Basic Human Genetics: Reproductive Health and Chromosome Abnormalities

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Training Course in Sexual and Reproductive Health Research - Geneva 2017
Categories of Genetic Diseases

- **Single gene abnormalities**
  - Autosomal dominant
  - Autosomal recessive
  - X-linked
  - Mitochondrial
  - Imprinting

- **Chromosomal abnormalities**
  - Numerical
  - Structural
  - Microdeletions

- **Multifactorial abnormalities** e.g. diabetes

- **Acquired somatic abnormalities** e.g. cancer
Types of Chromosome Abnormalities

**Numerical:**
- Trisomy
- Monosomy
- Mosaicism
- Triploidy

**Structural:**
- Translocation
- Deletion
- Inversion
- Microdeletions & microinsertions
46 Chromosomes in a human cell as seen under the microscope
Frequencies of chromosome abnormalities

- A chromosome abnormality is present in 40-50% of all recognized first-trimester pregnancy loss. Approximately 1 in 6 of all pregnancies results in spontaneous miscarriage.

- Birth prevalence of chromosome abnormalities is 0.5-1%
Chromosome abnormalities can cause:

- Infertility
- Repeated spontaneous abortions
- Stillbirths
- Infant mortality
- Birth defects
- Sexual ambiguity or abnormality in sexual development
- Unexplained short stature in female children
- Intellectual disability
Trisomy

Presence of an extra chromosome, the total number of chromosomes is 47 in a somatic cell.

Trisomy usually results from meiotic non-disjunction

There are 3 of number 21 chromosomes
Monosomy

- Absence of one chromosome, so the total number of chromosomes is 45 chromosomes in a somatic cell.
- Usually only seen as 45,X, (autosomal monosomy is usually lethal).
- Monosomy usually results from meiotic non-disjunction.
Mosaicism

There are 2 types of cells in an individual, for example normal 46,XY cells and abnormal trisomic cell line 47,XY,+21

The two cell lines are derived from the same zygote due to mitotic non-disjunction
Triploidy

- Presence of 3 haploid sets: $23 \times 3 = 69$ chromosomes
- (haploid set =23, diploid set =46)
- Usually incompatible with life and seen only in abortions.
- May result from 2 sperms fertilizing the ovum or retention of the polar body with the ovum
Normal meiosis, the 46 chromosomes become 23 in each gamete
Non-disjunction during meiosis means that one daughter cell gets 24 chromosomes and the other 22 chromosomes.
Fertilisation of the gamete carrying 24 chromosomes (extra number 21) with a normal gamete having 23 chromosomes results in a zygote of 47 chromosomes (trisomy 21 zygote)
Reciprocal translocation = exchange of segments between 2 non-homologous chromosomes

Exchange of segments
Robertsonian translocation occurs between 2 acrocentric chromosomes with breaks near centromeres and union of the long arms.
Carriers of balanced translocations are healthy but...

- They are at risk of having offspring with unbalanced chromosome constitution
- This may present as:
  - Repeated spontaneous abortions
  - Stillbirths
  - Birth defects
  - Intellectual disability
Deletion: loss of part of a chromosome
Pericentric inversion: two breaks with inversion of the segment in between
Karyotype description

- 46,XX  normal female karyotype
- 46,XY  normal male karyotype
- 45,X  monosomy X = Turner syndrome
- 47,XY,+21  trisomy 21 = Down syndrome
- 46,XY, 5p- deletion of part of short arm of chromosome 5 = Cri du Chat syndrome
- 46,XX, t(2;4)(q22;q23) translocation between long arms of chromosomes 2 and 4 with breakpoints at region 2 band 2 for chromosome 2 and region 2 band 3 for chromosome 4.
Consequences of chromosome abnormalities

- Infertility: examples: Turner and Klinefelter syndromes
- Repeated spontaneous abortions: healthy carriers of translocations and inversions
- Stillbirths and infant deaths: where the chromosome abnormality is very severe for example trisomy 13 and trisomy 18
- Congenital disorders: for example Down syndrome, microdeletion syndromes
Syndromes with chromosome abnormalities
Chromosome abnormalities at birth

- Trisomy 13  0.2/1000 births
- Trisomy 18  0.3/1000 births
- Trisomy 21  1.5/1000 births
- 45,X      0.2/1000 female births
- 47XXX     1/1000 female births
- 47,XXY    1/1000 male births
- 47,XYY    1/1000 male births
- Other unbalanced rearrangements  1/1000 births
- Balanced rearrangements Total  3/1000 births
Down syndrome (DS)

- The overall prevalence at birth is approximately 1 in 650 to 1 in 700 births
- May be higher in some countries where women continue to bear children at an advanced age
Clinical features of DS

- The most common finding in the newborn period is severe hypotonia.
- Single palmar creases are found in 50% of Down syndrome children in contrast to 2-3% of the general population.
- Congenital cardiac abnormalities are present in 40-45% of babies with Down syndrome.
- Hypothyroidism.
Facial features of DS

- upward sloping palpebral fissures
- brushfield spots and bilateral epicanthic folds.
- small ears
- protruding tongue
Natural history of DS

- Affected children show a broad range of intellectual disability with IQ scores ranging from 25 to 75. The average IQ of young adults with Down syndrome is around 40 to 45.

