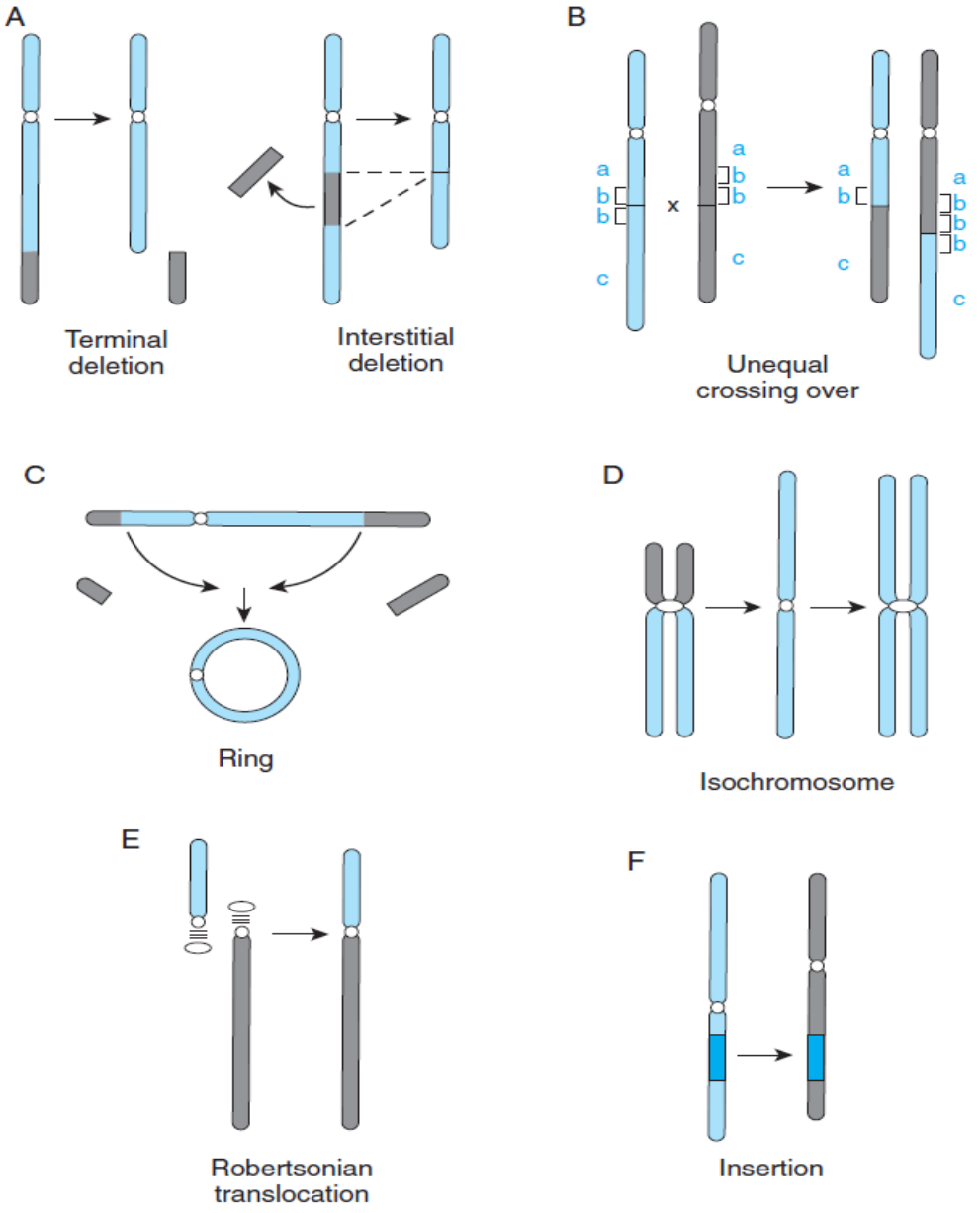
Abnormalities of Chromosome Structure

Structural rearrangements result from chromosome breakage, followed by reconstitution in an abnormal combination. Whereas rearrangements can take place in many ways, they are together less common than aneuploidy; overall, structural abnormalities are present in about 1 in 375 newborns. Chromosome rearrangement occurs spontaneously at a low frequency and may also be induced by breaking agents (clastogens), such as ionizing radiation, some viral infections, and many chemicals. Like numerical abnormalities, structural rearrangements may be present in all cells of a person or in mosaic form.

