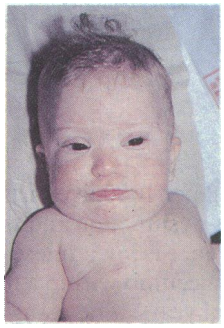
CHROMOSOMAL DISORDERS II

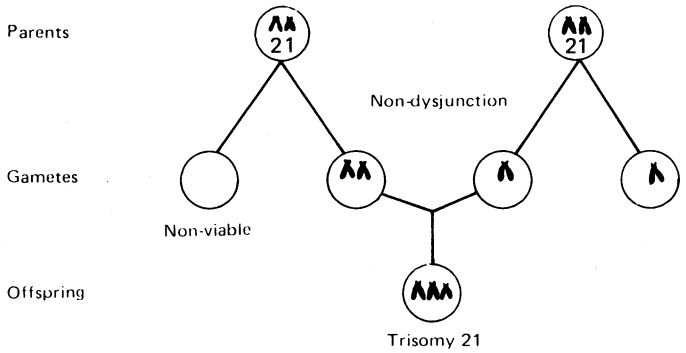
Helen M Kingston



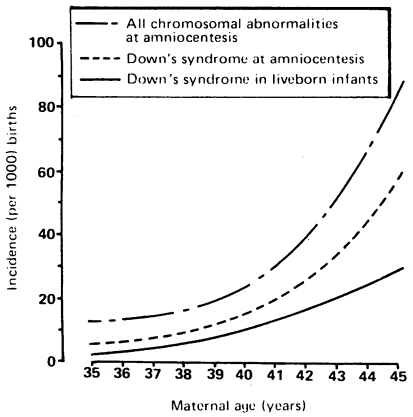
Developmental delay in child with deletion of chromosome 13.

Chromosomal abnormalities are generally associated with multiple congenital malformations and mental retardation. Children with more than one physical abnormality, particularly if retarded, should therefore undergo chromosomal analysis as part of their investigation. Chromosomal disorders are incurable but can be reliably detected by prenatal diagnostic techniques. Amniocentesis or chorionic villus sampling should be offered to women whose pregnancies are at increased risk—namely, women in their mid to late thirties, couples with an affected child, and couples in whom one partner carries a balanced translocation. Unfortunately, when there is no history of previous abnormality the risk in many affected pregnancies cannot be predicted beforehand.

Autosomal abnormalities



Non-dysjunction of chromosome 21 leading to Down's syndrome.



Incidence of chromosomal abnormalities and Down's syndrome by maternal age.

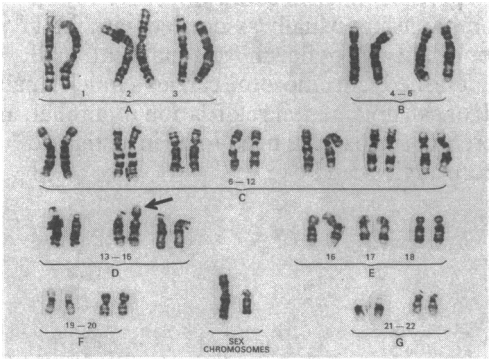
Risk for trisomy 21 in liveborn infants by maternal age

Maternal age at delivery	Risk
All ages	1 in 650
Age 30	1 in 700
Age 35	1 in 450
Age 36	1 in 400
Age 37	1 in 250
Age 38	1 in 200
Age 39	1 in 150
Age 40	1 in 100
Age 44	1 in 40

Trisomy 21 (Down's syndrome)

Down's syndrome is the commonest autosomal trisomy, the incidence in liveborn infants being one in 650, although more than half of conceptions with trisomy 21 do not survive to term. Affected children have a characteristic facial appearance, are mentally retarded, and often die young. They may have associated congenital heart disease and are at increased risk for recurrent infections, atlantoaxial instability, and acute leukaemia. They are often happy and affectionate children who are easy to manage.

