13

Chromosome Structural Aberrations

Structural chromosome abnormalities are relatively frequent in human populations. They are the result of breaks that disrupt the continuity of one or more chromosomes. Chromosome breaks in the germline can lead to heritable structural abnormalities; those occurring in somatic cells may increase the risk of cancer. Chromosomes may break at almost any point, but there are sites of preferred breakage, called *hotspots*. The breaks may be repaired, but because any two broken ends that are sufficiently close together in the nucleus may rejoin, an extremely wide variety of structurally altered chromosomes occur. The main classes of structural abnormalities are described in this and the next two chapters, and some of the resulting phenotypes, or clinical syndromes, in Chapters 15–20.

O. J. Miller et al., *Human Chromosomes*

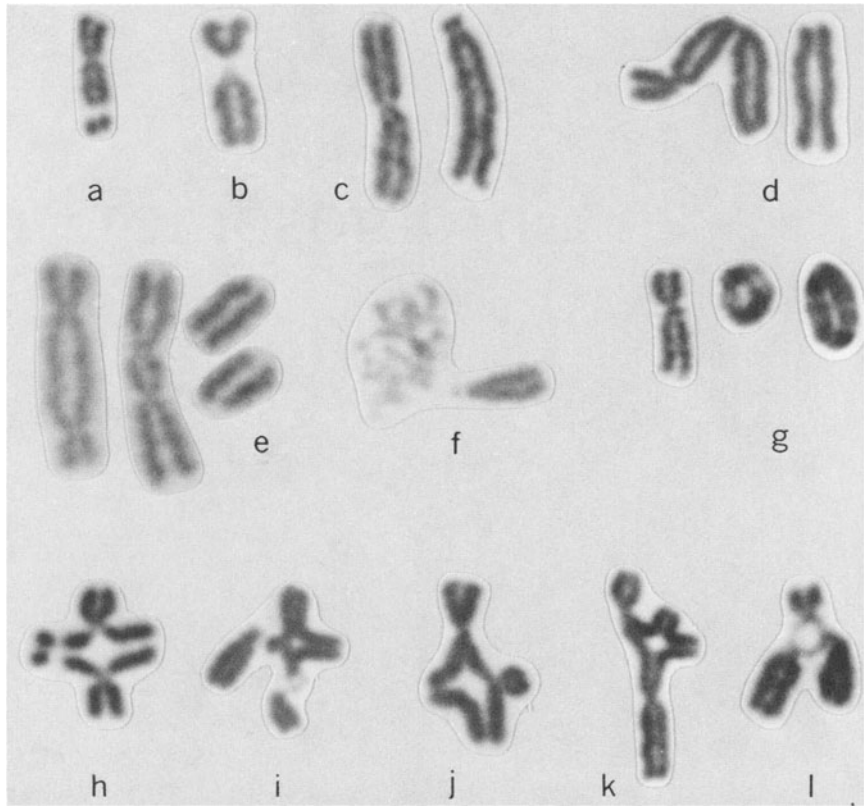

Figure 13.1. Structural aberrations: (a) Gap. (b) Gap at centromere. (c) Normal chromosome 1 and a pericentric inversion of its homologue. (d) Dicentric chromosome and acentric fragment. (e) Two dicentrics and two acentrics from one cell (courtesy of EM Kuhn). (f) A D group chromosome in satellite association with an interphase-like acrocentric. (g) Chromosome 9, ring (9) and double-sized ring (9). (Courtesy of ML Motl). (h) Mitotic chiasma between heteromorphic homologues. (i) Class II quadriradial between two D group chromosomes in satellite association with a D and a G. (j–k) Class IVb chromatid translocations. (l) Hexaradial chromatid translocation, or a satellite association between two D and one G (all, except as noted, courtesy of E Therman).

