Chromosome Disorders

Chromosome Abnormalities

The development of chromosome analysis in 1956 led to the discovery of several abnormality in chromosome number:

- Down syndrome (47,XXXY, +21),
- Klinefelter syndrome (47,XXY),
- Turner syndrome (45,X)

To date, at least 20,000 chromosomal abnormalities have been registered.

A large proportion of spontaneous pregnancy loss, childhood disability and malignancies.

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13</td>
<td>2</td>
</tr>
<tr>
<td>Trisomy 16</td>
<td>15</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>3</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>5</td>
</tr>
<tr>
<td>Other Trisomy</td>
<td>25</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>20</td>
</tr>
<tr>
<td>Triploidy</td>
<td>15</td>
</tr>
<tr>
<td>Tetraploidy</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
</tr>
</tbody>
</table>

Spontaneous pregnancy loss in commonly recognized aneuploidy syndromes

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Proportion undergoing spontaneous pregnancy loss(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13</td>
<td>95</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>95</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>80</td>
</tr>
<tr>
<td>Monosomy X</td>
<td>98</td>
</tr>
</tbody>
</table>


Down Syndrome (Trisomy 21)

- Derives its name from **Dr Langdon Down**, who first described it in 1866
- The chromosomal basis was established in **1959**
- Incidence is approximately 1:1000 in UK, 1:800 in USA
- Down syndrome and advancing **maternal age**

**Increased Risk of Down Syndrome with Maternal Age**

![Graph showing increased risk of Down Syndrome with maternal age]
Down Syndrome Clinical Features

- Congenital cardiac abnormalities in 40% to 45%

- Severe hypotonia in the newborn period

- Facial characteristics of
  - small ears,
  - protruding tongue,
  - upward sloping palpebral fissures

- Single palmar creases are found in 50%

Natural History

- IQ scores ranging from **25 to 75**, average of young adults is around 40 to 45
- Social skills are relatively well-advanced and most children are happy and very affectionate.
- Adult height is usually around **150 cm**
- Average life expectancy is 50 to 60 years, early death in 15% to 20% of cases
- Most affected adults develop **Alzheimer disease**

Chromosome Findings

- Trisomy in **95%**, 90% extra maternal chromosome
- Robertsonian translocations approximately **4%** of all cases, one-third have a carrier parent
- Mosaicism **1%**, are often less severely affected
- Down syndrome 'critical region' at the distal end of the long arm (21q22)
Recurrence Risk

- For straightforward trisomy 21, is related to maternal age, usually between 1:200 and 1:100

- In familial translocation cases, vary from around
  - 1% to 3% for male carriers
  - up to 10% to 15% for female carriers

- For carriers of a 21q21q translocation, the recurrence risk is 100%

Patau Syndrome (Trisomy 13), Edwards Syndrome (Trisomy 18)

- Incidence for both is approximately 1:5000

- Prognosis is very poor, with most infants dying during the first days or weeks of life

- Cardiac abnormalities occur in at least 90% of cases

- Both occur more frequently with advanced maternal age
Trisomy 13 (Patau Syndrome)

Clumsiness or mild learning difficulties, in childhood
Verbal IQ is reduced by 10 to 20 points
Adults tend to be slightly taller than average
Approximately 30% show gynecomastia (breast enlargement)
All are infertile (azoospermia)

Treatment with testosterone from puberty onward for the development of secondary sexual characteristics

Trisomy 18 (Edward Syndrome)

Klinefelter Syndrome (47,XXY)

1:1000 male live births
Clumsiness or mild learning difficulties, in childhood
Verbal IQ is reduced by 10 to 20 points
Adults tend to be slightly taller than average
Approximately 30% show gynecomastia (breast enlargement)
All are infertile (azoospermia)

Treatment with testosterone from puberty onward for the development of secondary sexual characteristics
**Chromosome Findings**

- Usually the karyotype shows an additional X chromosome, equal chance from mother or father.
- A small proportion of cases show mosaicism (e.g., 46,XY/47,XXY).
- Rarely, with more than two X chromosomes can be encountered, for example 48,XXXY or 49,XXXXY.

**Turner Syndrome (45,X)**

- The absence of a Barr body, was noted in 1954 and cytogenetic confirmation in 1959.
- Common in spontaneous abortions, 1:5000 to 1:10,000 in live born female infants.

**Clinical Features**

- May look normal at birth, some show edema with puffy extremities and neck webbing.
Clinical Features

- Intelligence in Turner syndrome is normal.

- The two main medical problems are:
  - Short stature
    - Without growth hormone treatment: 145 cm
    - Haploinsufficiency for the SHOX gene
  - Ovarian failure
    - Lead to infertility
    - Estrogen replacement therapy should be initiated at adolescence.

Chromosome findings in Turner syndrome

<table>
<thead>
<tr>
<th>Karyotype</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monosomy X 45,X</td>
<td>50</td>
</tr>
<tr>
<td>Mosaicism (e.g., 45,X/46,XX)</td>
<td>20</td>
</tr>
<tr>
<td>Isochromosome X 45,X,i(Xq)</td>
<td>15</td>
</tr>
<tr>
<td>Ring 46,X,r(X)</td>
<td>5</td>
</tr>
<tr>
<td>Deletion 46,X,del(Xp)</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
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XXX Females

- Approximately 0.1% of all females have a 47,XXX karyotype.
- Usually have no physical abnormalities, but can show a mild reduction in intellectual skills.
- Adults are usually fertile and have children with normal karyotypes.
- Women with more than three X chromosomes show a high incidence of learning difficulties.
**XYY Males**

- Incidence of about 1:1000 in males in newborn.
- Physical appearance is normal and stature is usually above average, fertility is normal.
- Intelligence is mildly impaired, with an overall IQ score of 10 to 20 points below a control sample.
- The additional Y chromosome must arise either as a result of non-disjunction in paternal meiosis II or as a post-zygotic event.

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**Parental origin of meiotic error leading to aneuploidy**

<table>
<thead>
<tr>
<th>Chromosome Abnormality</th>
<th>Paternal (%)</th>
<th>Maternal (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>15</td>
<td>85</td>
</tr>
<tr>
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<td>10</td>
<td>90</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>45, X</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>47, XXX</td>
<td>5</td>
<td>95</td>
</tr>
<tr>
<td>47, XXY</td>
<td>45</td>
<td>55</td>
</tr>
<tr>
<td>47, XYY</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

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**Wolf-Hirschhorn (4p−) and Cri-du-chat (5p−)**

- Deletions of the terminal portions of chromosomes 4 (4p−)
  - **Wolf-Hirschhorn**
  - Severe learning conditions
  - There is considerable variability
  - 1:50,000 births

- Deletions of the terminal portions of chromosomes 5 (5p−)
  - **Cri-du-chat**
  - Severe learning conditions
  - Cat-like cry of affected neonates
  - 1:50,000 births
Indications for Chromosome Analysis

- Multiple congenital abnormalities
- Unexplained mental retardation
- Sexual ambiguity or abnormality in sexual development
- Infertility
- Recurrent miscarriage
- Unexplained stillbirth
- Malignancy and chromosome breakage syndromes
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