Lecture-3

Chromosomal Abnormalities

Chromosome Abnormalities

- They can be divided into numerical and structural, with a third category consisting of different chromosome constitutions in two or more cell lines.

Numerical

- Aneuploidy
- Monosomy
- Trisomy
- Tetrasomy
- Polyploidy
- Triploidy
- Tetraploidy

Structural

- Translocations
- Reciprocal
- Robertsonian
- Deletions
- Insertions
- Inversions
- Paracentric
- Pericentric
- Rings
- Isochromosomes

Different Cell Lines (Mixoploidy)

- Mosaicism
- Chimerism

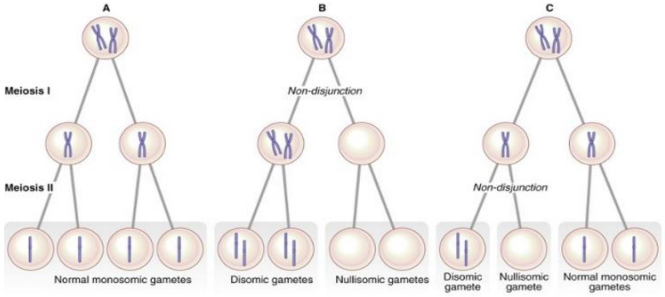
Numerical Abnormalities

- **Aneuploidy -** Loss or gain of one or more chromosomes.
  - **Monosomy -** Loss of a single chromosome (2n-1).
  - **Nullisomy** – Loss of a pair of chromosomes (2n-2).
  - **Trisomy -** Gain of one homologous chromosome (2n+1).
  - **Tetrasomy -** Gain of two homologous chromosomes (2n+2).
- **Polyploidy -** Addition of one or more complete haploid complements. Or they contain more than two haploid (n) sets of chromosomes. More common in plants.
  - **Triploidy** – Addition of one set (2n+n = 3n)
  - **Tetraploidy** – Addition of two sets (2n+2n = 4n)

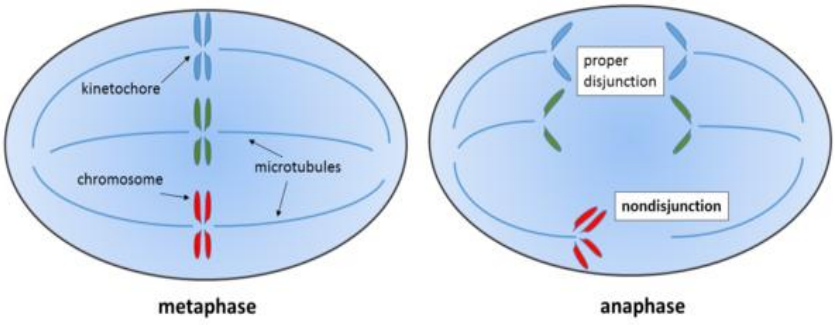
Trisomy

- The presence of an extra chromosome is referred to as **trisomy**.
- Most cases of Down syndrome are due to presence of an additional 21 chromosome; hence, **Down syndrome** is often known as **trisomy-21**.
- Other autosomal trisomies compatible with survival are **Patau syndrome (trisomy-13)** and **Edwards syndrome (trisomy-18).**
- Most other autosomal trisomies result in early pregnancy loss, with trisomy-16 being more common in first-trimester spontaneous miscarriages.
- The presence of an additional sex chromosome (X or Y) has only mild phenotypic effects.

- Trisomy 21 is usually caused by failure of separation of one of the pairs of homologous chromosomes during anaphase of maternal meiosis I.
- This failure of the bivalent to separate is called **non-disjunction**.
- Less often, trisomy can be caused by non-disjunction occurring during meiosis II when a pair of sister chromatids fails to separate.
- Consequently the gamete receives two homologous chromosomes (**disomy**); if subsequent fertilization occurs, a trisomic conceptus results.



Non-disjunction



Origin of Non-disjunction

- The consequences of non-disjunction in meiosis-I and meiosis-II differ in the chromosomes found in the gamete.
- An error in meiosis-I leads to the gamete containing both homologs of one chromosome pair.
- In contrast, non-disjunction in meiosis-II results in the gamete receiving two copies of one of the homologs of the chromosome pair.
- Studies have shown that most children with an autosomal trisomy have inherited their additional chromosome as a result of non-disjunction occurring during one of the maternal meiotic divisions

