Structural Chromosomal Aberrations

• Chromosome structure variations result from chromosome breakage and reunion in an abnormal way.
• Broken chromosomes tend to re-join; if there is more than one break, rejoining occurs at random and not necessarily with the correct ends.
• The result is structural changes in the chromosomes.
• Chromosome breakage is caused by X-rays, various chemicals, and can also occur spontaneously.
Types of Structural Chromosomal abnormalities

- Structural abnormalities either:
  - Balanced (usually normal phenotype): (no change in genetic material)
    - Translocations
    - Inversions
  - Unbalanced (abnormal phenotype): (increased or decreased genetic material)
    - Deletions
    - Duplications
    - Insertions
    - Rings
    - Isochromosomes
Deletion (Partial monosomy)

* Loss of a chromosome segment is a deletion.
* Must be at least 5Mb to been seen cytogenetically.
* It can be terminal deletion or interstitial (intercalary) deletion.
* A single break near the end of the chromosome would result in terminal deficiency.

* If two breaks occur, a section may be deleted and an intercalary deficiency created.
* Terminal deficiencies might seem less complicated.
* But majority of deficiencies detected are intercalary type within the chromosome.
Deletion ..... cont

– Intercalary deletions delete an interior portion
  • Only portion retaining centromere will be maintained in daughter cells
  • Synapsing with normal chromosome creates a deletion loop or compensation loop visible during meiosis
  • Crossover between direct repeats can result in an internal deletion

(c) Formation of deficiency loop

Area missing in deleted chromosome

Normal chromosome

Deleted chromosome

Synapsis

Formation of deletion loop
Deletion ..... cont

- Deletion generally produce striking **genetic and physiological effects**.

- When homozygous, most deletions are lethal, because most genes are necessary for life and a homozygous deletion would have zero copies of some genes.

- When heterozygous, the genes on the normal homologue are **hemizygous**: there is only 1 copy of those genes.

- Crossing over is absent in deleted region of a chromosome since this region is present in only one copy in deletion heterozygotes.
Deletion in Human:

- Chromosome deletions are usually lethal even as heterozygotes, resulting in zygotic loss, stillbirths, or infant death.
- Sometimes, infants with small chromosome deficiencies however, survive long enough to permit the abnormal phenotype they express. Eg. **Cri-du-Chat Syndrome**
ISCN

- del - deletion
- dic - dicentric
- fra - fragile site
- i - isochromosome
- inv - inversion
- p - short arm
- r - ring
- der - derivative
- dup - duplication
- h - heterochromatin
- ins - insertion
- mat - maternal origin
- q - long arm
- t - translocation
The name of the syndrome came from a catlike mewing cry from small weak infants with the disorder. Other characteristics are microcephaly (small head), broad face and saddle nose, physical and mental retardation. Cri-du-chat patients die in infancy or early childhood. Due to partial autosomal monosomy, loss of part of 5p arm (46, -5p). Incidence 1/50,000 births.
Partial Monosomy

Cri-du-chat Syndrome, (46, del(5p15))

- Mental retardation, abnormal development of glottis and larynx
- 1 / 50,000 live births
DiGeorge Syndrome  
(Chromosome 22q11.2 Deletion Syndrome)

- **Cardiac Abnormality**
- **Abnormal facies**
- **Thymic aplasia**
- **Cleft palate**
- **Hypocalcemia**
- **CATCH** syndrome

- This syndrome cannot be detected by standard karyotyping and needs FISH
DiGeorge Syndrome
**Duplication (Partial Trisomy)**

- The presence of an additional chromosome segment, as compared to that normally present, is known as **Duplication**.
- In a diploid organism, presence of a chromosome segment in more than two copies per nucleus is called duplication.
- Four types of duplication:
  1. Tandem duplication
  2. Reverse tandem duplication
  3. Displaced duplication
  4. Translocation duplication
**Duplication**

- The extra chromosome segment may be located immediately after the normal segment in precisely the same orientation forms the **tandem**

- When the gene sequence in the extra segment of a tandem in the reverse order i.e, inverted , it is known as **reverse tandem duplication**

- In some cases, the extra segment may be located in the same chromosome but away from the normal segment – termed as **displaced duplication**

- The additional chromosome segment is located in a non-homologous chromosome is **translocation duplication**.