Structural rearrangements are defined as **balanced**, if the chromosome set has the normal complement of chromosomal material, or **unbalanced**, if there is additional or missing material. Some rearrangements are stable, capable of passing through mitotic and meiotic cell divisions unaltered, whereas others are unstable. To be completely stable, a rearranged chromosome must have a functional centromere and two telomeres.

Figure 7. Structural rearrangements of chromosomes, described in the text. **A,** Terminal and interstitial deletions, each generating an acentric fragment. **B,** Unequal crossing over between segments of homologous chromosomes or between sister chromatids (duplicated or deleted segment indicated by the brackets). **C,** Ring chromosome with two acentric fragments. **D,** Generation of an isochromosome or the long arm of a chromosome. **E,** Robertsonian translocation between two acrocentric chromosomes. **F,** Insertion of a segment of one chromosome into a nonhomologous chromosome.



Mosaicism

When a person has a chromosome abnormality, the abnormality is usually present in all of his or her cells. Sometimes, however, two or more different chromosome

complements are present in an individual; this situation is called **mosaicism.** Mosaicism may be either numerical or, less commonly, structural. A common cause of mosaicism is nondisjunction in an early postzygotic mitotic division. For example, a zygote with an additional chromosome 21 might lose the extra chromosome in a mitotic division and continue to develop as a 46/47,+21 mosaic.

The significance of a finding of mosaicism is often difficult to assess, especially if it is identified prenatally. The effects of mosaicism on development vary with the timing of the nondisjunction event, the nature of the chromosome abnormality, the proportions of the different chromosome complements present, and the tissues affected. Clinical studies of the phenotypic effects of mosaicism have two main weaknesses. First, because people are hardly ever karyotyped without some clinical indications, clinically normal mosaic persons are rarely ascertained; second, there have been few follow-up studies of prenatally diagnosed mosaic fetuses.

Nonetheless, it is often believed that individuals who are mosaic for a given trisomy, such as mosaic Down syndrome or mosaic Turner syndrome, are less severely affected than nonmosaic individuals.

Genomic Imprinting

- The expression of the disease phenotype depends on whether the mutant allele or abnormal chromosome has been inherited from the father or from the mother.
- Differences in gene expression between the allele inherited from the mother and the allele inherited from the father are the result of **genomic imprinting.**
- **Imprinting** is a normal process caused by alterations in chromatin that occur in the germline of one parent**,** but not the other, at characteristic locations in the genome. These alterations include the covalent modification of DNA, such as methylation of cytosine to form 5-methylcytosine,

or the modification or substitution in chromatin of specific histone types which can influence gene expression within a chromosomal region. Notably, imprinting affects the expression of a gene but not its primary DNA sequence. It is a reversible form of gene inactivation but not a mutation, and thus it is an example of what is called an *epigenetic* effect. Epigenetics is an area of increasing importance in human and medical genetics, with significant influences

on gene expression and phenotype, both in normal individuals and in a variety of disorders, including cytogenetic abnormalities Imprinting takes place during gametogenesis, before fertilization, and marks certain genes as having come from the mother or father.

The imprint controls gene expression within the imprinted region in some or all of the somatic tissues of the embryo. The imprinted state persists postnatally into

adulthood through hundreds of cell divisions so that only the maternal or paternal copy of the gene is expressed. Yet, imprinting must be reversible: a paternally derived allele, when it is inherited by a female, must be converted in her germline so that she can then pass it on with a maternal imprint to her offspring. an imprinted maternally derived allele, when it is inherited by a male, must be converted in his germline so that he can pass it on as a paternally imprinted allele to his offspring (Fig. 8).