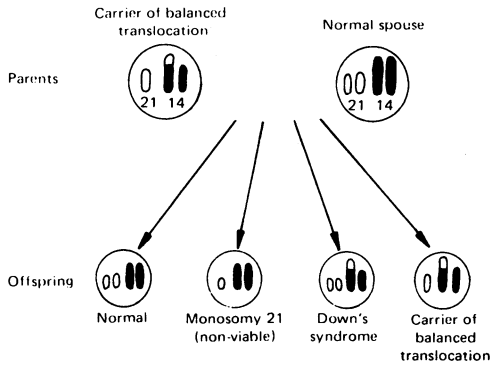
Most cases are due to non-dysjunction of chromosome 21 during meiosis in the formation of eggs or sperm. Although occurring at any age, non-dysjunction increases with maternal age. The risk of recurrence for a chromosomal abnormality in a liveborn infant after the birth of a child with trisomy 21 is about 1% (0·5% for trisomy 21 and 0·5% for other chromosomal abnormalities). For mothers aged 35 and over the risk is around four times the risk related to age, half being for Down's syndrome and half for other chromosomal abnormalities.



Down's syndrome due to Robertsonian translocation between chromosomes 14 and 21.

About 5% of cases of Down's syndrome are due to translocation, in which chromosome 21 is translocated on to chromosome 14 or, occasionally, chromosome 22. In half of these cases one of the parents has a balanced version of the same translocation. A healthy adult with a balanced translocation has 45 chromosomes, and the affected child has 46 chromosomes, the extra chromosome 21 being present in the translocation form.

The risk of Down's syndrome in the offspring is 10% when the balanced translocation is carried by the mother and 2·5% when carried by the father. If neither parent has a balanced translocation, an affected child represents a spontaneous, newly arising event, and the risk of recurrence is low (<1%).

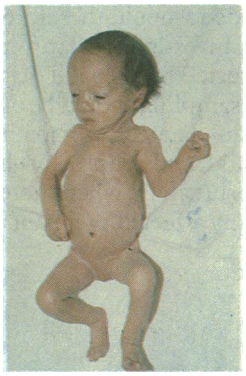


Possible chromosome arrangements in offspring of a carrier of a balanced 14:21 translocation.

Couples concerned about a family history of Down's syndrome can have their chromosomes analysed from a sample of blood to exclude translocation. This usually avoids unnecessary amniocentesis during pregnancy.

When a case of translocation occurs it is important to test other family members to identify all carriers of the translocation whose pregnancies would be at risk.

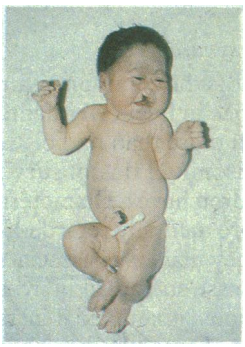
Occasionally, Down's syndrome is due to a 21:21 translocation. A parent with a balanced translocation would be unable to have normal children.



Trisomy 18—skull shape and facial features, short sternum, clenched hands, and rocker-bottom feet.

Trisomy 18 (Edwards's syndrome)

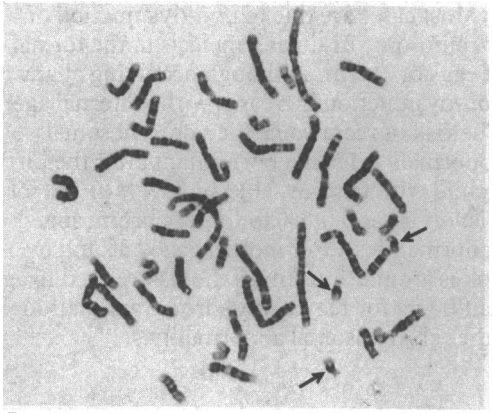
Trisomy 18 has an overall incidence of around 0·12 per 1000 live births. As with Down's syndrome most cases are due to non-dysjunction and the incidence increases with maternal age. Risk of recurrence is low, unless due to a parental translocation. Affected infants usually succumb within a few weeks or months but may occasionally survive several years. The main features include mental deficiency, growth deficiency, characteristic facial appearance, clenched hands, rocker bottom feet, and cardiac and renal abnormalities.