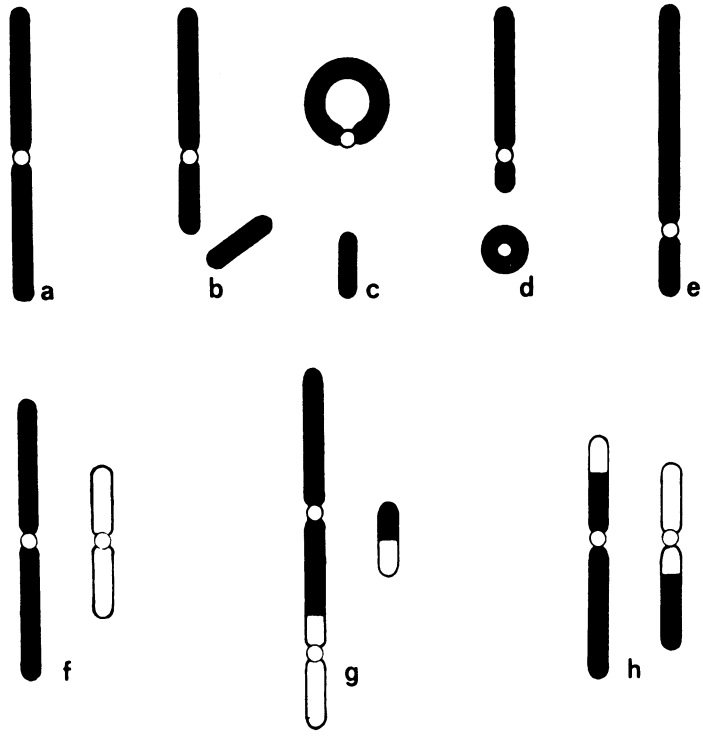

Figure 13.2. Results of G1 breaks in one chromosome (a–e), and in two chromosomes (f–h). (b) Broken chromosome. (c) Centric ring and acentric fragment. (d) Acentric ring and centric fragment. (e) chromosome with pericentric inversion. (g) Dicentric chromosome and acentric fragment. (h) Reciprocal translocation.

Chromosome and Chromatid Breaks and Rearrangements

A chromosome may break at any stage of the cell cycle. If it breaks during the G1 stage and is unrepaired through S, it will be visible in both chromatids (a *chromosome break*) in the next metaphase. If there is no displacement of the fragments, one sees only a gap (Fig. 13.1a and b). If one chromosome (Fig. 13.2a) undergoes a single break, this may lead to a terminally deleted chromosome and an acentric fragment (Fig. 13.2b) that can be lost in a subsequent mitosis. Alternatively, the acentric fragment may be included in a daughter nucleus and replicate, with double fragments visible at the next metaphase.

Two breaks in the same chromosome may result in the formation of either an

acentric fragment plus a centric ring chromosome or an acentric ring plus a centric chromosome with an interstitial deletion (Figs. 13.2c, d; Fig. 13.1g). Very small fragments are called minutes. If two breaks take place in the same arm and the deleted segment reunites with the chromosome in an inverted orientation, a *paracentric inversion* is produced, with no change in the position of the centromere. If one break occurs in each arm and the segment between the breaks is reunited in an inverted orientation, a pericentric inversion is produced (Fig. 13.2e; Fig. 13.1c). The latter rearrangement sometimes shifts the position of the centromere, but many pericentric inversions and all paracentric inversions would be undetectable without banding techniques or in situ hybridization with molecular probes.

If two chromosomes (Fig. 13.2f) undergo an interchange following a single break in each, this may produce a dicentric chromosome and an acentric fragment (Fig. 13.2g; Figs. 13.1d, e) or a reciprocal translocation (Fig. 13.2h). The acentric fragment will eventually be lost, and the dicentric one as well, if the two centromeres are some distance apart, because the centromeres may be pulled towards opposite poles, forming an anaphase bridge. This bridge may undergo breakage at a random point; each broken end is prone to fusion, forming another dicentric chromosome that is subject to the same *bridge-breakage-fusion-bridge cycle* and eventual loss. A three-break interchange may produce either an insertion of an interstitial segment from one chromosome into the same or another chromosome or interchanges among three chromosomes. Multiple breaks in a cell may lead to more complex rearrangements, including chromosomes with several centromeres.