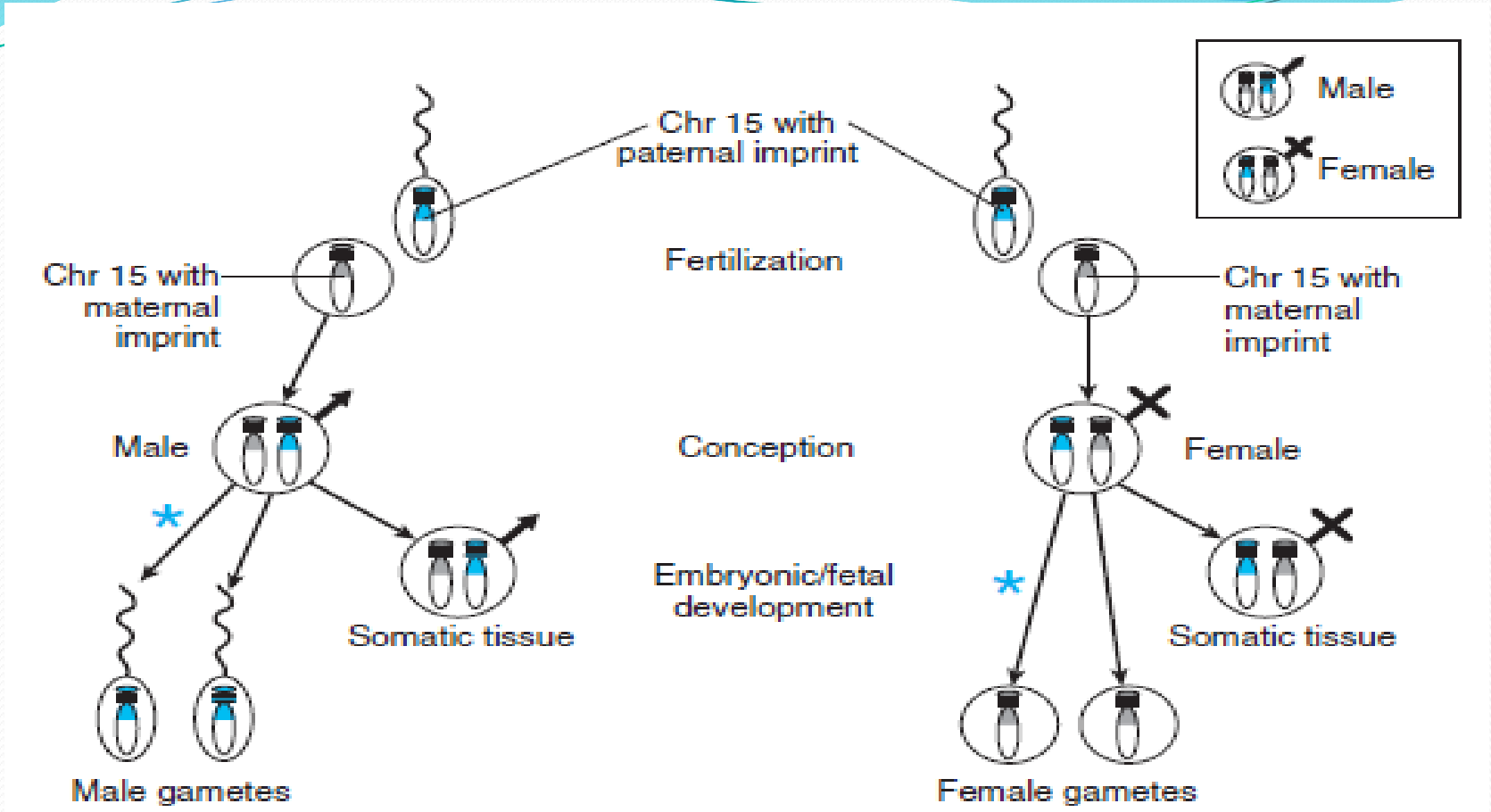


Figure 8. Diagram of conversion of maternal and paternal imprinting during passage through the germline to make male or female gametes. Erasure of uniparental imprint on one chromosome and conversion to imprint of the other sex is marked by the asterisk.

Control over this conversion process appears to be governed by DNA elements called imprinting centers that are located within imprinted regions throughout the genome; whereas their precise mechanism of action is not known, they must initiate the epigenetic change in chromatin, which then spreads outward along the chromosome over the imprinted region.

Uniparental disomy: defined as the presence of a disomic cell line containing two chromosomes, or portions thereof, inherited from only one parent. If the identical chromosome is present in duplicate, the situation is described as isodisomy; if both homologues from one parent are present, the situation is heterodisomy.

The Chromosomes in Down Syndrome

The specific abnormal karyotype responsible for Down syndrome usually has little effect on the phenotype of the patient, it is essential for determining the recurrence risk. Trisomy 21 In about 95% of all patients, Down syndrome involves trisomy for chromosome 21 resulting from meiotic nondisjunction of the chromosome 21 pair. The risk of having a child with trisomy 21 increases with maternal age, especially after the age of 30 years The meiotic error responsible for the trisomy usually occurs during maternal meiosis (about 90% of cases), predominantly in meiosis I, but about 10% of cases occur in paternal meiosis, usually in meiosis II.

