Lecture 13.
Chromosome disorders

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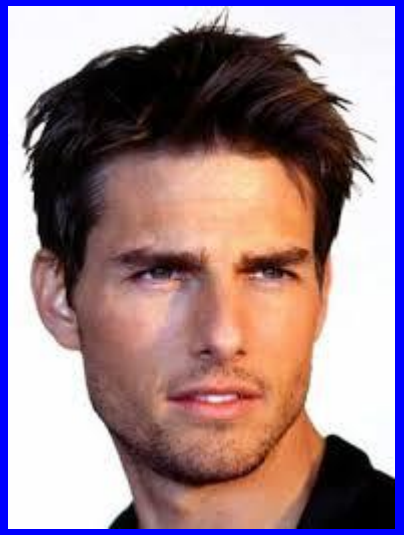
KLINEFELTER SYNDROME (47,XXY)

First described clinically in 1942, this relatively common condition with an incidence of 1:1000 male live births was shown in 1959 to be due to the presence of an additional X chromosome.

In childhood the presentation may be with clumsiness or mild learning difficulties, particularly in relation to verbal skills. The overall verbal IQ is reduced by 10 to 20 points below unaffected siblings and controls, and children can be rather selfobsessed in their behavior. Adults tend to be slightly taller than average with long lower limbs. Approximately 30% show moderately severe gynecomastia (breast enlargement) and all are infertile (azoospermia). There is an increased incidence of leg ulcers, osteoporosis, and carcinoma of the breast in adult life. Treatment with testosterone from puberty onward is beneficial for the development of secondary sexual characteristics and the long-term prevention of osteoporosis.

Harry Klinefelter
(1912-1990)



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KLINEFELTER SYNDROME (47,XXY)

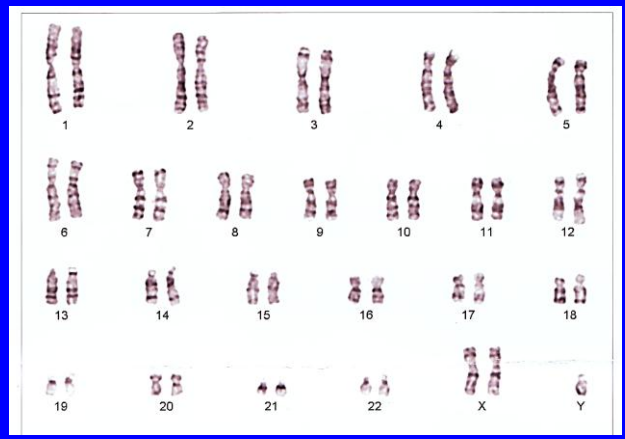
Klinefelter syndrome affects 1 in 500 to 1,000 newborn boys.

Usually the karyotype shows an additional X chromosome.

Molecular studies have shown that there is a roughly equal chance that this will have been inherited from the mother or from the father. The maternally derived cases are associated with advanced maternal age.

A small proportion of cases show mosaicism (e.g., 46,XY/47,XXY).

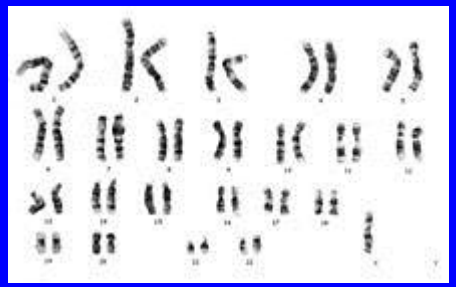
Rarely, a male with more than two X chromosomes can be encountered, for example 48,XXXY or 49,XXXXY. These individuals are usually quite severely retarded and also share physical characteristics with Klinefelter men, often to a more marked degree.



TURNER SYNDROME (45,X)

For the first time this disease as hereditary was described in 1925 with N.A. Shereshevsky. In 1938, Turner identified a triad of symptoms characteristic of this symptom complex: sexual infantilism, skin-winged folds on the lateral surfaces of the neck, and deformity of the elbow joints. The etiology of the disease (monosomy on the X chromosome) was discovered by C. Ford in 1959.

Although common at conception and in spontaneous abortions, the incidence in live-born female infants is low, with estimates ranging from 1:5000 to 1:10,000.



Shereshevsky N.A.
(1885-1961)

Henry H.Turner
(1892-1970)

TURNER SYNDROME (45,X)

Presentation can be at any time from pregnancy to adult life. Increasingly, Turner syndrome is being detected during the second trimester as a result of routine ultrasonography, showing either generalized edema (hydrops) or swelling localized to the neck (nuchal cyst or thickened nuchal pad). At birth many babies with Turner syndrome look entirely normal. Others show the residue of intrauterine edema with puffy extremities and neck webbing. Other findings may include a low posterior hairline, increased carrying angles at the elbows, short fourth metacarpals, widely spaced nipples, and coarctation of the aorta, which is present in 15% of cases.

Intelligence in Turner syndrome is within the normal range. The two main medical problems are short stature (145 cm) and ovarian failure, which commences during the second half of intrauterine life and almost invariably leads to primary amenorrhea and infertility.