When a break takes place during G2, it involves only one of the two chromatids and is therefore called a *chromatid break*. A single break yields a deleted chromatid and an acentric fragment. A chromatid break in each of two chromosomes can lead to chromatid exchanges and result in *quadriradial* configurations (Fig. 13.1i). These are of two types, one in which alternate chromatids will segregate to opposite poles (I, IIIa, and IVa in Fig. 13.3) and one in which adjacent chromatids will segregate to opposite poles (II, IIIb, and IVb in Fig. 13.3). Alternate segregation leads to a reciprocal translocation involving two of the chromatids, and two unchanged chromatids. Adjacent segregation gives rise to a dicentric chromatid, an acentric chromatid, and two unchanged chromatids. Mitotic chiasmata can occur as a result of crossing over between two homologous mitotic chromosomes (Fig. 13.1h) and form a special subgroup of the alternate type of quadriradial segregation.

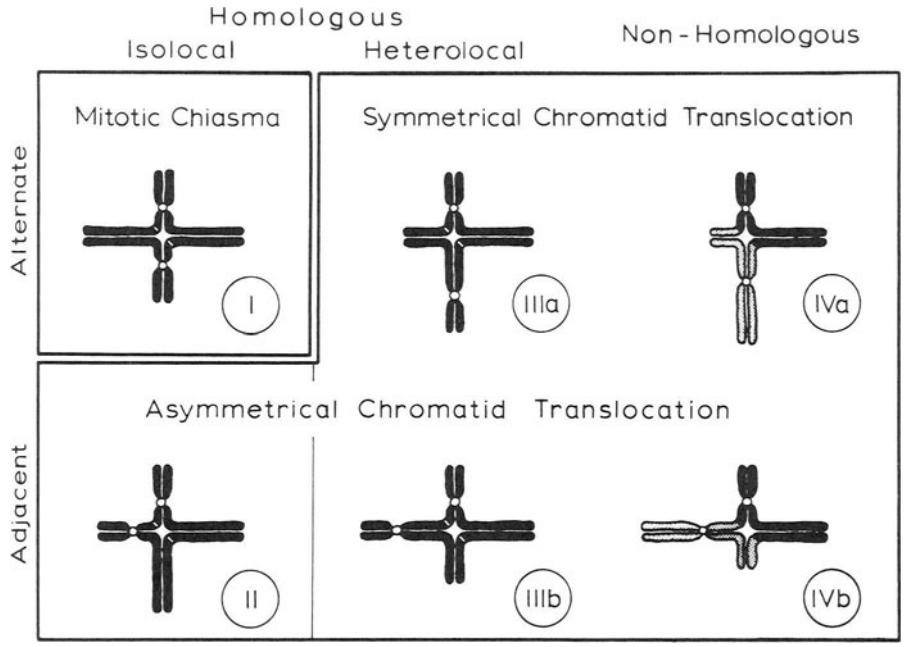

Figure 13.3. The classification of quadriradials. Breaks at homologous points are called isolocal, those at nonhomologous points heterolocal (Therman and Kuhn, 1976).

Deletions (Partial Monosomies), Including Ring Chromosomes

Chromosome deletions, or deficiencies, range in size from just a few base pairs to many megabase pairs in length. Their size can be evaluated by bivariate cytophotometric flow karyotyping, even with deletions as small as 9–26 Mb in size (Silverman et al., 1995). Deletions may arise from a single break (terminal deletion) or from two breaks, which can lead to an interstitial deletion if both breaks are in the same arm or to a ring chromosome if the breaks are in different arms. Large deletions are rare; some of the more important ones are 4p–, 5p–, 9p–, 11p–, 11q–, 13q–, 18p–, and 18q–. Deletions that appear to be terminal, as well as many interstitial deletions, have been found for every chromosome arm in liveborn children (Borgaonkar, 1997). They are common in deletion syndromes despite the known instability (stickiness) of broken ends.

