NUMERICAL ABNORMALITIES IN CHROMOSOMES

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Chromosomal abnormalities or aberration is a missing, extra or irregular portion of chromosomal DNA.

They usually occur as a result of errors in meiotic/mitotic cell division.

They can be inherited from a parent or be “de novo.”
There are 2 main types of chromosomal abnormalities:

- NUMERICAL
- STRUCTURAL
NUMERICAL ABNORMALITIES

- Known as aneuploidy (abnormal number chromosomes).

- Usually caused by failure of chromosome division (NON-DISJUNCTION) which results in cells with an extra chromosome or deficient chromosome.

- The causes of non-disjunction are:
  - Aging effect
  - Radiation
  - Delayed fertilization after ovulation.
Common Numerical Abnormalities

- Triploidy, Trisomy \( \rightarrow \) Autosomal Chromosomes
- Monosomy \( \rightarrow \) Sex chromosomes
- Mosaicism

Most aneuploidies are incompatible with life resulting in spontaneous abortions except for trisomy 21, 13 and 18 and monosomy X which can result in viable pregnancies.
Most frequent numerical anomalies in liveborn

**Autosomes**
- Down syndrome (trisomy 21: 47,XX,+21)
- Edwards syndrome (trisomy 18: 47,XX,+18)
- Patau syndrome (trisomy 13: 47,XX+13)

**Sex chromosomes**
- Turner syndrome 45,X
- Klinefelter syndrome 47,XXY

**All chromosomes**
- Triploidy (69 chromosomes)
Chromosomal findings in early miscarriages

40% apparently normal

60% abnormal:

- Trisomy (47 chromosomes – one extra) 30%
- 45,X (45 chromosomes – one missing) 10%
- Triploidy (69 chromosomes – three sets) 10%
- Tetraploidy (92 chromosomes – four sets) 5%
- Other chromosome anomalies (e.g. structural anomalies)
TRIPLOIDY

- Three copies of each chromosome making a total of 69 chromosomes.
- It occurs in 1 to 2% of all pregnancies.
- Most Triploid die early in preg - spontaneous miscarriages (~10%). Almost all other babies die later or are stillborn. Live born very rare.
- It is not hereditary.
- There are no specific risk factors.
- Not more common in older mothers.
- No increased risk in future pregnancies
TRIPLOIDY

Failure of meiotic division - 2 N gamete + haploid gamete of other parent = **Triploid Zygote** (69 XXX, 69 XXY, 69 XYY)
All trisomies (trisomy 21, 13, and 18) could be due to the following three causes:

- **NONDISJUNCTION**
- **TRANSLOCATION**
- **MOSAICISM**
NON-DISJUNCTION ERROR

- In either mitosis or meiosis.

- If a meiotic error produces a gamete with 2 copies of an A chromosome, fertilization with a normal gamete will result in trisomy for the A chromosome.

- Non-disjunction often occurs in the maternal oocyte, the incidence of which increases with maternal age.
In meiosis 1, a pair of homologous chromosomes fail to separate.

$\frac{46}{2} = 23$ ideally but nondisjunction causes
Non-dysJunction

47,XX + 21
Cause 2 : Translocation : Reciprocal and Robertsonian

For example : 46, XY, t (5; 10) STRUCTURAL ABNORMALITY ALSO

**RECIPROCAL TRANSLOCATION**

- Is usually an exchange of genetic material between non-homologous chromosomes

- Since the translocation is balanced and there is even exchange of material with no genetic information extra or missing, persons are healthy (46 chr)

- 6% can present as autism, intellectual disability or with congenital anomalies.

Occur due to errors in meiosis
A person with an unbalanced translocation has an increased risk of creating gametes with unbalanced chromosomes.