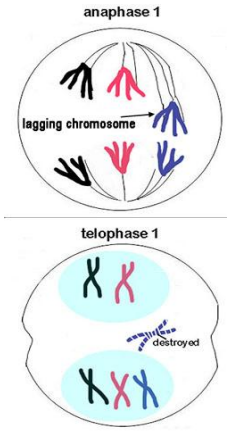
Chromosome Abnormality	Paternal (%)	Maternal (%)
Trisomy 13	15	85
Trisomy 18	10	90
Trisomy 21	5	95
45,X	80	20
47,XXX	5	95
47,XXY	45	55
47,XYY	100	0

Cause of Non-disjunction

- The cause of non-disjunction is uncertain.
- The most favored explanation is that of an aging effect on the primary oocyte, which can remain in a state of suspended inactivity for up to 50 years.
- This is based on the well-documented association between advancing maternal age and increased incidence of Down syndrome in offspring.
- A maternal age effect has also been noted for trisomies 13 and 18.
- Research has shown that absence of recombination in meiosis-I predisposes to subsequent non-disjunction. Chiasmata hold each pair of homologous chromosomes together. Failure of chiasmata formation could allow each pair of homologs to separate and segregate randomly to daughter cells.
- Thus, at least two factors can be involved in causing non-disjunction: an absence of recombination between homologous chromosomes in the fetal ovary, and an abnormality in spindle formation many years later.

Monosomy

- The absence of a single chromosome is called **monosomy**.
- Monosomy for an autosome is lethal and individuals do not survive.
- Lack of contribution of an X or a Y chromosome results in a 45,X karyotype, which causes the condition known as Turner syndrome.
- Monosomy can result from non-disjunction in meiosis. If one gamete receives two copies of a homologous chromosome (**disomy**), the other corresponding daughter gamete will have no copy of the same chromosome (**nullisomy**), which after fertilization will result in monosomy.
- Monosomy can also be caused by **anaphase lag,** which is a delayed movement of a chromosome so as is not incorporated in one of the daughter cells.

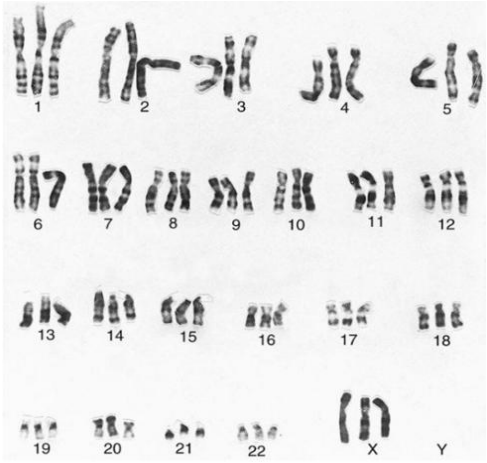


Polyploidy

- Polyploid cells contain multiples of the haploid number of chromosomes such as 69 (**triploidy)** or 92 (**tetraploidy)**.
- In humans, triploidy is found relatively often in material grown from spontaneous miscarriages, but survival beyond mid-pregnancy is rare. Only a few triploid live births have been described and all died soon after birth.
- Triploidy can be caused by failure of a maturation meiotic division in an ovum or sperm, leading to retention of a polar body or formation of a diploid sperm.
- Alternatively it can be caused by fertilization of an ovum by two sperm: this is known as **dispermy**.
- When triploidy results from the presence of an additional set of paternal chromosomes, the placenta is usually swollen. In contrast, when triploidy results from an additional set of maternal chromosomes, the placenta is small.
- Triploidy usually results in early spontaneous miscarriage.

Example of Polyploidy

Karyotype from products of conception of a spontaneous miscarriage showing **triploidy**

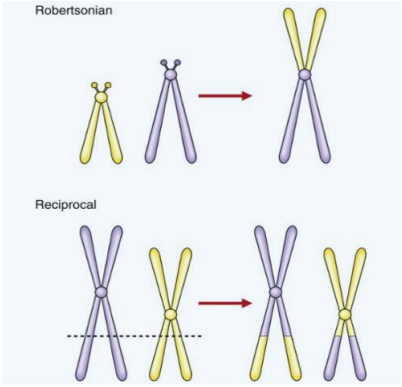


Structural Abnormalities

- Structural chromosome rearrangements result from chromosome breakage with subsequent reunion in a different configuration.
- They can be balanced or unbalanced.
- In balanced rearrangements the chromosome complement is complete, with no loss or gain of genetic material.
- Balanced rearrangements are generally harmless.
- However, carriers of balanced rearrangements are often at risk of producing children with an unbalanced chromosomal complement.
- When a chromosome rearrangement is unbalanced the chromosomal complement contains an incorrect amount of chromosome material and the clinical effects are usually serious.
- Structural abnormalities include: **translocations, insertions, deletions, inversions, and ring chromosomes**.

