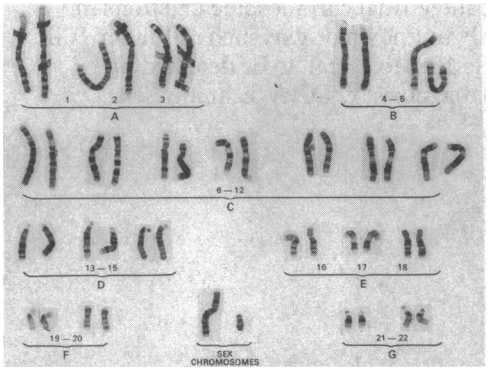
# CHROMOSOMAL DISORDERS I

Helen M Kingston




Normal male chromosome constitution.

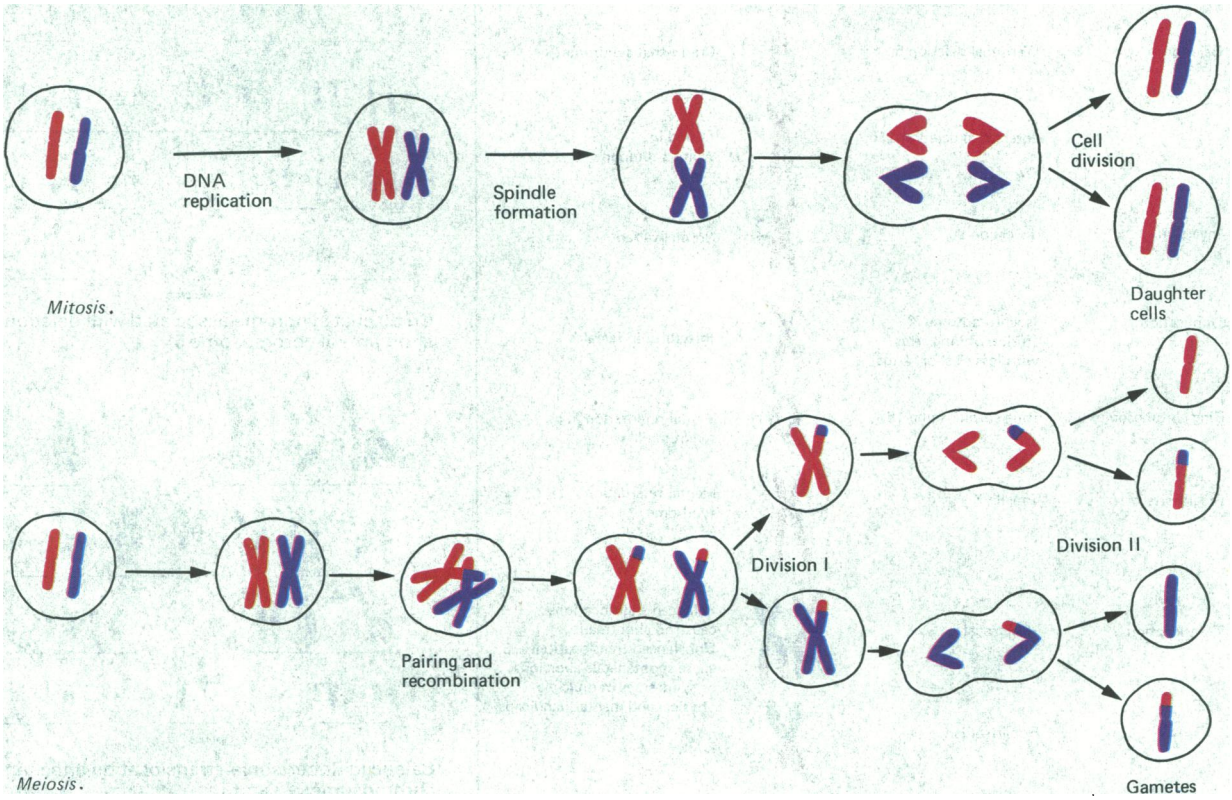
The correct chromosome complement in humans was established in 1956, and the first chromosomal disorders (Down's, Turner's, and Klinefelter's syndromes) were defined in 1959. Since then refinements in techniques of preparing and examining samples have led to the description of hundreds of disorders that are due to chromosomal abnormalities.

