Chromosomal Disorders

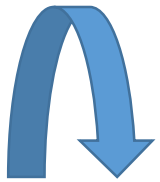
Prof. Dr. Hatice Ilgın Ruhi
Medical Genetics

Mechanisms of Chromosome Abnormalities and Genomic Imbalance

Spontaneous Pregnancy Loss in Commonly Recognized Aneuploidy Syndromes

Aneuploidy

- Trisomy 21
- Trisomy 18
- Trisomy 13



Intellectual disability

Dysmorphic facial features and multiple congenital anomalies

Developmental abnormalities and growth retardation

Life expectancy

- Trisomy 21 → 50-60 yr
- Trisomy 18 → Typically less than a few months, almost all < 1 yr
- Trisomy 13 → 50% die withinfirst month, >90% within first year

Down syndrome

DS

Dr. Langdon Down → 1866

Lejeune et al → 1959

incidence :1/850

There is a strong association between the incidence of DS and advancing maternal Age…

Common Findings in Down Syndrome

- **Newborn period:** Hypotonia, sleepy, excess nuchal skin
- **Craniofacial:** Brachycephaly, epicanthic folds, protruding tongue,small ears, upward sloping palpebral fissures
- **Limbs:** Single palmar crease, small middle phalanx of fifth finger, wide gap between first and second toes
- **Cardiac:** Atrial and ventricular saptal defects, common atrioventricular canal, patent ductus arterious
- **Other:** Anal atresia, duodenal atresia, Hirschsprung disease, short stature, strabismus

Natural History

- Intellectual disability (IQ scores 25-75 → average: 40-45)
- Social skills are relatively well (happy, very affectionate)
- Neonatal period → a fifteen fold increase in the risk for leukemia
- Adult height; ~ 150 cm
- Early death; 15-20%
- About 90% of live-born DS cases reach 20 years of age.
- Life expectancy; 50-60 yr
- Adult DS cases → Alzheimer disease risk ↑ (gene dosage effect; the amyloid precursor protein gene is on chr 21)

Chromosome Findings

- Trisomy (47,XX,+21 – 47,XY,+21) → 95%
- Translocation (46,XX,rob(14;21)(q10;q10),+21)→ 4%
- Mosaicism → 1%
- Partial trisomy → very rarely (DSCR; 21q22)

Recurrence Risk

- Trisomy 21 → ~ 1%
- Familial translocation;
  - Male carrier → 1% - 3%
  - Female carrier → 10% - 15%
- 21q21q translocation carriers → 100%

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

- These are very severe conditions.
- The incidence for both → ~ 1:5000
- The prognosis is very poor.
- Severe mental retardation
- Growth retardation
- Congenital malformation

Trisomy 18

- Dolichocephaly
- Prominent occiput
- micrognathia
- Low-set, malformed auricles
- Short sternum
- Clenched hand
- rocker-bottom feet
- Hypoplasia of nails
- Different dermatoglyphics

Trisomy 13

- Holoprosencephaly type defect
- Microcephaly
- Microphthalmia
- Cleft lip /palate
- Scalp defects
- Cardiac anomalies
- polydactyly

Disorders of the Sex Chromosomes

- Klinefelter Syndrome (47,XXY)
- Turner Syndrome (45,X)
- XXX Females (47,XXX)
- XYY Males (47,XYY)

Klinefelter Syndrome

- Prevalence: 1/600-1/1000
- Tall male
- Verbal IQ reduced to low-normal range, educational problems
- Behavioral phenotype: No major disorders, tendency poor social adjustments
- Hypogonadism, infertility
- 48,XXXY, 48,XXYY etc. (variant karyotypes)

Turner Syndrome

- Prevalence: 1/2500-4000
- Short stature,webbed neck, lymphedema
- Cardiac abnormalities
- Typically normal, but performance IQ lower than verbal IQ
- Behavioral phenotype: Typically normal, but impaired social adjustments
- Gonadal dysgenesis, delayed maturation, infertility
- 46,Xi(Xq), 45,X/46,XX etc (variant karyotypes)

Turner Syndrome

45,X	50-60%
Mosaics	20-25%
46.X,i(Xq)	15%

Monosomy X → an example compatible with survival (pregnancy loss 98%)

In 80% of cases, it arises through loss of a sex chromosome (X or Y) at paternal meiosis.

Mosaic cases with a Y chromosome → 15-20% gonadoblastoma risk

XXX Females

- Prevalence: 1/1000
- Tall female, delayed milestones
- Normal to low-normal range, learning difficulties
- No behavioral problem, reduced social skills
- Usually fertile
- 48,XXXX, 49,XXXXX etc. (variant karyotypes)

XYY Males

- Prevalence: 1/1000
- Tall male
- Verbal IQ reduced to low-normal range, reading difficulties
- Specific behavioral problem
- Fertility normal

Further reading

- Thompson&Thompson, Genetics in Medicine, eighth ed. 2016.
- Emery's Elements of Medical Genetics, 15th ed. 2017.