# Lecture 12. Human chromosomal disorders: Autosomal abnormalities

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The development of a reliable technique for chromosome analysis in 1956 soon led to the discovery that several previously described conditions were due to an abnormality in chromosome number.

In 1959 the causes of Down syndrome (47,XX+21/47,XY+21), Klinefelter syndrome (47,XXY), and Turner syndrome (45,X) had been established.

Shortly after, other autosomal trisomy syndromes were recognized, and over the ensuing years many other multiple malformation syndromes were described in which there was loss or gain of chromosome material.

Chromosome abnormalities account for a large proportion of spontaneous pregnancy loss and childhood disability, and also contribute to malignancy throughout life as a consequence of acquired translocations and other aberrations.

# INCIDENCE OF CHROMOSOME ABNORMALITIES

Chromosome abnormalities are present in at least 10% of all spermatozoa and 25% of mature oocytes. Some 15% to 20% of all recognized pregnancies end in spontaneous miscarriage, and many more zygotes and embryos are so abnormal that survival beyond the first few days or weeks after fertilization is not possible.

Approximately 50% of all spontaneous miscarriages have a chromosome abnormality and the incidence of chromosomal abnormalities in morphologically normal embryos is approximately 20%.

Using high resolution techniques, as many as 80% of embryos generated for in vitro fertilization may have genomic imbalances.

Chromosomal anomalies therefore account for the spontaneous loss of a very high proportion of all human conceptions.

Following implantation the incidence of chromosome abnormalities falls rapidly. By birth it has declined to a level of 0.5% to 1%, although the total is higher (5%) in stillborn infants.

Chromosome abnormalities:

- Autosomes (Down syndrome, Patau syndrome, Edwards syndrome);
- Sex chromosome (Klinefelter Syndrome, Turner syndrome);
- Classic' Chromosome Deletion Syndromes (Deletion 4p and 5p Syndromes, Angelman and Prader-Willi Syndromes);
- Microdeletion syndromes (DiGeorge/Sedlačkova/Velocardiofacial Syndrome)

**Table 17.1** Chromosome Abnormalities in Spontaneous Abortions (Percentage Values Relate to Total of Chromosomally Abnormal Abortuses)

| Abnormality | Incidence (%) |
|---|---|
| Trisomy 13 | 2 |
| Trisomy 16 | 15 |
| Trisomy 18 | 3 |
| Trisomy 21 | 5 |
| Trisomy other | 25 |
| Monosomy X | 20 |
| Triploidy | 15 |
| Tetraploidy | 5 |
| Other | 10 |

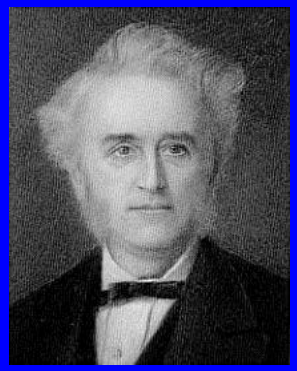
**Table 17.3** Spontaneous Pregnancy Loss in Commonly Recognized Aneuploidy Syndromes

| Disorder | Proportion Undergoing Spontaneous Pregnancy Loss (%) |
|---|---|
| Trisomy 13 | 95 |
| Trisomy 18 | 95 |
| Trisomy 21 | 80 |
| Monosomy X | 98 |

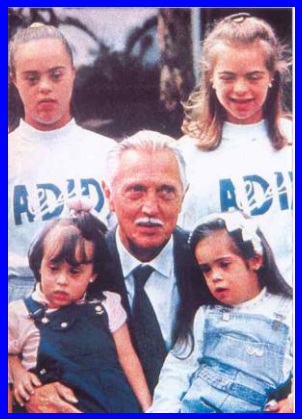
**Table 17.2** Incidence of Chromosome Abnormalities in the Newborn

| Abnormality | Incidence per 10,000 Births |
|---|---|
| *Autosomes* | |
| Trisomy 13 | 2 |
| Trisomy 18 | 3 |
| Trisomy 21 | 15 |
| *Sex Chromosomes* | |
| FEMALE BIRTHS | |
| 45,X | 1–2 |
| 47,XXX | 10 |
| MALE BIRTHS | |
| 47,XXY | 10 |
| 47,XYY | 10 |
| Other unbalanced rearrangements | 10 |
| Balanced rearrangements | 30 |
| Total | 90 |