![Diagram of chromosome duplication](image)
Origin

- Origin of duplication involves:
  - 1- **Chromosome breakage** and **reunion of chromosome segment** with its homologous chromosome.
  - As a result, one of the two homologous involved in the production of a duplication ends up with a **deficiency**, while the other has a duplication for the concerned segment.
  - 2- **Unequal crossing over**, also leads to exactly the same consequences for small chromosome segments.
  - Unequal crossing over between two homologous chromosomes results in **deletion** in one chromosome and **duplication** of the same segment in the other.
Crossing Over

• Crossing over is the exchange of genetic material between homologous chromosomes leading to increased genetic variations.

• During meiosis, the pair of homologous chromosomes should be paired exactly so that each gene should face the homologous gene in the other chromosome, so the exchanged material is equal.
Crossing Over—often results in an exchange of genetic material

(a) Unequal crossing-over

Duplication—2 copies of 16A (Bar)

Deletion
Ring chromosome

- Chromosome undergoes 2 breaks
- Broken ends reunite in a ring
- 46, XX, r (7) (p22q36)
- Very rare because of its mitotic instability.
- It may be found in a proportion of cells only.
Isochromosome

- The chromosome consists of two copies of the same arm (Mirror image around centromere).
- It is due to transverse centromere division instead of normal longitudinal division.
- The isochromosomes seen mostly o involving X-chromosome.
- One arm missing; other arm duplicated
  - Monosomy for 1 chromosome arm
  - Trisomy for the other arm
- Eg. 46, X, i(Xq) = isochromosome for Xq
Insertions

Segment of 1 chromosome inserted into another •

der  B  A  derA
Balanced Structural Rearrangements

Translocations

• In translocations, nonhomologous chromosomes exchange parts

• 3 types
  - Simple translocation
  - Reciprocal translocation
  - Robertsonian translocation
Translocations

• Simple translocation: Broken chromosome fragment becomes attached to a nonhomologous chromosome (very rare)

• Reciprocal translocation: Broken chromosome fragments become exchanged between non-homologous chromosomes
Reciprocal translocations

- More common than Robertsonian
- Break in any chromosome at any point
- Phenotypically normal – problems at meiosis
Reciprocal translocation

46,XX,t(5;9)(q32;p13)
Translocations

- Reciprocal translocations result from crossover events between non-homologous chromosomes
  - Balanced translocation
    - Abnormalities may result
The Philadelphia Chromosome

translocations can be analyzed using banding patterns and multicolor FISH. Characteristic chromosomal translocations are associated with certain genetic disorders and specific types of cancers. For example, in nearly all patients with chronic myelogenous leukemia, the leukemic cells contain the Philadelphia chromosome, a shortened chromosome 22 \([der (22)]\), and an abnormally long chromosome 9 \([der (9)]\). These result from a translocation between normal chromosomes 9 and 22. This translocation can be detected by classical banding analysis (a) and by multicolor FISH (b). [Part (a) from J. Kuby, 1997, *Immunology*, 3d ed., W. H. Freeman and Company, p. 576; part (b) courtesy of J. Rowley and R. Espinosa.]
The Philadelphia Chromosome*

* Mutation found in all cases of chronic myeloid leukemia
  • The ABL & BCR fuse due to translocation and form an oncogene
In Robertsonian translocation the short arms of 2 different acrocentric chromosomes break, leaving sticky ends that then cause the 2 long arms to adhere.

A new large chromosome forms from the long arms of the two different chromosomes.