Molecular cytogenetic methods have resolved this paradox: Many of these apparently terminal deletions are capped by a telomeric (TTAGGG)n repeat as a result of a cryptic translocation or the action of telomerase. The first clue to this was the demonstration that a terminal deletion of the short arm of chromosome 16 had been stabilized by the addition of a normal telomere at the point of breakage (Wilkie et al., 1990). Meltzer et al. (1993) showed, using chromosome-specific subtelomeric sequences, that translocations with one breakpoint in the subtelomeric region are very common. These provide a source of telomeres to cap broken chromosome ends, a process they called *telomere capture*. Such telomere capture would stabilize apparently terminal deletions.

This explanation could account for several seeming inconsistencies that have been observed. When human chromosomes are broken with x-rays, the sister chromatids rarely fuse to yield dicentrics that go through bridge-breakage-fusion-bridge cycles, as expected of chromosomes with broken ends. Ring chromosomes sometimes open up and act like normal biarmed chromosomes despite having what should be broken ends. Terminally deleted chromosomes occur too frequently, and have breakpoints that are too consistent, to be the result of two breaks. Niebuhr (1978) reported that in 35 cri du chat patients the 5p– deletion appeared to be terminal in 27, interstitial in four, and capped by a reciprocal translocation in four others. Vermeesch et al. (1998) showed that the distal end of all four 5p– and the one 4p– deletions they studied had telomeric repeats (see Fig. 15.3). Using chromosome microdissection to construct a probe from the area around the apparent deletion, they showed the absence of DNA from any other chromosome, thus ruling out a cryptic translocation.

Ring chromosomes are a class of chromosomes with deletions in which material is lost from the ends of both arms. Rings of almost every chromosome have been observed, with r(21) the most common (Melnyk et al., 1995). Ring chromosomes tend to generate new variants. A sister chromatid exchange may lead to a continuous double ring with one centromere. When the centromere divides in anaphase, the daughter centromeres may go to the same pole. This leads to a double-sized dicentric ring in one daughter cell and no ring in the other. If, on the other hand, the centromeres move to opposite poles, the ring may break at random and the broken ends rejoin, so daughter cells may have rings of unequal size. Thus, rings can generate mosaics in which different cells contain different derivatives of the original ring.

Ring chromosomes are unstable in both mitosis and meiosis and are frequently lost, probably as a result of dicentric formation and subsequent bridge-breakage-

fusion-bridge cycles. The result is a monosomic cell, which may or may not be viable. Ring-X chromosomes are frequently associated with Turner syndrome, due to the generation of an XO cell line. An unusual example of this is a woman who was diagnosed as having Turner syndrome at age 14 but went on to have three pregnancies. One of them produced a daughter who, like the mother, was a 45,X/46,X,r(X) mosaic and had signs of Turner syndrome (Blumenthal and Allanson, 1997). A different kind of mosaicism involves the presence of cells in which the ring chromosome has apparently recurred in two or three successive generations of a family, replacing one of the two normal homologues present in other cells of the individual. Examples involving several autosomes are known, and one involving chromosome 21 has been diagnosed prenatally (Melnyk et al., 1995).

Duplications (Partial Trisomies)

Duplications are seldom seen, in contrast to the more common duplication/deficiencies generated by aberrant meiotic segregation in translocation and inversion heterozygotes (Chapter 16). However, small accessory or supernumerary chromosomes are fairly frequent, occurring in about 1.5 per 1000 live births. At least half of these small chromosomes are derived from chromosome 15 and are inverted duplications, inv dup(15), of the pericentromeric region (Schreck et al., 1977), making this one of the most common structural aberrations. These are sometimes associated with phenotypic abnormalities and sometimes not, depending upon whether the deleted segment of 15q11 contains the Prader-Willi/Angelman syndrome critical region (Chapter 15; Wandstrat et al., 1998). The analysis of these small chromosomes has been aided by FISH analysis, especially using probes generated by PCR amplification of the DNA from flow-sorted or microdissected supernumerary chromosomes, a technique called *reverse chromosome painting* (Viersbach et al., 1998).