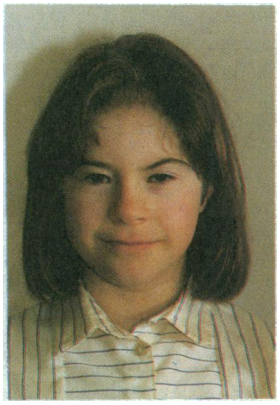
Trisomy 13—facial appearance associated with holoprosencephaly; postaxial polydactyly of hands and feet.

Trisomy 13 (Patau's syndrome)

The incidence of trisomy 13 is about 0·07 per 1000 live births, mainly due to non-dysjunction, with low risk of recurrence. Most affected infants succumb within hours or weeks of birth. The main features include severe mental deficit; structural abnormalities of the brain, including microcephaly and holoprosencephaly (a developmental defect of the forebrain); cleft lip and palate; polydactyly; and ophthalmic, cardiac, and renal malformations.



Trisomy 21 cell line in mosaic Down's syndrome. Normal cell line also present.

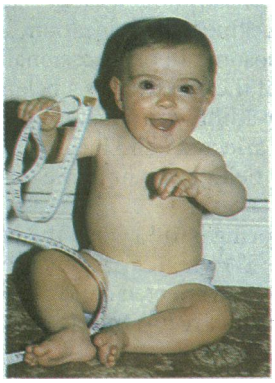


Girl with mosaic trisomy 21.

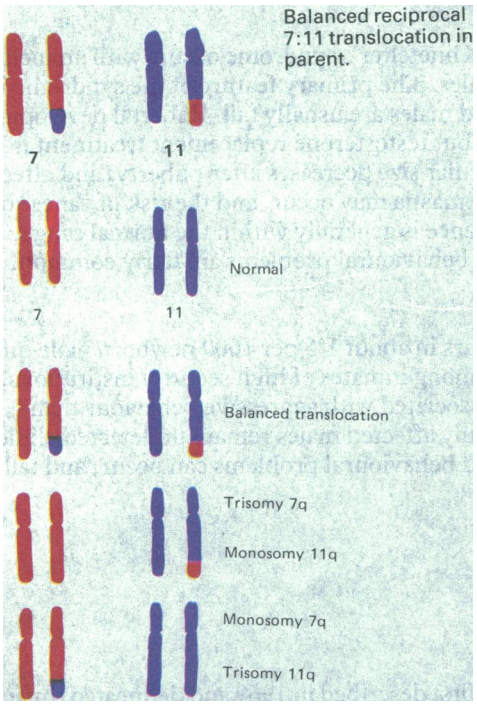
Mosaics

After fertilisation of a normal egg non-dysjunction may occur during a mitotic division in the developing embryo. This results in a fetus with two cell populations. In Down's mosaicism one cell line has a normal constitution of 46 chromosomes and the other has a constitution of 47+21. The proportion of each cell line varies among different tissues. The proportion of trisomic cells present influences the phenotypic expression of the disorder.

The clinical importance of a mosaic abnormality affecting other autosomes which is detected by amniocentesis can be difficult to interpret. Mosaicism of chromosome 20, for example, is not usually associated with fetal abnormality. Mosaicism for a marker (small unidentified) chromosome carries a much smaller risk of causing mental retardation if familial, and therefore the parents need to be investigated before advice can be given.



Normal 8 month old infant born after trisomy 20 mosaicism detected in amniotic cells.

