common Robertsonian translocation involves chromosomes 13 and 14. Unbalanced Robertsonian translocations involving chromosomes 13 and 21 result in trisomy 13 and Down syndrome, respectively. Approximately 4% of patients with Down syndrome have a translocation, and because recurrence risks are different for families of these individuals, all patients with clinically identified Down syndrome should have a karyotype to look for translocations.

*Inversions* are another type of chromosome abnormality involving rearranged segments, where there are two breaks within a chromosome, with the intervening chromosomal material inserted in an inverted orientation. As with reciprocal translocations, if a break occurs within a gene or control region for a gene, a clinical phenotype may result, but often there are no consequences for the inversion carrier; however, there is risk for abnormalities in the offspring of carriers, as recombinant chromosomes may result after crossing over between a normal chromosome and an inverted chromosome during meiosis.

*Deletion* refers to the loss of a chromosomal segment, which results in the presence of only a single copy of that region in an individual's genome. A deletion can be at the end of a chromosome (terminal), or it can be within the chromosome (interstitial). Deletions that are visible at the microscopic level in standard cytogenetic analysis are generally greater than 5 Mb in size. Smaller deletions have been identified by FISH and by chromosomal microarray. The clinical consequences of a deletion depend on the number and function of genes in the deleted region. Genes that cause a phenotype when a single copy is deleted are known as haploinsufficient genes (one copy is not sufficient), and it is estimated that less than 10% of genes are haploinsufficient. Genes associated with disease that are not haploinsufficient include genes for known recessive disorders, such as cystic fibrosis or Tay-Sachs disease.

The first chromosome deletion syndromes were diagnosed clinically and were subsequently demonstrated to be caused by a chromosome deletion on cytogenetic analysis. Examples of these disorders include the Wolf-Hirschhorn syndrome, which is associated with deletions of a small region of the short arm of chromosome 4 (4p); the cri-du-chat syndrome, associated with deletion of a small region of the short arm of chromosome 5 (5p); Williams syndrome, which is associated with interstitial deletions of the long arm of chromosome 7 (7q11.23); and the DiGeorge/velocardiofacial syndromes, associated with interstitial deletions of the long arm of chromosome 22 (22q11.2). Initial cytogenetic studies were able to provide a rough localization of the deletions in different patients, but with the increased usage of arrays, precise mapping of the extent and gene content of these deletions has become much easier. In many cases, one or two genes that are critical for the phenotype associated with these deletions have been identified. In other cases, the phenotype stems from the deletion of multiple genes. The increased utilization of genomic testing by array, which can identify deletions that are much smaller than those detectable by standard cytogenetic analysis, has resulted in the discovery of several new cytogenomic disorders. These include the 1q21.1, 15q13.3, 16p11.2, and 17q21.31 microdeletion syndromes.

*Duplication* of genomic regions is better tolerated than deletion, as evidenced by the viability of several autosomal trisomies (whole chromosome duplications) but no autosomal monosomies (whole chromosome deletions). There are several duplication syndromes where the duplicated region of the genome is present as a supernumerary chromosome. Utilization of chromosome microarray analysis has made analysis of the origins of duplicated chromosome material straightforward (Fig. 83e-2). Recurrent syndromes associated with supernumerary chromosomes include the inverted duplication 15 (inv dup 15) syndrome, caused by the presence of a marker chromosome derived from chromosome 15, with two copies of proximal 15q resulting in tetrasomy (four copies) of this region. The inv dup 15 syndrome has a distinct phenotype and is associated with hypotonia, developmental delay, intellectual disability, epilepsy, and autistic behavior. Another syndrome is the cat eye syndrome, named for the "cat-eye-like" appearance of the pupil, resulting from a coloboma of the iris. This syndrome results from a supernumerary chromosome derived from a portion of chromosome 22, and the marker chromosomes can vary in size and are often mosaic. Consistent with expectations of a mosaic disorder, the phenotype of this syndrome is highly variable and includes renal malformations, urinary tract anomalies, congenital heart defects, anal atresia with fistula, imperforate anus, and mild to moderate intellectual disability. Another rare duplication syndrome is the Pallister-Killian syndrome (PKS), which illustrates the principle of tissue-specific mosaicism. Individuals with PKS have coarse facial features with pigmentary skin anomalies, localized alopecia, profound intellectual disability, and seizures. The disorder is caused by a supernumerary isochromosome for the short arm of chromosome 12 (isochromosome 12p). Isochromosomes consist of two copies of one chromosome arm (p or q), rather than one copy of each arm. This isochromosome is not generally seen in peripheral blood lymphocytes when they are analyzed by G-banding, but it is detected in fibroblasts. Array technology has been reported to detect the isochromosome in uncultured peripheral blood in some patients, and it has been hypothesized that a growth bias against cells with the isochromosome prevents their identification in cytogenetic studies.