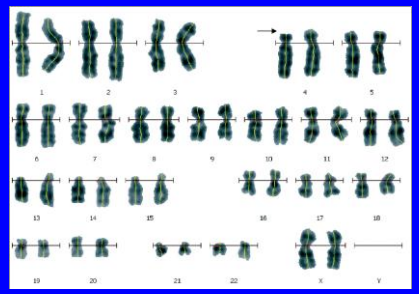
The most common finding is 45,X (sometimes erroneously referred to as 45,XO). In 80% of cases, it arises through loss of a sex chromosome (X or Y) at paternal meiosis. In a significant proportion of cases, there is chromosome mosaicism and those with a normal cell line (46,XX) have a chance of being fertile.

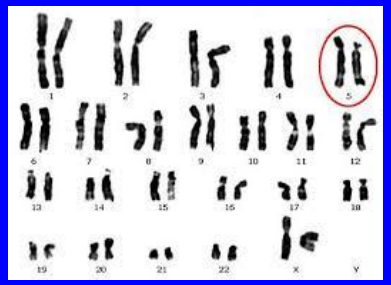
DELETION 4P AND 5P SYNDROMES

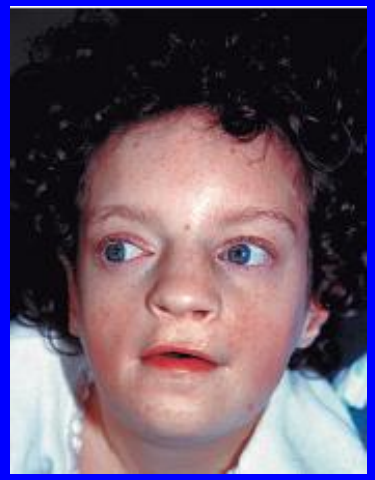
Microscopically visible deletions of the terminal portions of chromosomes 4 and 5 cause the ***Wolf-Hirschhorn*** (4p–) and ***cri-du-chat*** (5p–) syndromes, respectively. In both conditions severe learning difficulties are usual, often with failure to thrive. However, there is considerable variability, particularly in Wolf-Hirschhorn syndrome, and no clear correlation of the phenotype with the precise loss of chromosomal material.

Cri-du-chat syndrome derives its name from the characteristic cat-like cry of affected neonates—a consequence of underdevelopment of the larynx.

Both conditions are rare, with estimated incidences of approximately 1 : 50,000 births.







A child with deletion 4p syndrome; Wolf-Hirschhorn syndrome.

Facial view of a 2-year-old boy with cri-du-chat syndrome.

ANGELMAN AND PRADER-WILLI SYNDROMES

These two conditions have special place in medical genetics as paradigms for genomic imprinting.

Children with Angelman syndrome have inappropriate laughter, convulsions, poor coordination (ataxia), and severe learning difficulties.

Children with Prader-Willi syndrome are very hypotonic with poor feeding in infancy, and later develop hyperphagia and obesity, with mild-tomoderate learning difficulties.

A large proportion of children with these disorders have a microdeletion involving 15q11-13, always the paternally derived chromosome 15 in Prader-Willi syndrome. In contrast, a deletion occurring at the same region on the maternally inherited chromosome 15 causes Angelman syndrome.

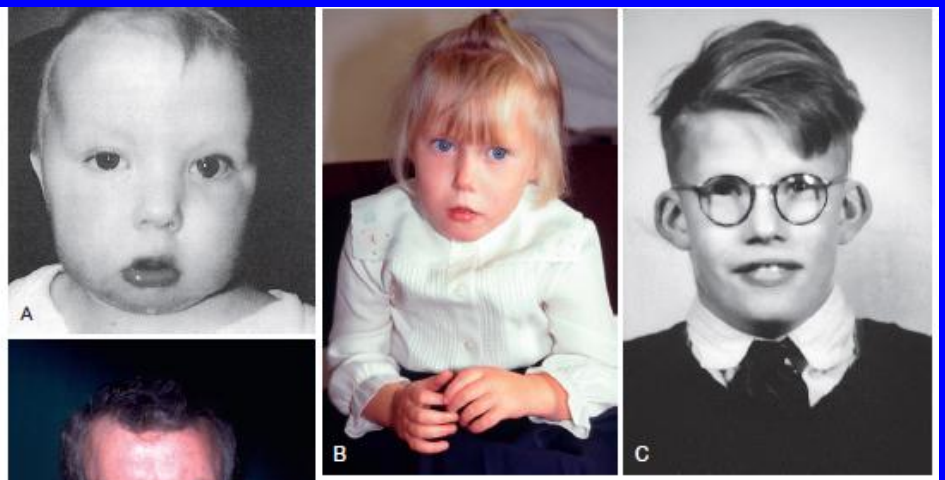
Angelman syndrome

Prader-Willi syndrome

DiGeorge/Sedlačkova/Velocardiofacial Syndrome

DiGeorge syndrome affects approximately 1:4000 births, is usually sporadic, and is characterized by heart malformations (particularly those involving the cardiac outflow tract), thymic and parathyroid hypoplasia, cleft palate and typical facies. The molecular defect is a 3-Mb microdeletion on chromosome 22 (22q11.2).

Those diagnosed should be investigated for cardiac malformations, calcium and parathyroid status, immune function, and renal anomalies. About half have short stature and a small proportion of these have partial growth hormone deficiency. Approximately 25% have schizophrenia-like episodes in adult life.



Deletion 22q11.2 (DiGeorge/Sedlačkova/velocardiofacial syndrome). **A**, A young infant. **B**, A young child. **C**, An older child. **D**, The same individual (shown in **C**) as an adult aged 49 years.

Thank you for attention!