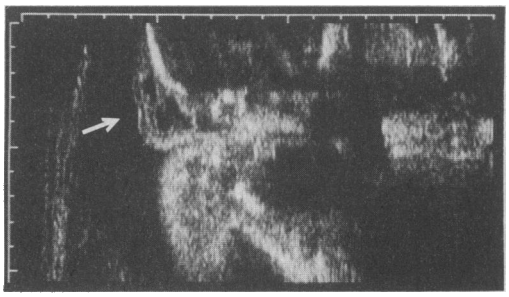


Possible chromosome arrangement in offspring.

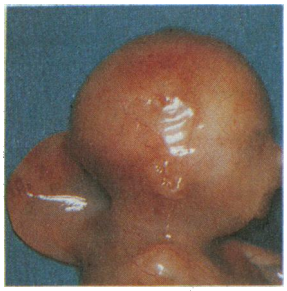
Reciprocal translocations

Abnormalities resulting from an unbalanced translocation karyotype depend on the particular chromosome fragments that are present in monosomic or trisomic form. Sometimes spontaneous abortion is inevitable; at other times a child with multiple abnormalities may be born alive. The risk of an unbalanced karyotype occurring in offspring depends on the individual translocation.

Once a translocation has been identified it is important to investigate relatives of that person to identify carriers of the balanced translocation whose offspring would be at risk. Pregnancies can be monitored with chorionic villus sampling or amniocentesis.



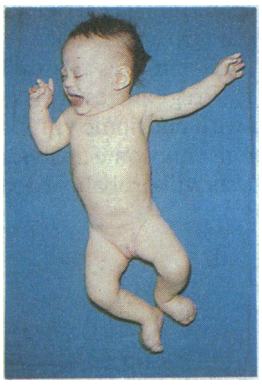
Cystic hygroma in Turner's syndrome detected by ultrasonography.



Fetus with Turner's syndrome.

Numerical abnormalities of the sex chromosomes are fairly common and cause less severe defects than autosomal abnormalities. They are often detected coincidentally at amniocentesis or during investigation for infertility, and risk of recurrence in families is low. When more than one additional sex chromosome is present mental retardation or physical abnormality is more likely.

Sex chromosomal abnormalities



Lymphoedema of the feet as only manifestation of Turner's syndrome in newborn infant.

Normal appearance and development in 22 month girl with triple X syndrome.

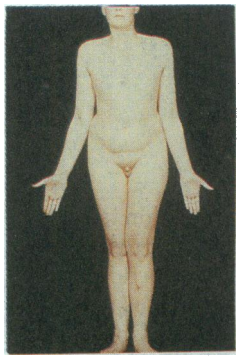
Turner's syndrome

Turner's syndrome results in early spontaneous loss of the fetus in over 95% of cases. Severely affected fetuses who survive to the second trimester can be detected by ultrasonography, which shows cystic hygroma, chylothorax, ascites, and hydrops.

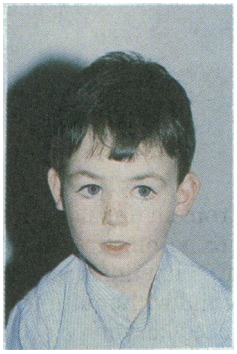
The incidence of Turner's syndrome in liveborn female infants is 0·4 per 1000. Phenotypic abnormalities vary considerably but are usually mild. In some infants the only detectable abnormality is lymphoedema of the hands and feet. The most consistent features of the syndrome are short stature and infertility, but neck webbing, cubitus valgus, and aortic coarctation may also occur. Intelligence is usually within the normal range, but a few girls have educational problems. Growth can be stimulated with androgens or growth hormone, and oestrogen replacement treatment is necessary for pubertal development.

Triple X syndrome

The triple X syndrome occurs with an incidence of 0·65 per 1000 liveborn female infants and is usually a coincidental finding. Apart from being taller than average, affected girls are physically normal. Educational problems are encountered more often in this group than in the other types of sex chromosomal abnormalities. Mean intelligence quotient is lower than in controls, about half of affected girls having delayed speech development and three quarters requiring some remedial teaching. Gonadal function is usually normal, but premature ovarian failure may occur.