Isodicentric chromosomes are symmetric structures consisting of segments of two homologous chromosomes that have broken at identical points. Each segment contains the same whole arm, a centromere, and part of the other arm. Usually one centromere is inactivated. An isodicentric chromosome represents an inverted duplication (partial trisomy) of part of a chromosome, combined with a deletion of the remainder. Most isodicentrics involve two X chromosomes (Fig. 22.2). This probably reflects the more severe phenotypic effects of autosomal trisomies or partial trisomies rather than preferential origin of isodicen-

tric X chromosomes. Isodicentrics consisting of two Y chromosomes also occur, and so do Robertsonian translocation chromosomes with two centromeres (Chapter 27).

Isochromosomes are inverted duplications: palindromic structures in which the breakpoints are very close to or in the centromere. Isochromosomes are thus metacentric and have two homologous arms that are either genetically identical (homozygous at all gene loci) or non-identical (heterozygous at some loci). Isochromosomes for acrocentric chromosomes, including the Y, are fairly common, because the lack of the short arm does not affect viability. Isochromosomes for Xq, designated i(Xq), are also fairly common, because preferential inactivation of the i(Xq) prevents abnormal dosage effects (Chapter 18). The presence of an isochromosome in addition to a normal chromosome complement has been described for very short arms, such as 9p (Jalal et al., 1991). In such cases, the individual is tetrasomic for the arm concerned. Even tetrasomy for major parts of chromosome 9 seems to be compatible with a limited life span. The largest partial tetrasomy has been described in a patient with an extra isodicentric, consisting of two chromosomes 9 attached long arm to long arm (both breakpoints in q22), with the second centromere inactivated. The infant was highly abnormal and lived for only a couple of hours (Wisniewski et al., 1978).

The most probable origin of isodicentric chromosomes, including dicentric isochromosomes, is segregation of an adjacent quadriradial (type II in Fig. 13.3), with the centromeres of the dicentric chromatid going to the same pole (Fig. 13.4b). Therman and Kuhn (1985) have shown that this is the usual mechanism for creating symmetric dicentrics in Bloom syndrome. Dicentrics between two non-homologous chromosomes arise through segregation of a type IVb quadriradial (Fig. 13.3) or through a G1 break in two nonhomologous chromosomes. Molecular studies have shown that in monocentric isochromosomes for Xq and 21q, the two arms may be homozygous or heterozygous (Lorda-Sanchez et al., 1991). The former may arise by misdivision of the centromere and the latter through segregation in an adjacent quadriradial between two homologous chromosomes. A quadriradial may segregate in various ways. However, common to all of them is that the daughter cells are different from each other, whereas descendants of a cell in which a G1 aberration has taken place are identical. A number of human mosaics display cell lines with different chromosome constitutions that may owe their origin to segregation in a quadriradial (Daly et al., 1977). Good examples of such mosaics are provided by persons having one cell line with an isodicentric t(X;X) chromosome and another with a 45,X karyotype.

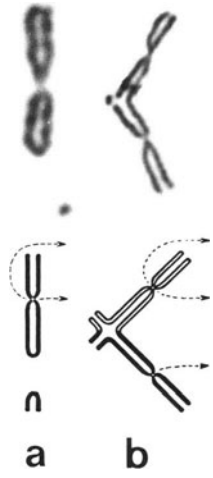

Figure 13.4. Possible origins of isodicentric chromosomes: (a) Isochromatid break and rejoining of the broken chromatids may result in a dicentric. (b) Segregation of an adjacent quadriradial is probably the main mechanism creating isodicentrics.

The simplest explanation for such mosaics, segregation in a quadriradial, has been largely ignored.

