the sex chromosomes also occur, with 47,XXX (trisomy X or triple X syndrome), 47,XXY (Klinefelter syndrome), and 47,XYY all reported in individuals with relatively mild phenotypes (Chap. 410). Klinefelter syndrome is the most common clinically recognized sex chromosome abnormality, and clinical features include gynecomastia, azoospermia, small testes, and hypogonadism. The 47,XYY karyotype is most often found in boys with developmental delay and or behavioral difficulties, but population-based studies have shown that intelligence for individuals with this karyotype is generally within the normal range, although slightly lower than that found in siblings.

STRUCTURAL CHROMOSOME ABNORMALITIES

Structural chromosome abnormalities include deletions, duplications, translocations, inversions, as well as other types of abnormalities, each relatively rare, but nonetheless contributing to clinical disease resulting from chromosome anomalies. These rare alterations include isochromosomes, ring chromosomes, dicentric chromosomes, and marker chromosomes (structurally abnormal chromosomes that cannot be identified based on cytogenetics alone). Both translocations and inversions can be completely balanced in some cases, such that there is no disruption of coding regions of the genome, with a completely normal clinical phenotype; however, carriers are at risk for unbalanced forms of these rearrangements in their offspring.

Reciprocal translocations are found in approximately 1/500–1/600 individuals in the general population and result from the exchange of chromosomal segments between at least two chromosomes. These usually occur between nonhomologous chromosomes and can be identified based on an altered banding pattern on G-banding. Balanced translocation carriers are at risk for abnormal chromosome segregation during meiosis and therefore have a higher risk for infertility, SAB, and live-born offspring with multiple congenital malformations. These phenotypes are observed when only one of the pairs of chromosomes involved in a translocation is inherited from a parent, resulting in an unbalanced genotype (Fig. 83e-3). Sometimes the exchanged segments are so small that they cannot be appreciated by banding (cryptic translocation), and these are sometimes recognized when a phenotypically affected child with an unbalanced form is born. Parental chromosomes can then be studied by FISH to determine if the rearrangement is inherited from a parent with a balanced form of the translocation. The majority of reciprocal, apparently balanced translocations occur in phenotypically normal individuals. The risk for a clinical abnormality when a new reciprocal translocation is identified (usually during prenatal diagnostic studies) is about 7%. Analysis of cytogenetically reciprocal translocations using arrays has demonstrated that translocations in clinically normal individuals are more likely to show no deletions or duplications at the breakpoint, whereas translocations in clinically affected individuals are more likely to have breakpoint-associated deletions or duplications. Most reciprocal translocations occur uniquely, at apparently random positions throughout the genome; however, there are a few exceptions with multiple cases of recurrent translocations occurring. These recurrent translocations include t(11;22), which results in Emanuel syndrome in the unbalanced form, and several translocations involving a region on 4p, 8p, and 12p. These recurrent translocations occur in regions of the genome that contain specific types of AT-rich repeats, or other repeat sequences, that are prone to rearrangement. A special category of translocations is the Robertsonian translocations, which involve the acrocentric chromosomes. An acrocentric chromosome has unique genetic material only on the long arm of the chromosomes, whereas the short arm contains repetitive DNA. The acrocentric chromosomes are 13, 14, 15, 21, and 22. Robertsonian translocations occur when an entire long arm of an acrocentric chromosome is translocated onto the short arm of another acrocentric chromosome. Balanced carriers of a Robertsonian translocation contain only 45 chromosomes, with one chromosome consisting of two long arms of an acrocentric chromosome. Technically, this is an unbalanced translocation, as two short arms of the acrocentric chromosomes are missing; however, because the short arms are repetitive, there is no phenotypic consequence. Unbalanced Robertsonian carriers have 46 chromosomes, but have three copies of the long arm of an acrocentric chromosome. The most

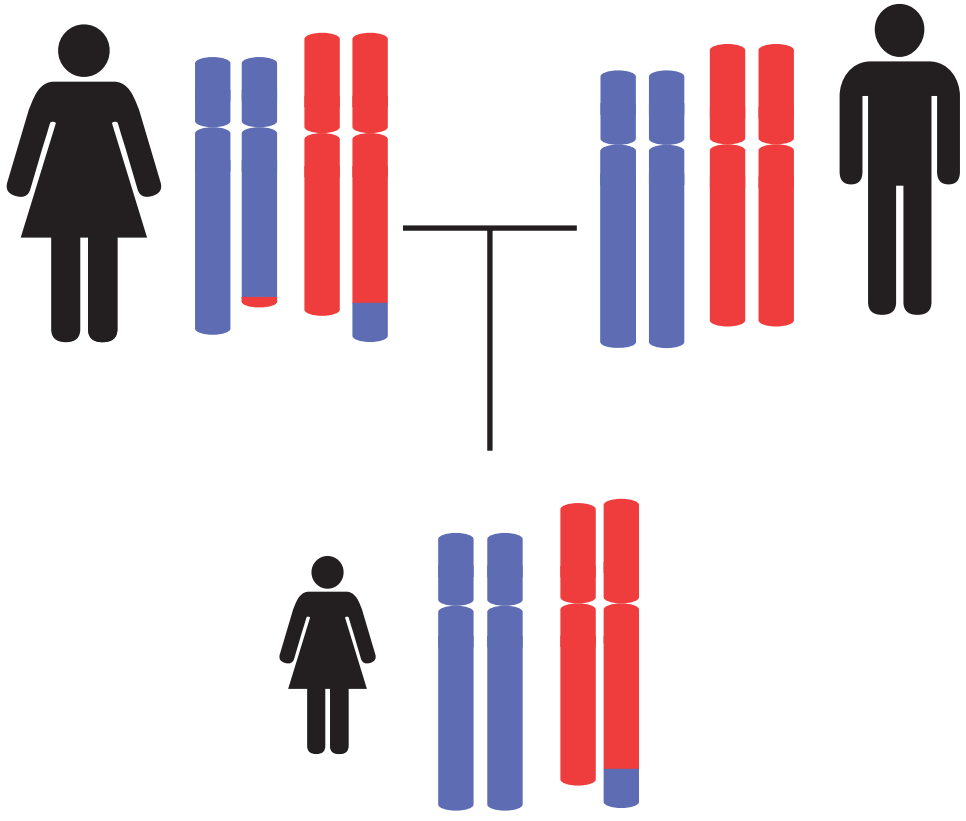

FIGURE 83e-3 Segregation of a balanced translocation in a mother, with inheritance of an unbalanced form in her child. Note that the mother has two rearranged chromosomes, but her child only received one of these, resulting in extra copies of a region of the blue chromosome, with loss of some material from the red chromosome.