This individual produces unbalanced gametes.
Robertsonian translocations

A  der(A;B)  B

A

der(A;B)

B
Robertsonian translocations result in:

- Lose of satellite and short arms
  - Short arms contain genes for rRNA
  - These genes are repeated on other acrocentric chromosomes, so no deficiency of rRNA gene product.
- Reduce chromosome number by one (45)
  - but no loss of chromatin from long arms
- Phenotypically normal – problems at meiosis
Most common Robertsonian translocations are:

- D:G translocation
  - Often 14:21 joined

- G:G translocation
  - 21:22 joined
  - 21:21 joined
    - 21 smallest chromosome

- Other translocations:
  - 45,XY,der(13q;14q)(q10;q10)
  - 45,XX,der(13q;21q)(q10;q10)
ROBERTSONIAN TRANSLOCATION

• A carrier parent with 45 chromosomes, one of which is the combined 14q21q, will produce 3 kinds of offspring
  – Phenotypically and karyotypically normal
  – Phenotypically unaffected translocation heterozygote
  – Eg. Translocation Down syndrome individual

• The risk of a carrier having a child with Down syndrome is 15%

• The condition is not related to age
### (A) Synapsis

- **Synapsis**
  - 14q21q
  - 14

### (B) Gametes

<table>
<thead>
<tr>
<th>Balanced normal karyotype</th>
<th>Balanced translocation</th>
<th>Unbalanced</th>
<th>Unbalanced</th>
<th>Unbalanced</th>
<th>Unbalanced</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>14q21q</td>
<td>14</td>
<td>14</td>
<td>14q21q</td>
<td>14</td>
</tr>
</tbody>
</table>

### (C) Fertilization with normal gamete

<table>
<thead>
<tr>
<th>Karyotypes</th>
<th>Normal chromosomes</th>
<th>Translocation carrier</th>
<th>Trisomy 21</th>
<th>Monosomy 21</th>
<th>Trisomy 14</th>
<th>Monosomy 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>14, 21</td>
<td>14, 21</td>
<td>14q21q, 21</td>
<td>14, 21</td>
<td>14</td>
<td>14, 21</td>
<td>14</td>
</tr>
<tr>
<td>14, 21</td>
<td>14q21q</td>
<td></td>
<td></td>
<td></td>
<td>14q21q, 14</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Chromosome numbers</th>
<th>46</th>
<th>45</th>
<th>46</th>
<th>45</th>
<th>46</th>
<th>45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenotypes</td>
<td>Normal</td>
<td>Normal</td>
<td>Down syndrome</td>
<td>Lethal</td>
<td>Lethal</td>
<td>Lethal</td>
</tr>
</tbody>
</table>
Robertsonian translocation family pedigree

Key
- male
- female
- miscarriage
- chromosome 13
- chromosome 21
- Robertsonian translocation der(13;21)(q10;q10)

Diagram:
- Normal
- Carrier
- Down syndrome
- Normal
Karyotypes of Down Syndrom

1- Stander trisomy (47,+21)
   - 95% of cases.
   - Mainly due to increase in maternal age.

2- Masaic (46/47,+21)
   - 2% of cases.
   - Due to postzygotic N.D.
   - No maternal age effect.

3- Translocation
   - 3% of cases.
   - No maternal age effect.
   - Family history may be involved.
Inversion

- Chromosome undergoes 2 breaks and the segment between the breaks is inverted. Genes are in reversed order.
- 2 types:
  - Paracentric
    - 2 breaks on one side of centromere; arm ratio unchanged
    - Unbalanced offspring (recombinants) usually not viable (acentric or dicentric)
    - Main difference in karyotypes of great apes and humans so important in evolution
  - Pericentric
    - One break in each arm; often arm ratio changed
    - Recombinants have duplications and deficiencies of chromosome segments
    - Risk of carrier having viable recombinant: 5-10%
    - Eg. 46, XY, inv(3) (q21q26)
Chromosomal Inversions

Paracentric inversion does not involve the centromere.

Pericentric inversion involves the centromeric region.

[Diagram showing paracentric and pericentric inversions with labeled breaks and changes in arm ratio.]
Chromosomal Inversions

- A certain segment may be broken in two places, and the breaks may be in close proximity because of chance loop in the chromosome.