Unequal exchange = extra or missing chromosomes: 1 to 2% chance of trisomic fetus. Others will be carrier and normal offspring.
Robertsonian translocation

Two long arms of acrocentric chromosomes (14 and 21) join at the centromere with loss of short arms, producing balanced two copies of all major chromosomal arms and essential genes. The acrocentric chromosomes that are lost (therefore 45 chr) do not have much important genetic material.

Carriers of this translocation have a 5% of having a child with trisomy 21 due to inheritance of a long arm of chromosome 21.
Possible gametes from robertsonian translocation

Possible gametes from translocation

Trisomy 14 Lethal
Normal
Translocation Trisomy 21 Down syndrome
Monosomy 14 Lethal
Monosomy 21 Lethal
Balanced Translocation

Offspring when combined with normal gamete
Cause 3: MOSAICISM

- **Mosaic**: When an individual has two or more cell populations with a different chromosomal make up.
- Results when some of the cells in the body are normal and other cells have a trisomic or monosomic complement e.g.: trisomy 21 (46 XX / 47 XX + 21) (45% / 55%)

Some chromosomal anomalies can happen after conception like mosaicism. This can result from:

1. non-disjunction event during an early mitotic cell division in a normal embryo or
2. A trisomic embryo undergoes non-disjunction and some of the cells revert to a normal chromosomal rearrangement.

Because normal cells are also present in an mosaic, the clinical effect may be less severe.
MOSIACISM

Diagram showing the concept of mosaicism in genetics. It illustrates the fusion of genetic material from a sperm and an egg to form a fertilized egg, which then develops into an organism with varying chromosomal configurations. The diagram highlights the presence of 46 chromosomes in normal cells and the occurrence of mosaicism where a cell may be missing an X chromosome.
TRISOMY 21- DOWNS

• The incidence is 1 in 700 live births.

• Three causes of trisomy 21 are :
  ➢ **Non –disjunction** : 47, XY + 21 (92 to 95 % of cases)
  ➢ **Translocation**: 4.8 % of cases (most of the cases are sporadic (de novo), 1/3 rd of the cases the parents are carriers)
  ➢ **Mosaics**: 46 XX / 47 XX + 21 (2.7 % of the cases)
Trisomy 21 due to non-disjunction

Karyotype due to Robertsonian translocation for trisomy 21
Trisomy 18 (Edward syndrome)

- 1:7500 in liveborn and more common in abortion and stillbirth
- Severe mental retardation and multiple structural anomalies
Trisomy 13 (Patau syndrome)

- 1:20,000 in liveborn and more common in abortion and stillbirth
- Severe structural anomalies lead to death in one month
Recurrence risk of trisomies

- Karyotyping of the affected child will show the cause of trisomy. (non-disjunction / unbalanced translocation / mosaicism)

- KARYOTYPING OF BOTH THE PARENTS if required.

- If there is no translocation or mosaicism detected in the affected child there is no need to test parental karyotype.

- If there is no translocation in the affected child, the risk of another child with trisomy is 1% increase above the age related risk.
Recurrence risk of trisomies

- If balanced translocation is detected in the parents, then the recurrence risk is 1% in male carriers and 12% in female carriers.

- In a parent having a balanced translocation between chromosomes 21:21, the recurrence risk is 100%.

- If the translocation in the affected child is not inherited (de novo), then the parents have a less than 1% risk of having another affected child with Downs syndrome.
Recurrence risk of trisomies

- The risk of recurrence for a mosaic pattern is also 1% above the age related risk.

- In cases where translocation or mosaic pattern is detected in parents, prenatal invasive testing is MANDATORY.

- There is no increased risk in second degree relatives, unless caused by unbalanced translocation in the index case.

