Chromosomal Aberrations

• The somatic (2n) and gametic (n) chromosome numbers of a species ordinarily remain constant.
• This is due to the extremely precise mitotic and meiotic cell division.
• Somatic cells of a diploid species contain two copies of each chromosome, which are called homologous chromosome.
• Their gametes, therefore contain only one copy of each chromosome, that is they contain one chromosome complement or genome.
• Each chromosome of a genome contains a definite numbers and kinds of genes, which are arranged in a definite sequence.
• Presence of the whole sets of chromosomes is called **Euploidy**.

• IT includes haploids, diploids, triploids, tetraploids,......

• In human, the normal chromosome complement is haploid number in gametes (**n,23chr.**) and diploid in somatic cells (**2n,46chr**).
Chromosomal Aberrations ...cont

• Chromosomal aberration are grouped into two broad classes:

  1. **Numerical**
  2. **Structural**
Chromosomal Abnormalities

A- Numerical abnormalities; change in chr. number:
   1- Aneupliody; increase or decrease in one or more of chr. 2n+1 or 2n-1...
   2- Polypliody: increase in a whole set of chr. 3n, 4n,.....

B - Structural abnormalities; change in chromosome structure.
Aneuploidy

• The variation in chromosome number not involved the whole set.
• Most commonly involve increase or decrease in one chromosome.
• May be in autosomes or sex chr.
• The main cause is non disjunction during gametogenesis.
• **Trisomy** : increase in one chr. (47 chr.)
• **Monosomy** : decrease in one chr. (45 chr.)
• **Tetrasomy** : increase in two chr. (48 chr)
Aneuploidy

**Autosomal Trisomy**
- Most are lethal
- 50% of cases of chromosomal abnormalities that cause fetal death are autosomal trisomies.

**Autosomal Monosomy**
- Lethal condition
- Rarely seen in spontaneous abortions and live births
- Majority are lost early in development.
Incidence

• More than 50% of spontaneous abortions are chromosomal abnormal.
• The earlier the abortion the more likely to be chromosomal.
• Mostly triploidy, 45 XO and trisomy 16.
• 98% of fetus with turner abort.
• Generally 7/1000 the incidence of chromosomal abnormalities in live births.
• 5-7% of early death in children are related to anuploidy.
# Chromosome abnormalities in miscarriages

<table>
<thead>
<tr>
<th>Condition</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>
Autosomal Trisomy

Survey of 4,088 spontaneous abortions
# Chromosome abnormalities in newborns

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Incidence / 10,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13</td>
<td>2</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>3</td>
</tr>
<tr>
<td>Trisomy 21</td>
<td>15</td>
</tr>
<tr>
<td>45,X</td>
<td>1</td>
</tr>
<tr>
<td>47,XXX</td>
<td>10</td>
</tr>
<tr>
<td>47,XXY</td>
<td>10</td>
</tr>
<tr>
<td>47,XYY</td>
<td>10</td>
</tr>
<tr>
<td>Unbalanced</td>
<td>10</td>
</tr>
<tr>
<td>Balanced</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
</tr>
</tbody>
</table>
Variations in Chromosome Number

Summary:

- **Polyploidy** – a chromosome number that is a multiple of the normal haploid set

- **Aneuploidy** – a chromosomal number that varies by something less than a set
  - **Monosomy** – having only one member of a homologous pair
  - **Trisomy** – having three copies of a single chromosome
Causes of Aneuploidy

• 1 – Non-disjunction (ND): is the failure of a pair of chromosomes to separate (or associate) during cell division resulting in unequal distribution of the chromosomes between the two daughter cells.
  - The most common cause of aneuploidy is ND in meiosis in females.

• 2 – Anaphase lag: is failure of a chromosome to be oriented to any of the daughter cells (loss of a chromosome). It will result in one abnormal daughter cell (monosomy) and one normal cell.
Most Common Cause of Aneuploidy Is Nondisjunction in Meiosis

• **Nondisjunction** is the failure of homologs or sister chromatids chromosomes to separate in meiosis or mitosis.