Translocations

- **Translocation** is the transfer of genetic material from one chromosome to another.
- There are two types of translocations: **Reciprocal** and **Robertsonian**.
- **Reciprocal translocation** - When breaks occur in two different chromosomes and their segments are exchanged.
- **Robertsonian translocation** - Breakpoints are located at, or close to, the centromeres of two acrocentric chromosomes. An entire chromosome is attached to another chromosome.

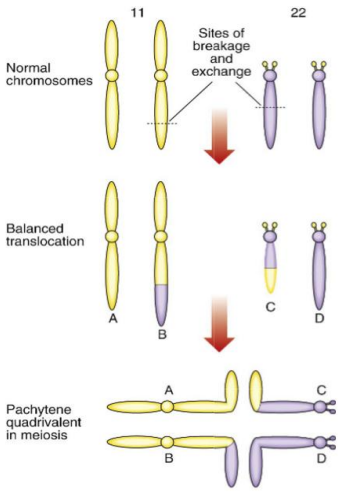


Reciprocal Translocations

- A reciprocal translocation involves breakage of at least two chromosomes with exchange of the fragments.
- Usually the chromosome number remains unchanged (46).
- In general, reciprocal translocations are unique to a particular family.
- A particular balanced reciprocal translocation involving the long arms of chromosomes 11 and 22 is relatively common.
- The overall incidence of reciprocal translocations in the general population is approximately 1 in 500.

Reciprocal Translocations

- Problems arise at meiosis because the chromosomes involved in the translocation cannot pair normally to form bivalents.
- Instead they form a cluster known as a **pachytene quadrivalent**. The key point to note is that each chromosome aligns with homologous material in the quadrivalent.
- The quadrivalent is formed to maintain homologous pairing.
- They segregate to generate significant chromosome imbalance.
- This can lead to early pregnancy loss or to the birth of an infant with multiple abnormalities.

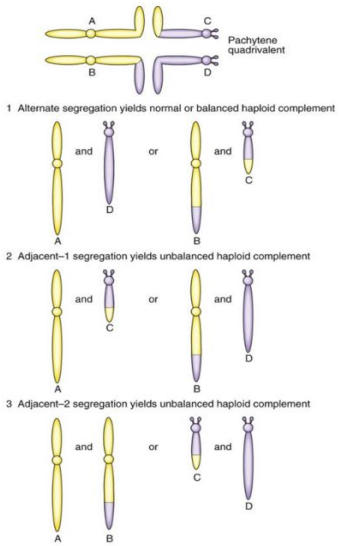


2:2 Segregation

- When the chromosomes in the quadrivalent separate during the later stages of meiosis-I, they can do so in several different ways.
- If alternate chromosomes segregate to each gamete, the gamete will carry a normal or balanced haploid complement and with fertilization the embryo will either have normal chromosomes or carry the balanced rearrangement.
- If adjacent chromosomes segregate together, this will result in the gamete acquiring an unbalanced chromosome complement.
- For example, if the gamete inherits the normal chromosome-11 and the derivative chromosome-22, then fertilization will result in an embryo with monosomy for the distal long arm of chromosome-22 and trisomy for the distal long arm of chromosome-11.

Pattern of Segregation

Pattern of Segregation	Segregating Chromosomes	Chromosome Constitution in Gamete
2 : 2		
Alternate	A + D	Normal
	B + C	Balanced translocation
Adjacent-1 (non-homologous centromeres segregate together)	A + C or B + D	Unbalanced, leading to a combination of partial monosomy and partial trisomy in the zygote
Adjacent-2 (homologous centromeres segregate together)	A + B or C + D	
3 : 1		
Three chromosomes	A + B + C A + B + D A + C + D B + C + D	Unbalanced, leading to trisomy in the zygote
One chromosome	A B C D	Unbalanced, leading to monosomy in the zygote