## Description of terms

| | |
|---|---|
| Euploid | Chromosome numbers are multiples of the haploid set (2n) |
| Polyploid | Chromosome numbers are greater than diploid (3n, triploid) |
| Aneuploid | Chromosome numbers are not exact multiples of the haploid set (2n+1 trisomy; 2n−1 monosomy) |
| Mosaic | Presence of two different cell lines derived from one zygote (46XX/45X, Turner's mosaic) |
| Chimaera | Presence of two different cell lines derived from fusion of two zygotes (46XX/46XY, true hermaphrodite) |

Human somatic cells contain 46 chromosomes organised into 22 autosomal pairs plus sex chromosomes. The basic haploid set (n=23) is present in the gametes. After fertilisation the zygote contains a diploid set of chromosomes (2n=46); one of each pair is maternal in origin, the other paternal.

During meiosis, which is the nuclear division giving rise to the gametes, recombination occurs between homologous parental chromosomes. The exchange of chromosomal material leads to the separation of genes originally located on the same chromosome, and gives rise to genetic variation within families.

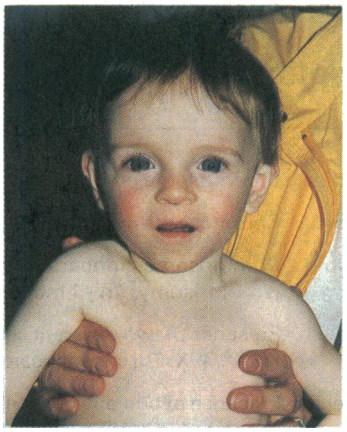


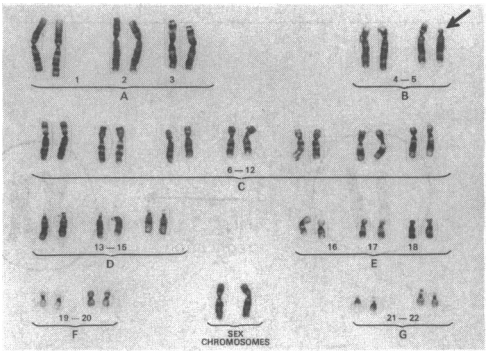

Simplified banding pattern of chromosome 1.

Each chromosome can be identified by light microscopy with staining techniques that give a characteristic pattern of alternating light and dark bands. During metaphase the two chromatids of each chromosome are joined at the centromere. The short arm of the chromosome is designated p and the long arm q. Each arm is subdivided numerically into a number of bands, according to the Paris convention, which permits precise localisation of a structural abnormality. High resolution cytogenetic techniques have permitted identification of small interstitial chromosome deletions in recognised disorders of previously unknown origin, such as Prader-Willi and Angelman's syndromes. Deletions too small to be detected by microscopy may be amenable to diagnosis by DNA techniques.

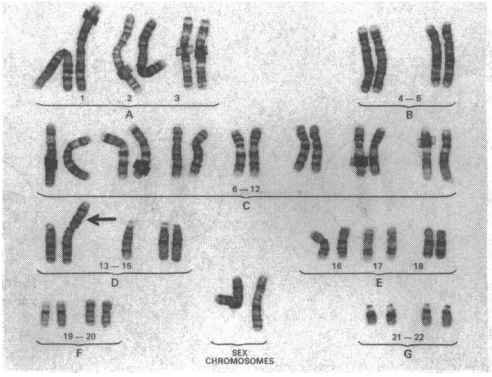
## Types of chromosomal disorders

| Type of disorder | Example | | Outcome |
|---|---|---|---|
| *Numerical* | | | |
| Polyploid | Triploidy | 69 chromosomes | Lethal |
| Aneuploid | Trisomy of chromosome 21 | | Down's syndrome |
| | Monosomy of X chromosome | | Turner's syndrome |
| | 47 chromosomes (XXY) | | Klinefelter's syndrome |
| *Structural* | | | |
| Deletion | Terminal deletion 5p | | Cri du chat syndrome |
| | Interstitial deletion 11p | | Found in Wilms's tumour |
| Inversion | Inversion 9q | | Normal variant |
| Duplication | Isochromosome X (fusion of long arms with loss of short arms) | | Infertility in females |
| Ring chromosome | Ring chromosome 18 | | Mental retardation syndrome |
| Fragile site | Fragile X | | Mental retardation syndrome |
| Translocation | Reciprocal | | Balanced translocations cause no abnormality. Unbalanced translocations cause spontaneous abortions or syndromes of multiple physical and mental handicaps |
| | Robertsonian | | |