Misdivision of the Centromere: Centric Fusion and Centric Fission

Another mechanism (rare) that can lead to isochromosome formation is misdivision of the centromere. This involves transverse fission of centromeric elements rather than the usual longitudinal separation. It segregates the two chromosome arms instead of the two sister chromatids. This is possible because the centromere is a repetitive structure whose subunits are capable of centromeric function (Zinkowski et al., 1991; Chapter 4). Misdivision may occur during either mitosis or meiosis and can lead to isochromosomes by centric fusion. If misdivision takes place between S phase and anaphase, when the chromosomes have already been duplicated, the result is two isochromosomes. The most frequently seen isochromosome involves the long arm of the X chromosome, i(Xq); i(Xp) is not seen, presumably because 46,X,i(Xp) is not viable. Xp has no inactivation center, and trisomy for an active Xp is lethal (Chapter 19).

Most isochromosomes arise by translocation rather than misdivision (Chapter 14). Meiotic misdivision is ruled out because it would produce 46, i(Xq),i(Xp), and this is never seen. If misdivision of an unduplicated chromosome were to occur between anaphase and S phase, two telocentric chromosomes would be produced, a process called centric fission. Janke (1982) observed centric fission of chromosome 7 in three generations of one family. Reports of two telocentrics are rare, involving only chromosomes 4, 7, and 10 (Therman et al., 1981; Rivera and Cantu, 1986). Individuals with two cell lines, one with a telocentric chromosome 13, 21, or X and the other with an isochromosome 13q, 21q, or Xq, have also been described (Therman et al., 1981). In these cases, either the telocentric chromosome or the isochromosome arose through misdivision of a normal chromosome, and the other through further misdivision of the resulting abnormal chromosome. Once a centromere misdivides, it often continues to be unstable.

Pericentric and Paracentric Inversions

Pericentric inversions (Fig. 13.2e) have been described for all chromosomes except number 20, but with quite different frequencies; for instance, the C-band heteromorphism, inv(9), comprises nearly 40% of all pericentric inversions, and inversions of chromosome 7 comprise about 20%. Breakpoints are also nonrandom: for example, those in bands 2pl3, 2q21, 5q31, 6q21, 10q22, and 12ql3 are seen most often (Kleczkowska et al., 1987). Some pericentric inversions are obvious because of a change in the position of the centromere or the banding pattern, but many are not. Bailey et al. (1996) developed a method capable of detecting any pericentric inversion, using FISH with strand-specific probes for centromeric and telomeric repeats (Fig. 13.5) Microscopically observable paracentric inversions are far less common than pericentric inversions, although they have involved almost every chromosome. Submicroscopic inversions are relatively common, especially the very short ones, and are a major cause of disease (Chapter 16).

The most frequent cytologically visible paracentric inversions have breakpoints in chromosome arms 11q, 7q, and 3p. Of the 184 inversions cited by Madan (1995), 38 had a breakpoint in 11q and in 31 of these it was in 11q21–q23. An additional 24 had a breakpoint in 7q, although these were not so tightly clustered. The rarity of microscopically observed paracentric inversions is probably due to the difficulty of detecting them, since they do not

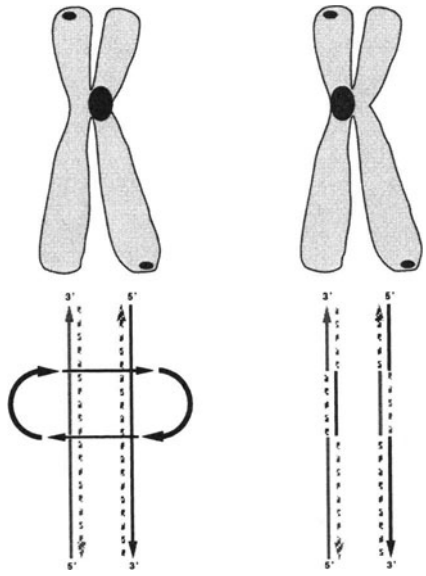

Figure 13.5. COD-FISH, using strand-specific telomeric and centromeric probes that hybridize to only one of the two chromatids. The chromatid to which the centromeric marker hybridizes is switched by a pericentric inversion, as explained in the DNA diagram below each chromosome. (Left) Normal arrangement. (Right) After inversion (modified by Julianne Meyne, from Bailey et al., 1996, reproduced with permission of S. Karger AG, Basel).