• Produces abnormal gametes.

• Phenotypic effects of aneuploidy vary widely.
Nondisjunction

Chromosome alignments at metaphase I

Nondisjunction at anaphase I

Alignments at metaphase II

Anaphase II

Chromosome number in gametes:

- $n + 1$
- $n + 1$
- $n - 1$
- $n - 1$
Non-Disjunction

• Generally during gametogenesis, the homologous chromosomes of each pair separate out (disjunction) and are equally distributed in the daughter cells.
• But sometime there is an unequal distribution of chromosomes in the daughter cells.
• The failure of separation of homologous chromosome is called non-disjunction.
• This can occur either during mitosis or meiosis or embryogenesis.
• **Mitotic non-disjunction**: The failure of separation of homologous chromosomes during mitosis is called mitotic non-disjunction.
• It occurs after fertilization.
• May happen during early or late cleavage.
• Here, one cell will receive 45 chromosomes, while other will receive 47.
• Usually the cell with 45 chr. will die.
• The cell with 47 chr. will divide and give a cell line with 47 chr.
• This will cause an individual with karyotype 46/47 chromosomes (mosaic).
• **Meiotic non-disjunction**: The failure of separation of homologous chromosomes during meiosis is called meiotic non-disjunction.

• Occurs during gametogenesis.

• If ND occurs in meiosis I, two gametes will contain 22 chromosome, while the other two will be contain 24 chromosomes.

• If ND occurs in meiosis II, two gametes will contain 23 chromosome (normal), one will be contain 24 chromosomes and one with 22 chromosomes.
Aneuploidy

- **Trisomy**: results from fertilization between one normal gamete & another gamete that contains an extra chromosome.
- **In Humans**: Autosomal Trisomy usually results in spontaneous abortion.

- The only autosomal trisomies seen in live births are **trisomy 13, 18 and 21**.
- Trisomosy 21 (Down Syndrome) is the only autosomal trisomy that allows survival until adult hood.
Aneuploidy ...cont

- **Monosomy**: results from fertilization between one normal gamete & one gamete that is **missing a chromosome**.
- **In Humans**: Autosomal monosomy extremely serious (considered lethal). *Embryo usually ceases development very early (spontaneous abortion).*
- The only monosomy seen in humans is **Turner syndrome** (*45,XO*)
Uses of Aneuploidy

• They have been used to determine the phenotypic effect of loss or gain of different chromosome

• Aneuploidy permits the location of a gene as well as of a linkage group onto a specific chromosome.
Aneuploidy in Human

- Seven types occur in live births:
  - Three in autosomes.
  - Four involving sex chromosomes.

## Autosomal Aneuploidy in Human

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency (# of live births)</th>
<th>Syndrome</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>1/800</td>
<td>Down</td>
<td>Mental retardation, abnormal pattern of palm creases, slanted eyes, flattened face, short stature</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>1/6,000</td>
<td>Edward</td>
<td>Mental and physical retardation, facial abnormalities, extreme muscle tone, early death</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>1/15,000</td>
<td>Patau</td>
<td>Mental and physical retardation, wide variety of defects in organs, large triangular nose, early death</td>
</tr>
</tbody>
</table>
Trisomy 21: Down Syndrome (47,+21)

- First chromosomal abnormality discovered in humans (1959)
- The best known and most common chromosomal syndrome.
- 1/700 live births.
- 2/3 of down fetus spontaneously abort.
- Trisomy 21 in 94% of cases with extra chromosome from mother.
- Risk correlate with maternal age
  - <25 y/o 1/1600
  - >40 y/o 1/80
- 2% are mosaic.
- Leading cause of mental retardation and heart defects in US.
Clinical features