Robertsonian Translocation About 4% of Down syndrome patients have 46 chromosomes, one of which

is a Robertsonian translocation between chromosome 21q and the long arm of one of the other acrocentric chromosomes (usually chromosome 14 or 22). The translocation chromosome replaces one of the normal acrocentric chromosomes, and the karyotype of a Down syndrome patient with a Robertsonian translocation between chromosomes 14 and 21 is therefore 46,XX or XY,rob(14;21)(q10;q10),+21

Unlike standard trisomy 21, translocation Down syndrome shows no relation to maternal age but has a relatively high recurrence risk in families when a parent, especially the mother, is a carrier of the translocation. For this reason, karyotyping of the parents and possibly other relatives is essential before accurate genetic counseling can be provided.

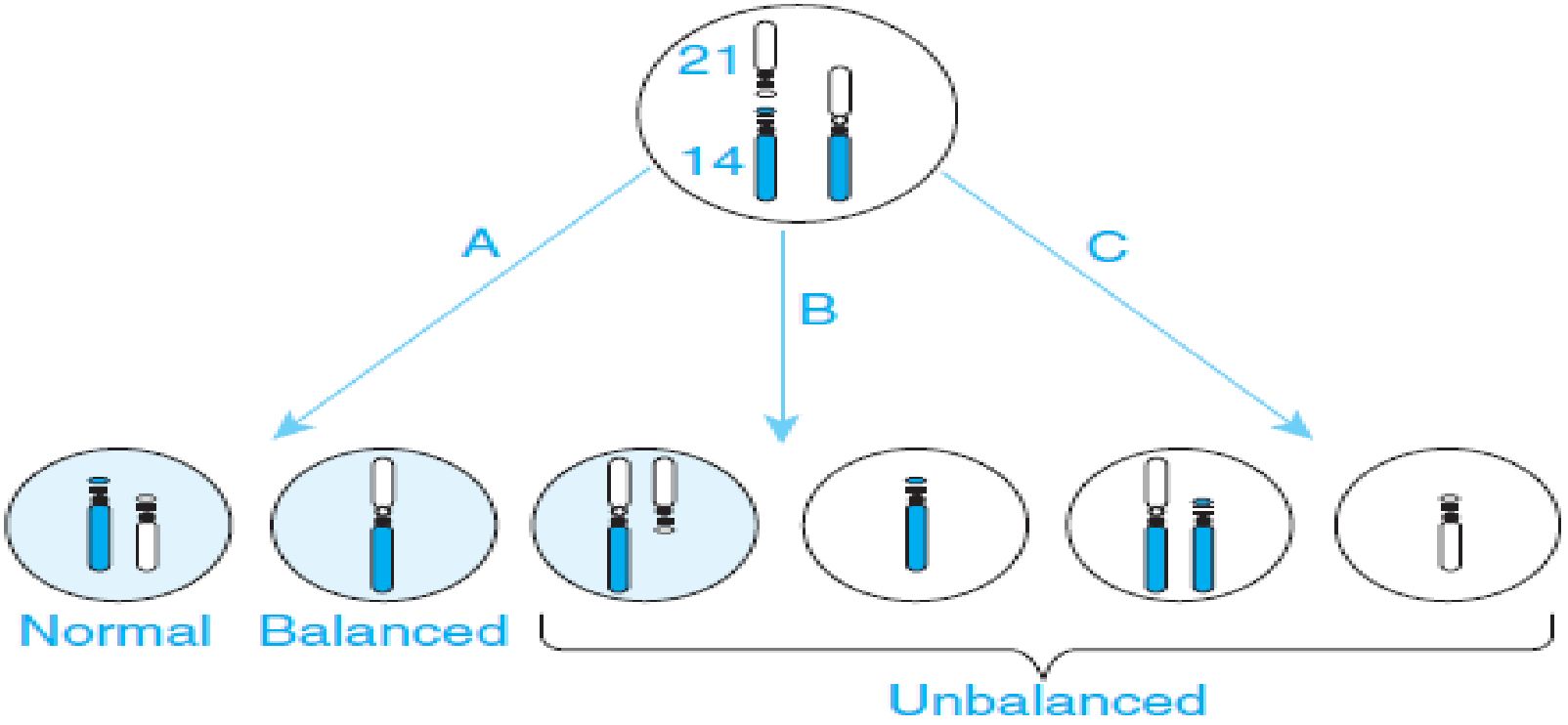


Figure 9. Chromosomes of gametes that theoretically can be produced by a carrier of a Robertsonian translocation, rob(14;21). A, Normal and balanced complements. B, Unbalanced, one product with both the translocation chromosome and the normal chromosome 21, and the reciprocal product with chromosome 14 only. C, Unbalanced, one product with both the translocation chromosome and chromosome 14, and the reciprocal product with chromosome 21 only.