Numerical abnormalities, translocations, and deletions are the most common chromosome alterations observed in the diagnostic laboratory, but in addition to inversions and duplications, several other types of abnormal chromosomes have been reported, including ring chromosomes, where the two ends of the chromosome fuse to form a circle, and insertions, where a piece of one chromosome is inserted into another chromosome or elsewhere into the same chromosome.

*Uniparental disomy (UPD)* is the inheritance of a pair of chromosomes (or part of a chromosome) from only one parent. This usually occurs as a result of nondisjunction during meiosis, with a gamete missing or having an extra copy of a chromosome. A resulting fertilized egg would then have only one parental contribution for a given chromosome pair, or a trisomy for a given chromosome. If the monosomy or trisomy is not compatible with life, the embryo may undergo a "rescue" to normal copy number. If a monosomy is rescued, the single chromosome may be duplicated, resulting in a cell with two identical chromosomes (monosomy rescue) (Fig. 83e-4). In the case of trisomies, a subsequent nondisjunction can result in cells where one of the extra chromosomes is lost (trisomy rescue) (Fig. 83e-4). For trisomy rescue, there is a one in three chance that the lost

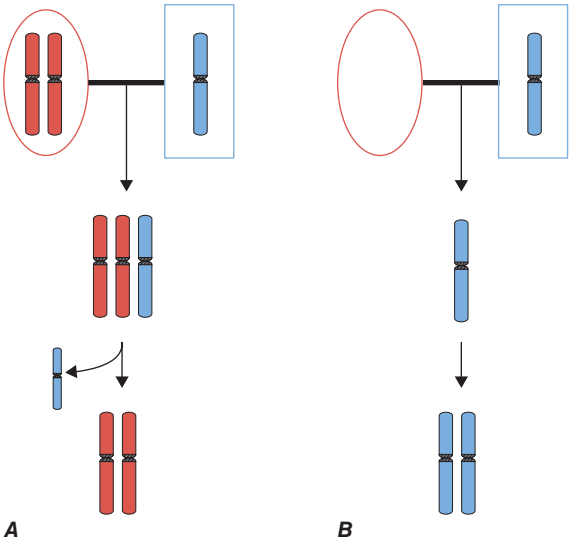


**FIGURE 83e-4 Mechanisms of formation of uniparental disomy.** ***Panel A*** demonstrates nondisjunction in one parent (mother, represented in *red*), with trisomy in the zygote. A subsequent nondisjunction, with loss of the paternal chromosome (represented in *blue*), restores the diploid karyotype but leaves two copies of the maternal chromosome (maternal uniparental disomy [UPD]). ***Panel B*** demonstrates nondisjunction in one parent (mother, indicated by *red oval*), resulting in only one copy of this chromosome in the zygote. Subsequent nondisjunction duplicates the single chromosome, rescuing the monosomy, but resulting in two copies of the paternal chromosome (represented in *blue*; paternal UPD).