- Patients having Down syndrome have Short stature, epicanthal fold, broad short skulls, wild nostrils, large and protruding tongue, stubby hands, short necks, small hands, and short fingers, poor muscle tone (hypotonia).
- All parts of their bodies are shortened due to poor skeletal development, including the hands and fingers.
- They have low IQ (mentally retarded).
- Hypothyriodism.
- 50% of the children with Down syndrome are born with severe heart malformations.
- 15% of the babies die in their first year from heart abnormalities.
- Many others die before the age of 5.
- Those who do live beyond the fifth year of life have an average life expectancy of 50 years.
Down syndrome, trisomy 21

47,XX,+21 or 47,XY,+21
MATERNAL EFFECT

• The risk for mothers less than 25 years of age to have the trisomy is about 1 in 1500 births.
• At 40 years of age, 1 in 100 births
• At 45 years 1 in 40 births.
• Frequency of Down syndrome births increases with advancing maternal age
Incidence of Down Syndrome Increases with Maternal Age

All eggs are formed by birth and arrested in meiosis; the correlation of increased age and the syndrome due to more non-disjunction in older eggs.
MATERNAL EFFECT

• The effect may be a consequence of the long delay between prophase I and the first meiotic division in human oocytes.
• Human oocytes begin meiosis before the female is born.
• They remain in a state of suspended animation until the girl hits puberty about 13 years later.
• Egg ovulated by a 45 year old female has been in suspended animation for 45 years.
• Plenty of time for exposure to mutagens.
Trisomy 13:
Patau Syndrome (47,+13)

- 1/15,000 births
- Lethal; mean survival time 1 month.
- Facial malformations, eye defects, extra fingers or toes.
- Severe malformations of brain, nervous system, and heart.
- Parental age only known risk factor.
Patau Syndrome

- Main Phenotypic Characteristics:
  - Mental deficiency
  - Micrcephaly
  - Growth failure
  - Deafness
  - Cleft lip and palate
  - Deformed ears
  - Cardiac anomalies
  - Polydactyly
Edwards syndrome (trisomy 18)
Karyotype: 47, +18

• 1/11,000 births
• Average survival time 2–4 months
• Affected infants small at birth grow slowly and are mentally retarded
• Multiple congenital malformation of many organs as heart, malformed ears, small mouth and nose, malformed hands, and feet
• 90% die in the first 6 months.
• For unknown reasons 80% of all trisomy 18 are female
• Advanced maternal age is a risk factor
Edwards syndrome (trisomy 18)

Malformed hands and feet
Sex Chromosome Aneuploidy

- Sex Chromosome aneuploidy is more common than Autosome Aneuploidy!
- In order to survive and develop embryo needs at least one X chromosome.
- Y chromosome carries a gene called SRY that codes for testosterone production. This turns indifferentiate gonads into male testes.
- SEX is determined by the PRESENCE or ABSENCE of a “Y” chromosome
- An individual who has an intact Y-chromosome will be male, regardless of the number of X chromosomes he possesses.
- In the absence of an intact Y chromosome an individual will be female.
- In healthy females, one X chromosome will be inactivated in each somatic cell. The inactivated X chromosome is referred to as a “Barr body”.
Barr Bodies

- **females XX, males XY**
- Females have two copies of every X-linked gene; males have only one.
- How is this difference in gene dosage compensated for? OR
- How to create equal amount of X chromosome gene products in males and females?
- In cells with two X chromosomes or more, only one X remains genetically active and all the others become inactivated.
- Levels of enzymes or proteins encoded by genes on the X chromosome are the same in both males and females.
- In human embryos, sex chromatin bodies have been observed by the 16\textsuperscript{th} day of gestation.
Barr Bodies

Barr bodies represent the inactive X chromosome and are normally found only in female somatic cells.
A woman with the chromosome constitution 47, XXX should have 2 Barr bodies in each cell.