Tall stature, truncal obesity, and underdeveloped genitalia in Klinefelter's syndrome.



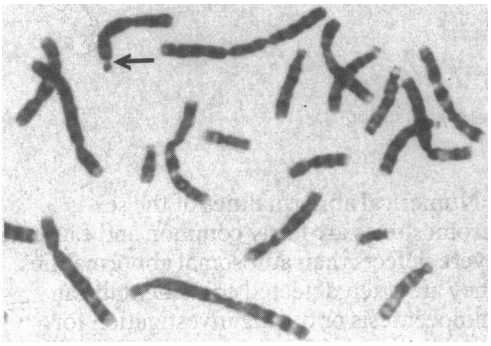
Normal facial appearance in mildly retarded boy with 48XYYY karyotype.

Klinefelter's syndrome

The XXY karyotype of Klinefelter's syndrome occurs with an incidence of 2·0 per 1000 liveborn males. The primary feature of the syndrome is hypogonadism, and affected males are usually tall. Pubertal development often progresses normally, but testosterone replacement treatment is sometimes required. Testicular size decreases after puberty, and affected males are infertile. Gynaecomastia may occur, and the risk of cancer of the breast is increased. Intelligence is generally within the normal range, but educational difficulties and behavioural problems are fairly common.

XYY syndrome

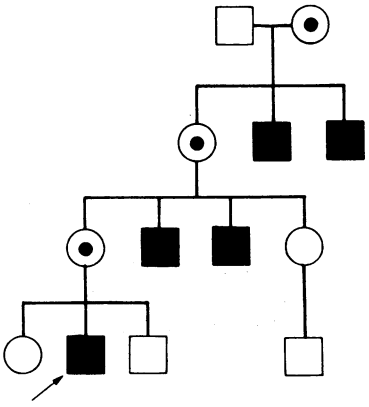
The XYY syndrome occurs in about 1·5 per 1000 newborn male infants. Although more prevalent among inmates of high security institutions, the syndrome is less strongly associated with aggressive behaviour than previously thought, and many affected males remain undetected clinically. Mild mental retardation and behavioural problems can occur, and tall stature is usual.



Fragile X chromosome.

Fragile X syndrome

The fragile X syndrome, first described in 1969 and delineated during the mid-1970s, is the most common single cause of severe mental retardation after Down's syndrome. Analysis of chromosomes with special culture techniques identifies a fragile site near the end of the long arm of the X chromosome in a proportion of cells in affected males and in female carriers.



X linked recessive pedigree in fragile X syndrome.

Mentally retarded brothers with fragile X syndrome.

The syndrome is inherited as an X linked disorder. Affected males usually have severe mental retardation (intelligence quotient 20-80, mean 50). Physical characteristics include macro-orchidism, prominent forehead, and large jaw and ears. The incidence in males is about 1·0 per 1000.

Mild to severe mental retardation also occurs in around 30% of heterozygous female carriers. Not all female carriers show the chromosomal abnormality on testing, which makes counselling difficult in these families. Pregnancies at risk can currently be monitored with chorionic villus and fetal blood sampling for chromosome analysis, but in future DNA analysis will probably become the best method.

Dr Helen M Kingston, MD, is consultant clinical geneticist at St Mary's Hospital, Manchester.

Illustrations reproduced by kind persmission of colleagues at St Mary's Hospital, Manchester, were: Down's syndrome karyotypes, Dr Lorraine Gaunt; fragile X karyotype, Mr M McKinley; cystic hygroma scan, Dr Sylvia Rimmer; trisomy 13, trisomy 18, Turner's syndrome, cystic hygroma fetus, and Klinefelter's syndrome, Dr Dian Donnai.