3:1 Segregation

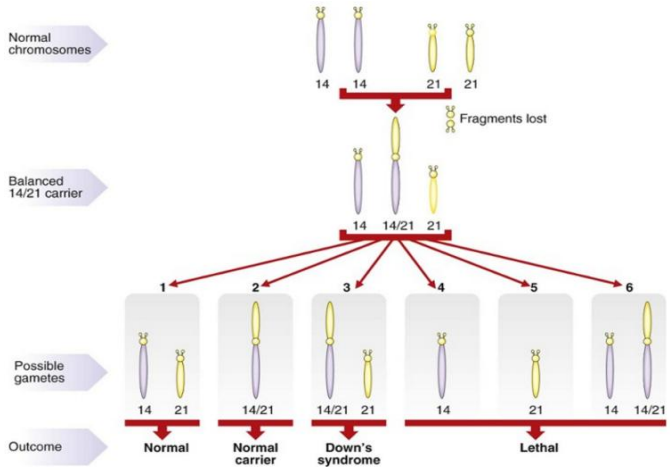
- 3 chromosomes segregate to one gamete with only 1 chromosome in the other gamete.
- If chromosomes 11, 22 and the derivative 22 segregate together to a gamete that is subsequently fertilized, this will result in the embryo being trisomic for the material present in the derivative 22 chromosome. This is sometimes referred to as **tertiary trisomy.**
- This particular reciprocal translocation, tertiary trisomy for the derivative 22 chromosome is the only viable unbalanced product.
- All other patterns of malsegregation lead to early pregnancy loss.
- Unfortunately, tertiary trisomy for the derivative 22 chromosome is a serious condition in which affected children have multiple congenital abnormalities and severe learning difficulties.

Robertsonian Translocations

- Caused by the breakage of two acrocentric chromosomes (numbers 13, 14, 15, 21, and 22) at or close to their centromeres, with subsequent fusion of their long arms.
- This is also referred to as **centric fusion**.
- The short arms of each chromosome are lost, this being of no clinical importance as they contain genes only for ribosomal RNA, for which there are multiple copies on the various other acrocentric chromosomes.
- The total chromosome number is reduced to 45.
- Because there is no loss or gain of important genetic material, this is a functionally balanced rearrangement.
- The overall incidence of Robertsonian translocations in general population is approximately 1 in 1000, with by far the most common being fusion of the long arms of chromosomes 13 and 14.

Robertsonian Translocations

Segregation at Meiosis



Only half of the gametes are viable. This condition is called semi-sterility.

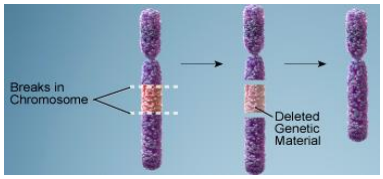
Robertsonian Translocations

As with reciprocal translocations, the importance of Robertsonian translocations lies in their behavior at meiosis. For example, a carrier of a 14q21q translocation can produce gametes with:

1. A normal chromosome complement (a normal 14 and a normal 21).
2. A balanced chromosome complement (a 14q21q translocation). Viable.
3. An unbalanced chromosome complement possessing both the translocation chromosome and a normal 21. This will result in the fertilized embryo having Down syndrome (trizomy 21).
4. An unbalanced chromosome complement with a normal 14 and a missing 21. Will result in zygote with monosomy 21 (no survival).
5. An unbalanced chromosome complement with a normal 21 and a missing 14. Will result in zygote with monosomy 14 (no survival).
6. An unbalanced chromosome complement with the translocation chromosome and a normal 14 chromosome. Will result in zygote with trisomy 14 (no survival).

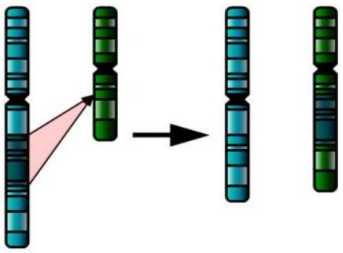
Deletions

- A **deletion** involves loss of part of a chromosome and results in monosomy for that segment of the chromosome.
- A very large deletion is usually incompatible with survival to term, and as a general rule any deletion resulting in loss of more than 2% of the total haploid genome will have a lethal outcome.
- A 'large' chromosomal deletion can be visualized under light microscope. Examples are Wolf-Hirschhorn and Cri du chat syndromes, which involve loss of material from short arms of chromosomes 4 and 5, respectively.
- Submicroscopic micro-deletions are identified with the help of FISH studies and include Prader-Willi syndrome (15p del) and Angelman syndrome (deletion in UBE3A gene located at 15q11.2).



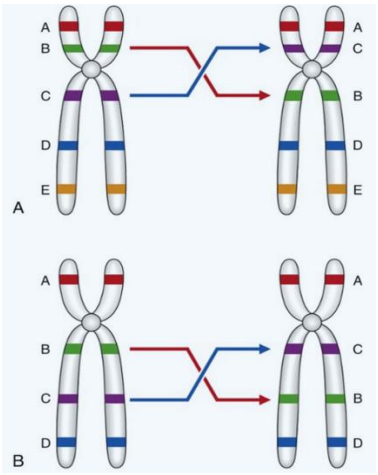
Insertions

- An **insertion** occurs when a segment of one chromosome becomes inserted into another chromosome.
- This can happen due to unequal crossover during meiosis.
- Carriers of a balanced deletion–insertion rearrangement are at a 50% risk of producing unbalanced gametes, as random chromosome segregation at meiosis will result in 50% of the gametes inheriting either the deletion or the insertion, but not both.



