploidy
   - abnormal euploidy
Chromosomal rearrangements

consequence of chromosome breaks

possible causes:

1. high-energy (ionizing) radiation
   • X-rays
   • α, β, and γ emissions (from man-made or natural radioactive sources)
   • cosmic rays

2. “spontaneous”
   • unequal crossing over
   • mitotic recombination
Unequal crossing-over
Deletions

= deficiencies = losses of chromosome segments

• can occur terminally or internally, e.g. caused by…

• breakage and rejoining within one chromosome:
Consequences of deletions

- almost always **lethal** when homozygous
- often also lethal when heterozygous

- example of a viable deletion in humans: *Cris-du-chat* syndrome
  - terminal deletion of short arm of one chromosome #5
  - can be seen in karyotype analysis as loss of bands/interbands
  - leads to mental retardation
How deletions can be identified:

- by finding a visible change in chromosome structure:
- by the fact that deletions “uncover” genes:

Diagram: Polytene chromosome structure showing normal and deletion homologs with specific genes and deletion regions.
Mapping genes with deletions

Regions
Band numbers

Small segment of banded polytene chromosome

Specific deletions

Df 258-45
Df 67c23
Df N8
Df 264-32
Df 264-33

Regions of genes

Phenotype of mutation/Del heterozygote

w\textsuperscript{-}rst\textsuperscript{+}fa\textsuperscript{+}
w\textsuperscript{-}rst\textsuperscript{+}fa\textsuperscript{+}
w\textsuperscript{-}rst\textsuperscript{-}fa\textsuperscript{-}
w\textsuperscript{+}rst\textsuperscript{-}fa\textsuperscript{-}
w\textsuperscript{+}rst\textsuperscript{+}fa\textsuperscript{-}
w\textsuperscript{+}rst\textsuperscript{+}fa\textsuperscript{-}

w = white
rst = roughest
fa = facet
Duplications

(a) Tandem duplication

Normal chromosome: ABCDEFG
- Same order: ABCBCDEFG
- Reverse order: ABCCBDEFG

Nontandem (dispersed) duplications
- Same order: ABCDEFGBCG
- Reverse order: ABCDEFCBG

(b) X rays break one chromosome in two places

Nontandem duplication

X rays break homologous chromosome in one place

(c) Duplicated chromosome

Normal chromosome: ABCD

- Duplicated chromosome: ABCDCBD
Consequences of duplications

- most duplications have no phenotypic consequence
- sometimes effects can be seen due to increased gene dosage

- play a very important role in evolution:
  - increase gene number
  - evolution of new genes (paralogs!)
Inversions

result from insertion of a chromosome fragment in reverse orientation:

- usually no phenotypic consequences
- can sometimes lead to a mutant phenotype:
Inversion chromosome pairs with normal chromosome under formation of an inversion loop.
Inversions suppress genetic recombination by crossing-over.
Inversions are used to “balance” chromosomes.

-chromosome to be balanced

-balancer chromosome

inversion I

inversion II
Translocations

= attachments of chromosome fragments to non-homologous chromosomes

• reciprocal translocations arise from exchange of chromosome fragments between non-homologous chromosomes:

• non-reciprocal translocations arise from attachment of chromosome fragment to a non-homologous chromosome; lead to duplications and deletions in progeny
Consequences of translocations

• usually none in homozygotes; genetic material is neither lost nor gained:

![Diagram of normal segregation during meiosis]

• none in heterozygotes if translocation chromosomes segregate together ("balanced" translocation); if translocation chromosomes are separated, genetically imbalanced gametes result with deletions or duplications; zygotes produced by these gametes are not viable

--- semisterility
Robertsonian translocation or centric fusion

= fusions of two acrocentric chromosomes after short arms broke off

no important genes; may get lost
How a Robertsonian translocation can lead to Down syndrome

- 21 14 Normal
- Translocation carrier 14/21

Gamete formation

Gametes

- Normal
- Translocation carrier
- Trisomy 21 (Down)
- Monosomic (lethal)

Chromosome number

- 46
- 45
- 46
- 45

translocation Down syndrome accounts for ~ 5% of all cases (familiar Down syndrome)
Transposition

= movement of DNA elements from one site in the genome to another

- transposable elements = transposons:
  - some related to viruses (transposons & viruses: mobile genetic elements)
  - found in all organisms (bacteria to humans)
  - have no obvious function (are dispensible)
    - are considered as “selfish” DNA
  - impact on evolution of genomes
  - can be used as transformation vectors and for mutagenesis
- 2 main classes:
  1. retrotransposons (= retroposons)
  2. DNA-only transposons
Life cycle of a retrovirus

- **Retrovirus**
  - Capsid enters host cell and leaves envelope on the membrane.
  - Capsid breaks down; reverse transcriptase synthesizes a DNA copy of the viral RNA.
  - Reverse transcriptase synthesizes a second strand from the DNA copy.

- **Host chromosome**
  - DNA

- **Host cell**
  - RNA

- **Viral mRNA**
  - Viral mRNA is transcribed from the integrated viral DNA.

- **Viral DNA (provirus)**
  - Double-stranded viral DNA is integrated by unknown enzymes into the DNA of the host chromosome.

- **Reverse transcriptase**
  - Synthesizes new viral components to construct new viruses.
Retrotransposons (retroposons) transpose via RNA intermediate

LTR = long terminal repeat

Retrotransposon at original genomic position

Reverse transcriptase gene

RNA transcript

Reverse transcription

Double-stranded cDNA copy of retroposon

Insertion into new site in the genome

5-bp repeat of new target DNA

5-bp repeat of target DNA

Retroposon remains in place and new copy inserts into other location
DNA-only transposons

Transposase enzyme recognizes inverted repeats and excises the transposon.

Genomic DNA at original insertion site

Inverted repeats (IR)

Transposon
P-elements in *Drosophila*

Transposition of P element to new location

P element in original genomic position

P element excised

Transposase

Transposon no longer at original position

↓

excision can be imprecise

↓

deletion
P-element transformation

- P element end
- pCaSpeR vector
- Gene
- w⁺
- Transposase gene
- Transformation plasmid
- Helper plasmid
- early embryo
- M w⁻
- pole cells (prospective germ cells)
- Grows into
- Gametes with transformed DNA in genome
- ×
- germ line transformation!
- Drosophila genomic DNA
Changes in chromosome number

Aneuploidy
= change in the number of single chromosomes (but not in the number of sets)

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Examples (humans)</th>
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<tbody>
<tr>
<td><strong>Monosomy</strong></td>
<td>2n - 1; Turner (45, XO); loss of an autosome is lethal</td>
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<tr>
<td><strong>Trisomy</strong></td>
<td>2n + 1; Trisomy 21 (Down syndrome), 18, 13; Klinefelter (47, XXY), Triple-X (47, XXX), XYY males (47, XYY)</td>
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<tr>
<td><strong>Nullisomy</strong></td>
<td>2n - 2; not viable in diploids</td>
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(abnormal) Euploidy
= change in the number of chromosome sets

- Diploid 2n
- Polyploid (Triploid, Tetraploid etc.) 3n, 4n etc.

- is not viable in humans; many plants polyploid
Turner Syndrome (45, X)

- sterile females

1 in 3000 female births
Klinefelter Syndrome (47, XXY)

- sterile males

2 in 1000 male births
Down Syndrome (47, +21)