# DOWN SYNDROME (TRISOMY 21)



Langdon Down
(1828-1896)



Jérôme Lejeune
(1926-1994)

This condition derives its name from Dr Langdon Down, who first described it in 1866. The chromosomal basis of Down syndrome was not established until 1959 by Lejeune and his colleagues.

The overall birth incidence, when adjusted for the increasingly widespread impact of antenatal screening, is approximately 1:1000 in the United Kingdom, approximately 1:800 in United States. According to the Ministry of Health of Kazakhstan in country for 3 years (2014-2016), an increase by 15% in the incidence rate of Down syndrome per 100 thousand children under 14 years old is observed.

There is a strong association between the incidence of Down syndrome and advancing maternal age.

**Table 17.4** Incidence of Down Syndrome in Relation to Maternal Age

| Maternal Age at Delivery (Years) | Incidence of Down Syndrome |
|---|---|
| 20 | 1 in 1500 |
| 25 | 1 in 1350 |
| 30 | 1 in 900 |
| 35 | 1 in 400 |
| 36 | 1 in 300 |
| 37 | 1 in 250 |
| 38 | 1 in 200 |
| 39 | 1 in 150 |
| 40 | 1 in 100 |
| 41 | 1 in 85 |
| 42 | 1 in 65 |
| 43 | 1 in 50 |
| 44 | 1 in 40 |
| 45 | 1 in 30 |

# DOWN SYNDROME (TRISOMY 21)

The most common finding in the newborn period is significant hypotonia. Usually the facial characteristics of upward sloping palpebral fissures, small ears, and protruding tongue prompt rapid suspicion of the diagnosis, although this can be delayed in very small or premature babies. Single palmar creases are found in 50% of children with Down syndrome, in contrast to between 2% and 3% of the general population, and congenital cardiac defects in 40% to 45%, the four most common lesions being atrioventricular canal defects, ventricular septal defects, patent ductus arteriosus, and tetralogy of Fallot.

**Box 17.1 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 septal defects, common atrioventricular canal, patent ductus arteriosus
Other
Anal atresia, duodenal atresia, Hirschsprung disease, short stature, strabismus

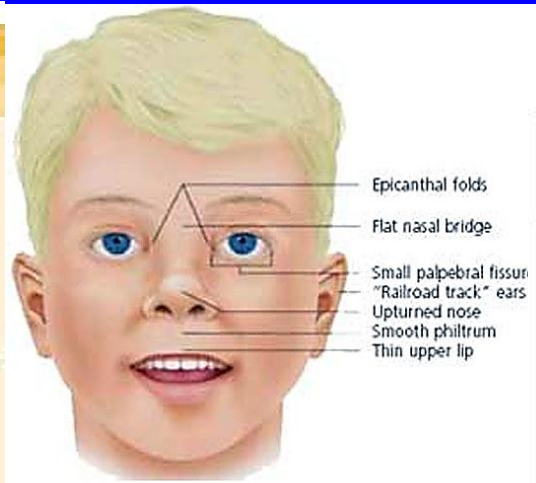



FIGURE 17.4 The hands of an adult with Down syndrome. Note the single palmar crease in the left hand plus bilateral short curved fifth fingers (clinodactyly).

# DOWN SYNDROME (TRISOMY 21)

Affected children show a broad range of intellectual ability with IQ scores ranging from 25 to 75. The average IQ 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 approximately 150 cm.

In the absence of a severe cardiac anomaly, which despite modern surgery and intensive care leads to early death in 15% to 20% of cases, average life expectancy is 50 to 60 years. Overall, about 90% of live-born individuals with Down syndrome reach 20 years of age.