  But routine screening as done for all pregnancies should be done (Nuchal translucency and 11 to 14 week scan, blood screening and detailed anomaly scan)
# Recurrence Risk of Down's Syndrome

<table>
<thead>
<tr>
<th>Chromosomal Constitution</th>
<th>Risk to Offspring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Affected Child</strong></td>
<td><strong>Father</strong></td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>N</td>
</tr>
<tr>
<td>MOTHER &lt; 30 YRS</td>
<td></td>
</tr>
<tr>
<td>IN PRESENT PREG</td>
<td></td>
</tr>
<tr>
<td>MOTHER &gt; 30 YRS,</td>
<td></td>
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<tr>
<td>HAD BABY WITH DOWNS</td>
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<tr>
<td>BEFORE AGE 30</td>
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<tr>
<td>MOTHER &gt; 30 YRS,</td>
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<td>AFTER 30 YRS</td>
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## RECURRENCE RISK OF DOWNS SYNDROME

### CHROMOSOMAL CONSTITUTION

<table>
<thead>
<tr>
<th>AFFECTED CHILD</th>
<th>FATHER</th>
<th>MOTHER</th>
<th>RISK TO OFFSPRING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TRANSLOCATION</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14/21, 15/21, 13/21, 21/22</td>
<td>N</td>
<td>N</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>21/21</td>
<td>C</td>
<td>N</td>
<td>12%</td>
</tr>
<tr>
<td>21/21</td>
<td>C</td>
<td>N</td>
<td>2-3%</td>
</tr>
<tr>
<td><strong>TRANSLOCATION 21 / 21</strong></td>
<td></td>
<td></td>
<td>100%</td>
</tr>
<tr>
<td><strong>MOSAIC</strong></td>
<td>N</td>
<td>N</td>
<td>2-3%</td>
</tr>
</tbody>
</table>
Sex chromosome abnormalities (aneuploidy) are less severe in their effects because all but one of the X chromosome gets inactivated because of the Lyon hypothesis (Barr body) and the number of genes on the Y chromosome are limited.

Cause of sex chromosome aneuploidy are non-disjunction errors during meiosis. However, prenatal invasive testing should be done.

Recurrence risk in sex chromosome aneuploidies is very low.
Sex chromosome abnormalities (aneuploides)

MITOSIS AFTER FORMATION OF THE EMBRYO
TRIPLE XXX Syndrome

- Often goes undetected throughout life.
- They are often taller than normal and may have learning difficulties.
- Fully fertile and generally have chromosomally normal children.
TURNER SYNDROME (MONOSOMY X, 45 XO)

- 45 X karyotype
- Only monosomy compatible with life
- Live born females are usually mosaics (45,X/46 XX, 45,X/46, XY)
  Pure 45 X is often lethal.
- Cause: Occurs due to loss of the paternal X chromosome
  - Nondisjunction in male gamete
  - Structural abnormalities of X chromosome
  - One X chromosome is missing
  - Mitotic nondisjunction
- Phenotype is highly variable in mosaics.
- This abnormality is unrelated to maternal age.
Turner syndrome – monosomy X (45 XO)

Karyotype from a female with Turner syndrome (45,X)

Turner syndrome only affects girls.

It is caused by a problem with one of the X chromosomes.
Turners syndrome

Fertilized egg

Early embryo

45,X/46,XX

a. A female with Turner (XO) syndrome
47, XYY

- Patients are clinically indistinguishable from 46 XY.
- XYY often goes undetected throughout life.
- XYY affects 1 in 1000 live births and is the failure of paternal meiosis.
- Characteristics include tall structure, normal intelligence and normal fertility.
KLINEFELTER’S SYNDROME - 47, XXY

- Have 47 chromosomes (XXY) & a sex chromatin Barr body or 48(XXXY); more the number of X more the chances of mental impairment.
- **Cause:** 50 % are due to meiosis 1 error in the father
  - Nondisjunction of XX homologue
- Found only in males, detected at puberty
- **Incidence** ---1 in 500 males
- **S/S:**
  - Sterility, testicular atrophy, hyalinization of seminiferous tubules, gynecomastia.
KLINEFELTER’S SYNDROME - 47, XXY
Thanks!