- Social skills are relatively well advanced and most children with Down syndrome are happy and very affectionate.
Natural history of DS

- Adult height is usually around 150cm.

- In the absence of a severe cardiac anomaly, which leads to early death in 15-20% of cases, average life expectancy is 50-60 years.

- Most affected adults develop Alzheimer disease in later life due to dosage effect of the amyloid precursor protein gene.
Chromosome abnormalities in Down syndrome

- 95% of cases are trisomy 21, 47,XX,+21 (47,XY,+21), risk of having trisomy 21 increases with advanced maternal age.

- 4% are due to translocation between chromosome 21 and another acrocentric with a total number of chromosomes =46, but the genetic material of chromosome 21 is present in triplicate. The translocated chromosome is usually inherited from a normal carrier parent. Such a translocation carrier parent has a risk of having a Down syndrome with each pregnancy (about 20% if mother is carrier and 5% if father is carrier).

- 1% mosaic cases (46,XY/47,XY,+21).
<table>
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<th>Maternal Age at Delivery (yr)</th>
<th>Risk of Down's Syndrome</th>
<th>Risk of Any Chromosomal Abnormality</th>
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Meiosis in Robertsonian translocation carrier who has 45 chromosomes (only one 21) but the other chromosome 21 is translocated to chromosome 22 = normal amount of genetic material
The gamete carrying 23 chromosomes but one is a translocation 21/22 is fertilised by a normal gamete resulting in a zygote with translocation Down syndrome
Turner syndrome: monosomy X

- The two main medical problems are short stature and ovarian failure.
- Ovarian failure leads to primary amenorrhea and infertility.
- Estrogen replacement therapy should be initiated at adolescence for the development of secondary sexual characteristics and long-term prevention of osteoporosis.
Normal female karyotype and Monosomy X
Turner syndrome features

- lymphedema at birth
- low posterior hair-line
- increased carrying angles at the elbows
- short fourth metacarpals
- widely spaced nipples
- coarctation of the aorta present in 15% of cases
Chromosome anomalies in Turner syndrome

- $45,X = 50\%$
- mosaics: $46,XX/45,X = 35\%$
- Structural abnormalities
  (deletion, isochromosome, ring X)
Turner syndrome is being detected early in pregnancy as a result of routine detailed ultrasound scanning, which can reveal either generalized edema (hydrops) or swelling localized to the neck (nuchal cyst or thickened nuchal pad).
Klinefelter syndrome: 47,XXY

- Infertility
- Hypogonadism
- Diminished secondary sexual characters
- Clumsiness or mild learning difficulties. The overall verbal IQ is reduced by 10-20 points below that of unaffected siblings and controls
- 30% of adult males will show gynecomastia (enlargement of the breasts)
Chromosome abnormalities in Klinefelter syndrome

- 47,XXY
- 48,XXXY, 48,XXYY
- 49,XXXXY
- 46,XY/47,XXY
XYY male
XYY MALES

- Fertility is normal.
- Physical appearance is normal and stature is usually above average.
- Intelligence is mildly impaired, with an overall IQ score of 10-20 points below a control sample.
- The additional Y chromosome must arise as a result of non-disjunction in paternal meiosis II or as a post-zygotic event.
XXX females

- These women usually have no physical abnormalities but can show a mild reduction of between 10 and 20 points in intellectual skills below their siblings. This is rarely of sufficient severity to require special education.

- Women with a 47,XXX karyotype usually show normal fertility and have children with normal karyotypes.
Chromosome microdeletion syndromes
Prader-Willi syndrome

▪ Hypotonia
▪ Poor sucking and feeding in neonates
▪ Fair skin and hair
▪ Downturned mouth corners and narrow bifrontal diameter
▪ Hyperthermia
▪ Gestational History of diminished fetal movements
▪ Hyperphagia and Obesity
▪ Short stature
▪ Small hands and feet
▪ Mental subnormality
▪ Hypogonadotropic hypogonadism
▪ Caused by microdeletion of paternal 15q11.2-12 (75%)
Diagnosis of microdeletion syndromes

- FISH techniques using specific probes
- Array comparative genomic hybridisation (array CGH)
- Microdeletions usually cannot be detected in the standard banded karyotype
Prader-Willi Syndrome

Fluorescent in situ hybridization (FISH) demonstrating deletion (del) of SNRPN probe on one of the chromosomes 15s.
Indications for chromosome analysis in lymphocytes

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

- Around 20,000 chromosome abnormalities have been registered in laboratory databases

- Chromosome abnormalities contribute to about 8% of all birth defects

- Chromosome abnormalities can be diagnosed in the fetus through chorion villus biopsy or amniocentesis (prenatal diagnosis), or by preimplantation genetic diagnosis following IVF