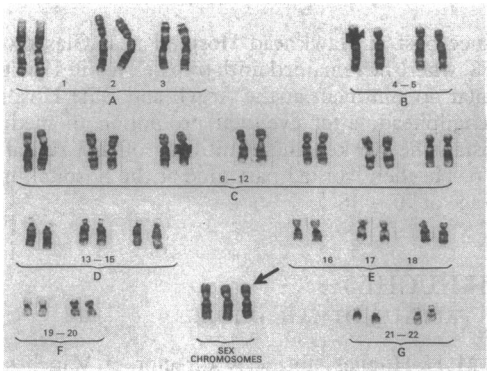



Cri du chat syndrome associated with deletion of short arm of chromosome 5.




Balanced Robertsonian translocation affecting chromosomes 13 and 14.

# Reporting of karyotypes



47XXX karyotype in triple X syndrome.

- Total number of chromosomes given first followed by constitution of sex chromosomes:

**46XX** Normal female
**47XXY** Male with Klinefelter's syndrome
**47XXX** Female with triple X syndrome

- Additional or lost chromosomes are indicated by + or −:

**47XY+21** Male with trisomy 21 (Down's syndrome)
**46XX12p+** Additional unidentified material on short arm of chromosome 12

- All cell lines present are shown for mosaics:

**46XX/47XX+21** Down's mosaic
**46XX/47XXX/45X** Turner's/triple X mosaic

- Structural rearrangements are described, identifying p and q arms and location of abnormality:

**46XY del 11 (p13)** Deletion of short arm of chromosome 11 at band 13
**46XX t (X;7) (p21;q23)** Translocation between chromosome X and 7 with break points in respective chromosomes

# Incidence of chromosomal abnormalities

*Incidence of chromosomal abnormalities in spontaneous abortions and stillbirths*

| | % |
|---|---|
| Spontaneous abortions: | |
| All | 50 |
| Before 12 weeks | 60 |
| 12-20 Weeks | 20 |
| Stillbirths | 5 |

*Types of chromosomal abnormalities in spontaneous abortions*

| | % |
|---|---|
| Trisomy | 52 |
| Monosomy X | 18 |
| Triploidy | 17 |
| Translocations | 2-4 |

Chromosomal abnormalities are particularly common in spontaneous abortions. About 15-20% of all conceptions are estimated to be lost spontaneously, and about half of these are associated with a chromosomal abnormality. Most chromosomal abnormalities lead to spontaneous abortion, some inevitably so—for example, trisomy 16 is commonly found in aborted fetuses but never in liveborn infants.

*Chromosomal abnormalities in newborn infants (per 1000)*

| | |
|---|---|
| All | 6·5 |
| Autosomal trisomy | 1·7 |
| Autosomal rearrangements | 1·9 |
| Other autosomal abnormality | 0·4 |
| Sex chromosomal | 2·5 |

**Common abnormalities**

*Autosomal*
Trisomy 21—Down's
Trisomy 18—Edwards's } syndrome
Trisomy 13—Patau's

*Sex chromosomal*
XO—Turner's
XXX—Triple X } syndrome
XXY—Klinefelter's
XYY—XYY Male

In liveborn infants chromosomal abnormalities occur at about six per 1000 births. The incidence of abnormalities of autosomes and sex chromosomes is about the same. The effect on the child depends on the type of abnormality. Abnormalities do not occur in balanced rearrangements and are mild in disorders of the sex chromosomes. Unbalanced autosomal abnormalities cause disorders with multiple congenital malformations, almost invariably associated with mental retardation.

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The illustrations of normal male, cri du chat, Robertsonian translocation 13;14, and triple X karyotypes were reproduced by kind permission of Dr Lorraine Gaunt, St Mary's Hospital, Manchester.