- **XXY** individuals are male, but have a Barr body.
- **XO** individuals are female but have no Barr bodies.
Sex Chromosomes Aneuploidy

- Abnormalities more tolerated
- If have extra Y, few genes mainly for sex determination
- If have extra X, excess X is inactivated
- There have been no reported cases of cases being born without the X chromosome, indicating that the X chromosome contains genes that are vital for the survival and development.
Common Sex Chromosome Aneuploidy

- Turner Syndrome (female) 45,XO
- Trisomy X (female) 47, XXX
- Klinefelter Syndrome (male) 47,XXY
- Extra “Y” chromosome (male) 47,XYY
# Sex Chromosomes Aneuploidy in Human

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency (# of live births)</th>
<th>Syndrome</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXY</td>
<td>1/1,000 (males)</td>
<td>Klinefelter</td>
<td>Sexual immaturity (no sperm), breast swelling (males)</td>
</tr>
<tr>
<td>XYY</td>
<td>1/1,000 (males)</td>
<td>Jacobs</td>
<td>Tall</td>
</tr>
<tr>
<td>XXX</td>
<td>1/1,500 (females)</td>
<td>Triple X</td>
<td>Tall and thin, menstrual irregularity</td>
</tr>
<tr>
<td>XO</td>
<td>1/5,000 (females)</td>
<td>Turner</td>
<td>Short stature, webbed neck, sexually undeveloped</td>
</tr>
</tbody>
</table>
Nondisjunction of X chromosome

Diagram showing the process of nondisjunction in the division of chromosomes during meiosis. The diagram includes stages of division and fertilization events leading to different genetic outcomes such as Klinefelter syndrome, Turner syndrome, and normal sex chromosome configurations.
Klinefelter syndrome

- In males, Klinefelter’s has an extra X (XXY)
- 47 XXY in 80% and mosaic in 20%
- IQ is normal
- Male hypogonadism
- Elongated body
- Reduced body hair
- Developed breast
- Feminine
- Testis atrophy (blocked spermatogenesis) → azoospermia → sterility
XYY Syndrome: 47, XYY

- 1/1000 births
- Males above average in height
Turner syndrome

- Most common abnormality in early abortion
- 1/10,000 births
- Female, short stature, primary amenorrhea, sterility, spares hair and underdeveloped breast
- Neonatal: wide spaced nipple, shield chest
- Cardiac abnormalities
- Normal IQ scale
- Present with short stature and delay sex maturation
- infertile
- Secondary sex characters can be treated by hormonal therapy
Turner Syndrome

- Short
- Absence of a menstrual period
- Produce little estrogen
- Sterile
- Extra skin on neck
## Parental origin of aneuploidy

<table>
<thead>
<tr>
<th></th>
<th>Paternal %</th>
<th>Maternal %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 13</td>
<td>15</td>
<td>85</td>
</tr>
<tr>
<td>Trisomy 18</td>
<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>
Polyploidy

• Presence of additional set of chromosomes; 3n, 4n, 5n ...

• Origin
  – Failure of the spindle mechanism after the chromosomes have been duplicated which result in 2n gamete.
  – Multiple sperm fertilize an egg

• Polyploidy is present in certain cells of the body, some liver cells, and frequently seen in the chromosomes of tumour tissues.

• Experimentally produced by cold or heat shock during meiosis or by colchicine
Polyploidy

Caused by

• Errors in meiosis
• Events at fertilization
• Errors in mitosis
Triploidy

- Complete extra set of chromosomes, $3n$; 69 chromosomes.
- Most common form of human polyploidy.
- 15-18% of all spontaneous abortions.
- Approximately 75% have two sets of paternal chromosomes, probably due to polyspermy, fertilization by two sperms.
- Two types:
  - Digynic; the extra chromosomal set is maternal.
  - Diandric; the extra set is paternal.
- Fetal wastage skeleton more than cephalic, 2% survive to be recognized.
- 1% conceptions are triploid but 99% die before birth (lethal condition).
- Genital and CNS abnormalities.
Triploid Karyotype (69, XXY)
Tetraploidy

- Four sets of chromosomes (92)
- 5% of all spontaneous abortions
- Extremely uncommon in live births
- May result from failure of cytokinesis in the 1\textsuperscript{st} mitotic division of the zygote
- Mosaics occur, mixture of diploid and tetraploid cells.
- Life threatening