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Overview of Sex Chromosome Anomalies

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Sex chromosome anomalies may involve aneuploidy, partial deletions or duplications of sex chromosomes, or mosaicism.

(See also Overview of Chromosomal Anomalies.)

Sex chromosome anomalies are common and cause syndromes that are associated with a range of congenital and developmental anomalies. The majority are not suspected prenatally but may be incidentally discovered if karyotyping is done for other reasons, such as advanced maternal age. The anomalies are often hard to recognize at birth and may not be diagnosed until puberty.

The effects of X chromosome anomalies are not as severe as those from analogous autosomal anomalies. Females with 3 X chromosomes often appear normal physically and mentally and are fertile. In contrast, all known autosomal trisomies have devastating effects. Similarly, whereas the absence of 1 X chromosome (monosomy X) leads to a specific syndrome (Turner syndrome), the absence of an autosome is invariably lethal.

Lyon hypothesis (X-inactivation)

By virtue of having 2 X chromosomes, females have 2 loci for every X-linked gene, as compared with a single locus in males. This imbalance would seem to cause a genetic “dosage” problem. However, according to the Lyon hypothesis, 1 of the 2 X chromosomes in each female somatic cell is inactivated genetically early in embryonic life (on or about day 16). In fact, no matter how many X chromosomes are present, all but 1 are inactivated. However, molecular genetic studies have shown that some genes on the inactivated X chromosome (or chromosomes) remain functional, and these few are essential to normal female development. *XIST* is the gene responsible for inactivating the genes of the X chromosome, producing RNA that triggers inactivation.

Whether the maternal or paternal X is inactivated usually is a random event within each cell at the time of inactivation; that same X then remains inactive in all descendant cells. Thus, all females are mosaics, with some cells having an active maternal X and others having an active paternal X.

Pearls & Pitfalls

Because of random X-inactivation, all females are mosaics, with some cells having an active maternal X and others having an active paternal X.

Sometimes, random statistical distribution of inactivation in the relatively small number of cells present at the time of inactivation results in a particular descendant tissue having a preponderance of active maternal or paternal X chromosomes (skewed inactivation). Skewed inactivation may account for the occasional manifestation of minor symptoms in females who are heterozygous for X-linked disorders such as hemophilia and muscular dystrophy (all would presumably be asymptomatic if they had a 50:50 distribution of active X chromosomes). Skewed inactivation also may occur by postinactivation selection.