change the arm ratio and only very rarely lead to abnormal offspring. The reason for this is that crossing over in a paracentric inversion results in a dicentric and an acentric chromosome that usually segregate to different gametes and produce inviable zygotes. Any family in which a presumed paracentric inversion carrier has produced chromosomally abnormal progeny is generally segregating an intrachromosomal insertion instead; this carries a 15% risk of chromosomally unbalanced progeny (Allderdice et al., 1983; Madan and Menko, 1992).

Reciprocal Translocations

Many different reciprocal translocations (Fig. 13.2h) have been identified and characterized by chromosome banding techniques and, increasingly, by molecular methods, including FISH analysis with chromosome paints (Chapter 8). Reciprocal translocations involving all human chromosome arms have been

observed (Borgaonkar, 1997). Translocations usually come to attention (are ascertained) through infertility, a phenotypically abnormal child, or by chance, as in population surveys. The inferred spontaneous rate of interchanges is at least 1–10 per 1000 gametes per generation. The population frequency is so low that matings between heterozygous carriers almost never occur.

The breakpoints in translocations ascertained through a chromosomally unbalanced individual are distributed differently from those detected by chance, because the former reflect the differential viability of individuals who are partially trisomic or monosomic for various chromosome regions. When reciprocal translocations are ascertained by chance, the breaks are distributed at random (at a cytological level; but see Chapter 14). When they are ascertained through chromosomally unbalanced descendants, the breakpoints are most frequent in some parts of the genome (for example, telomeres), with 65% located in R-positive bands, especially those that contain a fragile site and those that are rich in CpG islands and poor in *Alu* repeats. Breakpoint distribution depends to some extent on the agent that induced the chromosome breakage (Cohen et al., 1996).

Translocations involving no more than 2–5 Mb of DNA often can be detected by high-resolution banding methods, but determining the origin of such small translocated segments usually requires molecular cytogenetic techniques. Chromosomal microdissection of the affected region, PCR amplification of the microdissected DNA, and its use as a painting probe for FISH can frequently pinpoint the origin of the rearranged or extra material (Stone et al., 1996). Comparative genomic hybridization (CGH) can detect gains or losses of an extremely short chromosome segment (Chapter 8). For example, CGH, FISH, and genotyping with molecular markers were combined to recognize a complex abnormal karyotype, 46,XY,−13,+der(13)t(6;13)(q23;q34)de novo mat, in an infant with congenital malformations (Erdel et al., 1997).

Analysis of polymorphic molecular markers can clarify the origin of reciprocal translocations and their unbalanced segregation products. A newborn female with multiple anomalies had the karyotype 46,XX,der(18)(18pter–18q23::13q14.3–13qter), with a duplication of 13q14–qter and a deficiency of 18q23–qter. Both parents had normal karyotypes, but could one of them be a germline (gonosomal) mosaic, with an increased risk of further abnormal children? Molecular genotyping showed that the der(18) chromosome was of combined maternal and paternal origin, indicating that the translocation occurred during early embryogenesis in the proband, with the subsequent loss of the der(13) chromosome and duplication of the normal 13 (Eggerman et al., 1997).

Robertsonian Translocations (RTs)

Whole-arm transfers constitute a special class of reciprocal translocations. They almost always involve two acrocentric chromosomes (*Robertsonian translocations*, or RTs). Whole-arm transfers between nonacrocentric chromosomes are extremely rare. RTs are the most commonly observed chromosome aberrations, with a frequency of nearly 4 per 10,000 gametes per generation. This reflects their virtual lack of phenotypic effect and consequent high rate of retention; for example, 85–95% of DqDq translocations are familial (Nielsen and Rasmussen, 1976). Nearly 75% of RTs are 13q14q, and 10% are 14q21q. The eight other possible types involving acrocentric chromosomes account for the rest, with 21q21q the most common. Nucleolar fusion and satellite association can bring acrocentric chromosomes together but play no role in the nonrandom participation of chromosomes in RTs (Therman et al., 1989).