Most affected adults develop Alzheimer disease in later life, possibly because of a gene dosage effect—the amyloid precursor protein gene is on chromosome 21. This gene is known to be implicated in some familial cases of Alzheimer disease.

# DOWN SYNDROME (TRISOMY 21)

In cases resulting from trisomy 21, the additional chromosome is maternal in origin in more than 90% of cases, and DNA studies have shown that this arises most commonly as a result of non-disjunction in maternal meiosis I. Robertsonian translocations account for approximately 4% of all cases, in roughly one-third of which a parent is found to be a carrier. Children with mosaicism (1%) are often less severely affected than those with the full syndrome.

For straightforward trisomy 21, the recurrence risk is related to maternal age (variable) and the simple fact that trisomy has already occurred (approximately 1%). The combined recurrence risk is usually between 1 : 200 and 1 : 100. In translocation cases, similar figures apply if neither parent is a carrier. In familial translocation cases, the recurrence risks vary from 1% to 3% for male carriers and up to 10% to 15% for female carriers, with the exception of very rare carriers of a 21q21q translocation, for whom the recurrence risk is 100%.

Prenatal diagnosis can be offered based on analysis of chorionic villi or cultured amniotic cells. Prenatal screening programs have been introduced based on the so-called triple or quadruple tests of maternal serum at 16 weeks' gestation.

# PATAU SYNDROME (TRISOMY 13)

Trisomy 13, also called Patau syndrome, is a chromosomal condition associated with severe intellectual disability and physical abnormalities in many parts of the body.

Individuals with trisomy 13 often have heart defects, brain or spinal cord abnormalities, very small or poorly developed eyes (microphthalmia), extra fingers or toes, an opening in the lip (a cleft lip) with or without an opening in the roof of the mouth (a cleft palate), and weak muscle tone (hypotonia).

Due to the presence of several life-threatening medical problems, many infants with trisomy 13 die within their first days or weeks of life. Only 5-10% of children with this condition live past their first year.

Trisomy 13 occurs in about 1 in 16,000 newborns. Although women of any age can have a child with trisomy 13, the chance of having a child with this condition increases as a woman gets older.

Most cases of trisomy 13 result from having three copies of chromosome 13, can also occur to translocation, and mosaicism.

# EDWARDS SYNDROME (TRISOMY 18)

Trisomy 18, also called Edwards syndrome, is a chromosomal condition associated with abnormalities in many parts of the body.

Individuals with trisomy 18 often have slow growth before birth (intrauterine growth retardation) and a low birth weight. Affected individuals may have heart defects and abnormalities of other organs that develop before birth. Other features of trisomy 18 include a small, abnormally shaped head; a small jaw and mouth; and clenched fists with overlapping fingers.

Due to the presence of several life-threatening medical problems, many individuals with trisomy 18 die before birth or within their first month. 5-10% of children with this condition live past their first year, and these children often have severe intellectual disability.

Trisomy 18 occurs in about 1 in 5,000 live-born infants. The chance of having a child with this condition increases as a woman gets older.

Most cases of trisomy 18 result from having three copies of chromosome 18 in each cell in the body instead of the usual two copies, and approximately 5 % of people with trisomy 18 have translocation.

# TRIPLOIDY

Triploidy (69,XXX, 69,XXY, 69,XYY) is a relatively common finding in material cultured from spontaneous abortions, but is seen only rarely in a live-born infant.

Such a child almost always shows severe intrauterine growth retardation with relative preservation of head growth at the expense of a small narrow trunk. Syndactyly involving the third and fourth fingers and/or the second and third toes is a common finding.

Cases of triploidy resulting from a double paternal contribution usually miscarry in early to mid-pregnancy and are associated with partial hydatidiform changes in the placenta. Cases with a double maternal contribution survive for longer but rarely beyond the early neonatal period.

***Thank you for attention!***