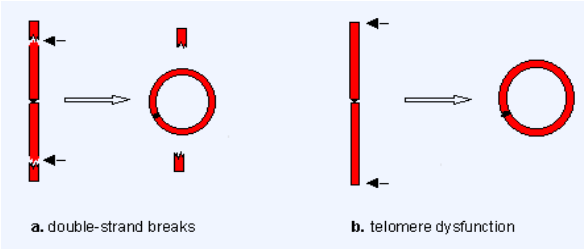
Inversions

- An inversion is a two-break rearrangement involving a single chromosome in which a segment is reversed in position (i.e., inverted).
- If the inversion segment involves the centromere it is termed a **Pericentric Inversion**.
- If it involves only one arm of the chromosome it is known as a **Paracentric Inversion.**
- Inversions are balanced rearrangements that rarely cause problems in carriers unless one of the breakpoints has disrupted an important gene.



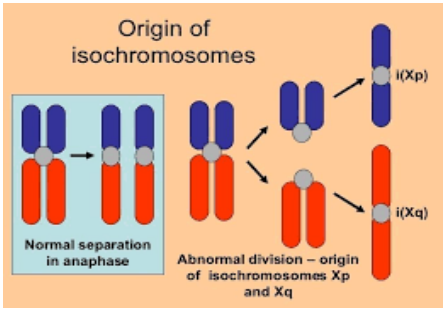
Ring Chromosomes

- A **ring chromosome** is formed when a break occurs on each arm of a chromosome leaving two 'sticky' ends that reunite as a ring. The two distal chromosomal fragments are lost that may cause serious effects.
- **Ring chromosome** may also be formed by telomere dysfunction triggering fusion of chromosome ends without major loss of genetic material.



Isochromosomes

- An isochromosome shows loss of one arm with duplication of the other.
- Isochromosome is formed when centromere divides transversely rather than longitudinally.
- The most commonly encountered isochromosome consists of two long arms of the X chromosome. This accounts for up to 15% of all cases of **Turner syndrome**.

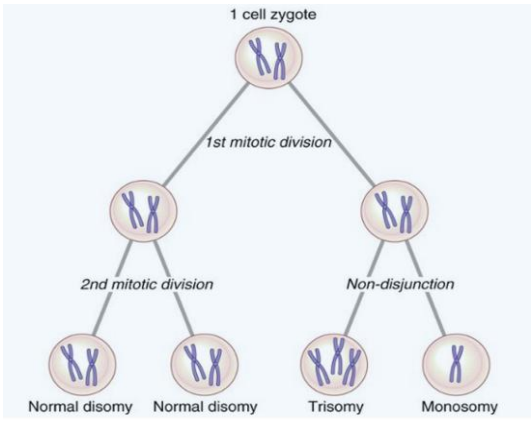


Mosaicism

- **Mosaicism** can be defined as the presence in an individual, or in a tissue, of two or more cell lines that differ in their genetic constitution but are derived from a single zygote.
- They have different genotypes but same genetic origin (single zygote).
- **Somatic mosaicism** usually results from non-disjunction in an early embryonic mitotic division with the persistence of more than one cell line.
- For example, if two chromatids of a number 21 chromosome failed to separate at the second mitotic division in a human zygote, this would result in the four-cell zygote having two cells with 46 chromosomes, one cell with 47 chromosomes (trisomy 21), and one cell with 45 chromosomes (monosomy 21). The ensuing cell line with 45 chromosomes would probably not survive, so that the resulting embryo would be expected to show approximately 33% mosaicism for trisomy 21.
- **Germline mosaicism** is caused by a mutation that occurred in an early stem cell that gave rise to gametes. As a results, some gametes carry a mutation but others are normal.

Mosaicism

Somatic mosaicism caused by mitotic non-disjunction.



Chimerism

- **Chimerism** can be defined as the presence in an individual of two or more genetically distinct cell lines derived from more than one zygote.
- They have a different genetic origin.
- The word *chimera* is derived from the mythological Greek monster that had the head of a lion, the body of a goat and the tail of a dragon.
- Human chimeras are of two kinds: dispermic chimeras and blood chimeras.
- **Dispermic chimeras:** They result from double fertilization where two genetically different sperm fertilize two ova and the resulting two zygotes fuse to form one embryo.
- **Blood chimeras:** They result from an exchange of cells, via the placenta, between non-identical twins in utero.