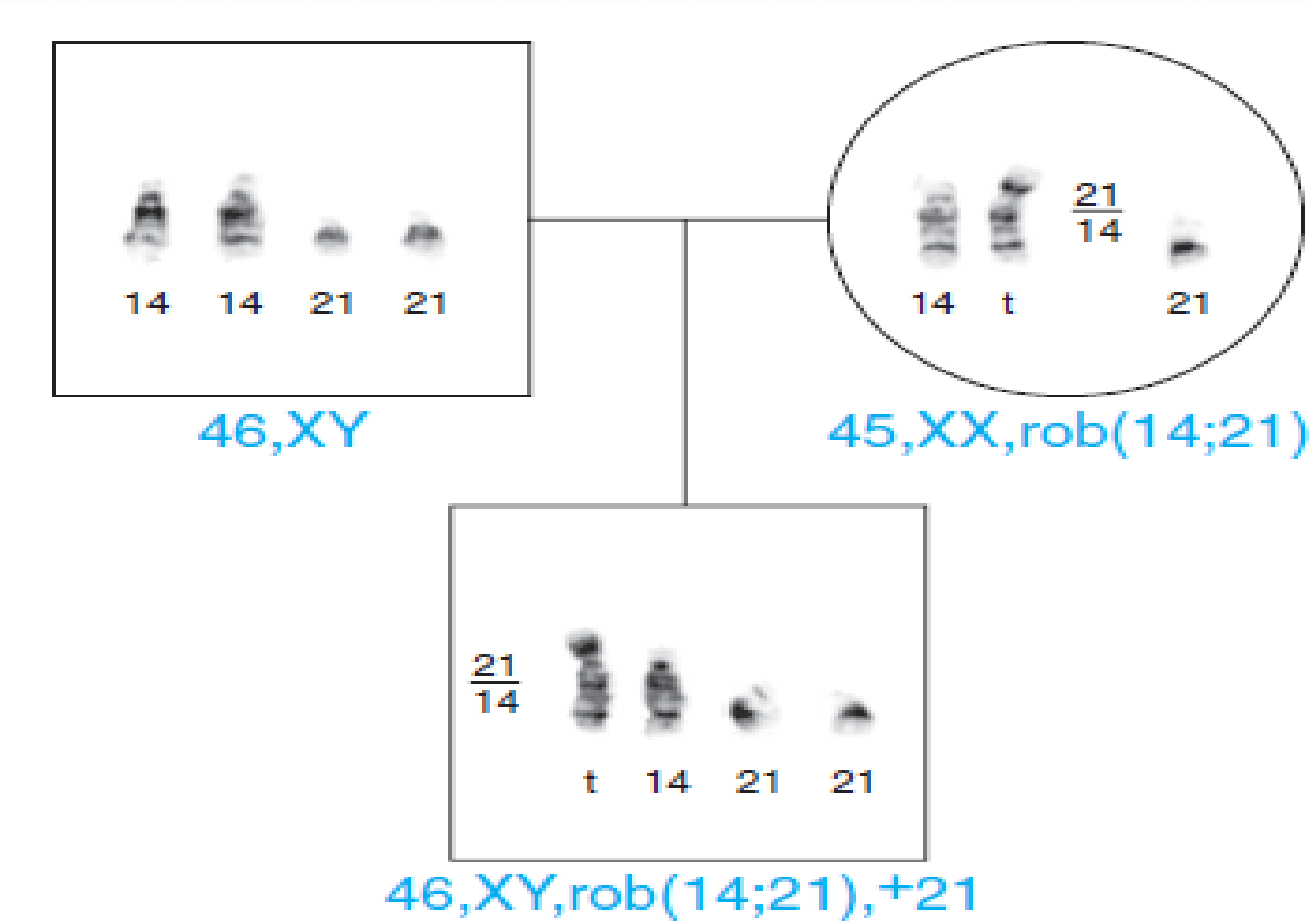


Figure 10. Robertsonian translocation 14q21q transmitted by a carrier mother to her child, who has Down syndrome. The father's chromosomes are normal. Only chromosomes 14, 21, and rob(14;21) are shown. t, translocation.