- When they rejoin, the wrong ends may become connected.

- The part on one side of the loop connects with broken end different from the one with which it was formerly connected.

- This leaves the other two broken ends to become attached. The part within the loop thus becomes turned around or inverted.
Allderdice syndrome

- Pericentric inversion of chromosome 3 \([\text{inv} \ (3) \ (p25q21)]\)
- Carriers of \(\text{inv}(3)\):
  - healthy (one normal 3; one inversion 3)
  - have 40% risk of abnormal offspring (23/55 pregnancies)
  - unbalanced offspring have one \textit{recombinant} chromosome 3
    - duplication of segment distal to 3q21
    - deficiency of segment distal to 3p25
Crossing over within inversion loops formed at meiosis I in carriers of a chromosome with segment B-C inverted (order A-C-B-D, instead of A-B-C-D). A, Paracentric inversion. Gametes formed after the second meiosis usually contain either a normal (A-B-C-D) or a balanced (A-C-B-D) copy of the chromosome because the acentric and dicentric products of the crossover are inviable. B, Pericentric inversion. Gametes formed after the second meiosis may be normal, balanced, or unbalanced. Unbalanced gametes contain a copy of the chromosome with a duplication or a deficiency of the material flanking the inverted segment (A-B-C-A or D-B-C-D).
Inversions and Gametogenesis

• One member of homologous pair has inversion
  – Normal pairing during meiosis not possible
    • Inversion loop forms
• When no recombination occurs, 50% of gametes have inversion
  – But recombination can occur...
Inversions and Recombination

- Many defective gametes can be produced
- It can give:
  - Acentric chromosomes – no centromere
  - Dicentric chromosomes – two centromeres
- Acentric and dicentric chromosomes are mitotic unstable and lost during cell division.
Dicentric and Acentric Chromosomes

Dicentric chromosome plus acentric fragment
Fragile Sites

• There are some mutant/fragile sites on chromosomes where chromatin fails to become properly compacted
  – Areas often subject to breakage
  – Can be associated with mental retardation and cancer
Fragile Sites

- **Fragile X Syndrome:** normally CGG is repeated 50 times; in fragile X, up to 1000 times
- Makes a very thin physical region of the chromosome.
- Results in range of mental retardation and behavioral problems
- Occurs in both sexes; most females with fragile X are heterozygous
Fragile X Syndrome

- 1/4000 males, 1/8000 females
  Dominant, not fully penetrant (Penetrance in females is 50%-60%)
- Folate-sensitive site on X chromosome
  - Breakage more likely when cells grown under folate deficiency conditions
- FMR1 (fragile X mental retardation gene,
  - many CGG tandem repeats in the 5’UTR
  - 6-54 is normal, 55-200 is a carrier, above 200 expresses syndrome
  - More than 200 copies of the repeat lead to excessive methylation of cytosines in the promoter of FMR1; this interferes with replication or chromatin condensation or both, producing the characteristic chromosomal fragile site, a form of DNA modification that prevents normal promoter function or blocks translation.
Molecular Basis for Fragile X Syndrome

- FMR1 gene mapped to Xq27.3
- Expansion of CGG trinucleotide repeat located at the 5’ untranslated region of exon 1 of FMR1
  - Normal: 59 or less, premutation: 60 – 200, full mutation: 200 or greater
- Expansion of the CGG repeat leads to methylation of promotor region of FMR1 gene blocking FMR1 protein (FMRP) expression (shuts down gene expression)
- FMRP1 is RNA binding protein highly expressed in neurons in the CNS. Transports specific RNAs from nucleus to ribosomes in cytoplasm
Fragile X Syndrome

1) Mental Retardation - IQ < 50 in affected males, IQ 70-90 in affected females

2) Characteristic Facies
   - low set ears, prominent jaw

3) Behavioural abnormalities
   - hyperkinetic
   - autistic like behaviour
   - learning disabilities

4) Macroorchidism