THE SEX CHROMOSOMES AND THEIR ABNORMALITIES

The X and Y chromosomes have long attracted interest because they differ between the sexes, because they have their own specific patterns of inheritance, and because they are involved in primary sex determination. They are structurally distinct and subject to different forms of genetic regulation, yet they pair in male meiosis.

The Chromosomal Basis of Sex Determination

The different sex chromosome constitution of normal human male and female cells has been appreciated for more than 50 years. Soon after cytogenetic analysis became feasible, the fundamental basis of the XX/XY system of sex determination became apparent. Males with Klinefelter syndrome were found to have 47 chromosomes with two X chromosomes as well as a Y chromosome (karyotype 47,XXY), whereas most Turner syndrome females were found to have only 45 chromosomes with a single X chromosome (karyotype 45,X).

The sex chromosomes play a determining role in specifying primary (gonadal) sex, a number of genes located on both the sex chromosomes and the autosomes are involved in sex determination and subsequent sexual differentiation. In most instances, the

role of these genes has come to light as a result of patients with abnormalities in sexual development.

The Y Chromosome

In male meiosis, the X and Y chromosomes normally pair by segments at the ends of their short arms and undergo recombination in that region.

The pairing segment includes the pseudoautosomal region of the X and Y chromosomes, so called because the X- and Y-linked copies of this region are essentially identical to one another and undergo homologous recombination in meiosis I. (A second, smaller pseudoautosomal segment is located at the distal ends of Xq and Yq.) By comparison with autosomes and the X chromosome, the Y chromosome is relatively gene poor and contains only about 50 genes. the functions of a high proportion of these genes are related to gonadal and genital development.

The X Chromosome

Aneuploidy for the X chromosome is among the most common of cytogenetic abnormalities. The relative tolerance of the human karyotype for X chromosome abnormalities can be explained in terms of X chromosome inactivation, the process by which most genes on one of the two X chromosomes in females are silenced epigenetically and fail to produce any product.

X Chromosome Inactivation

The theory of X inactivation is that in somatic cells in normal females (but not in normal males), one X chromosome is inactivated early in development, thus equalizing the expression of X-linked genes in the two sexes. Thus, females are mosaic with respect to X-linked

gene expression; some cells express alleles on the paternally inherited X but not the maternally inherited X, whereas other cells do the opposite Although the inactive X chromosome was first identified cytologically by the presence of a heterochromatic mass (called the Barr body) in interphase cells, there are many epigenetic features that distinguish the active and inactive X chromosomes.

Chromosomal Features of X Inactivation

- Inactivation of most X-linked genes on the inactive X.
- Random choice of one of two X chromosomes in female cells.

Inactive X:

- Heterochromatic (Barr body)
- Late-replicating in S phase
- Expresses XIST RNA
- Associated with macroH2A histone modifications in chromatin

Table 1. Incidence of Sex Chromosome Abnormalities

Sex	Disorder	Karyotype	Approximate Incidence
Male	Klinefelter syndrome	47,XXY	1/1000 males
		48,XXXY	1/25,000 males
		Others (48,XXYY; 49,XXXYY; mosaics)	1/10,000 males
	47,XYY syndrome	47,XYY	1/1000 males
	Other X or Y chromosome abnormalities		1/1500 males
	XX males	46,XX	1/20,000 males
			Overall incidence: 1/400 males
Female	Turner syndrome	45,X	1/5000 females
		46,X,i(Xq)	1/50,000 females
		Others (deletions, mosaics)	1/15,000 females
	Trisomy X	47,XXX	1/1000 females
	Other X chromosome abnormalities		1/3000 females
	XY females	46,XY	1/20,000 females
	Androgen insensitivity syndrome	46,XY	1/20,000 females
			Overall incidence: 1/650 females

Table 2. Follow-up Observations on Patients with Sex Chromosome Aneuploidy

Disorder	Karyotype	Phenotype	Sexual Development	Intelligence	Behavioral Problem
Klinefelter syndrome	47,XXY	Tall male (see text)	Infertile; hypogonadism	Learning difficulties (some patients)	May have poor psychosocial adjustment
XYY syndrome	47,XYY	Tall male	Normal	Normal	Frequent
Trisomy X	47,XXX	Female, usually tall	Usually normal	Learning difficulties (some patients)	Occasional
Turner syndrome	45,X	Short female, distinctive features (see text)	Infertile; streak gonads	Slightly reduced	Rare (but see text)