Robertsonian translocations were originally thought to arise by fusion of two chromosomes that had each broken at the centromere. However, banding and molecular studies have shown that this is rarely the case. Most Robertsonian translocations are dicentric but contain no rRNA genes, so the breakpoints are in the short arm, proximal to the NOR (Fig. 13.6 left). FISH analysis enabled

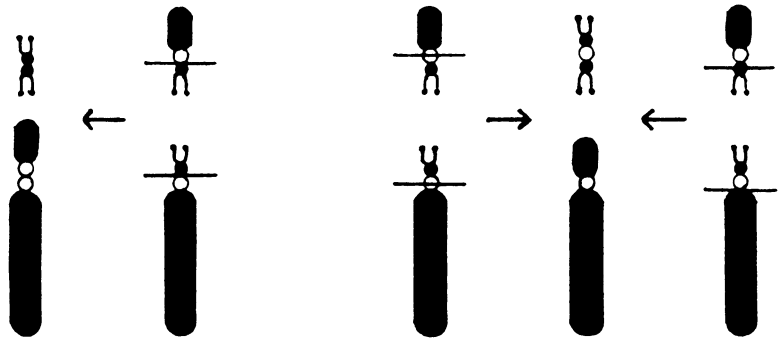

Figure 13.6. Two mechanisms of Robertsonian translocation formation between a G- and a D-group chromosome. (left) (common): Breaks in the short arms produce a dicentric chromosome (bottom) and an acentric fragment (top). (right) (rare): Breaks through the centromeres (open circles) or one break in a short arm and one in a long arm produce two monocentric chromosomes (center).

Han et al. (1994) to narrow the region of the breakpoints in 17 rob(13q14q) translocations to the satellite III region of 14p11 and adjacent to the retained satellite I region of 13p11. Page and Schaffer (1997) isolated rob(13q14q) and rob(14q21q) translocations in human-rodent somatic cell hybrids to facilitate molecular genotyping. They showed that both of the contributing chromosomes are almost always from the same parent, that 90% arise in female meiosis, and that the breakpoints are highly consistent. In contrast, analysis of genetic markers has demonstrated a different (somatic) origin of most isochromosomes and RTs between homologous chromosomes, such as t(14q;14q) and t(21q;21q). The isochromosomes are homozygous at all loci and associated with uniparental disomy (Chapter 21), suggesting a postmeiotic origin. The RTs involving homologous chromosomes contain both a maternal and a paternal contribution and can have arisen only postmeiotically, during early mitotic divisions (Robinson et al., 1994).

The rare formation of a Robertsonian translocation by centric fusion should lead to reciprocal chromosomes, one with the short arms from two acrocentrics plus a centromere (Fig. 13.5). Abeliovich et al. (1985) reported a family in which the reciprocal RT chromosomes were present in both a balanced carrier mother and her daughter with Down syndrome. Such cases are very rare, because most RTs arise from breaks in the short arms, so only the long-arm RT has a centromere. In fact, most RTs have two centromeres, but this does not lead to anaphase bridges and breaks. Is the mitotic and meiotic stability of these chromosomes due to inactivation of one of the two centromeres, or are they so close to each other that there is never a twist between them? Studies with the centromeric proteins C and E (CENP-C and CENP-E), markers for active centromeres, support both explanations.

Intrachromosomal and Interchromosomal Insertions

Insertions require three breaks. Consequently, they are considerably rarer (about one in 5000 live births) than two-break abnormalities (one in 500 live births). An insertion may occur either within one chromosome (intrachromosomal), by a shift in position of a chromosome segment, or between two chromosomes (interchromosomal), by translocation of a segment of one chromosome to an interstitial location in the other. The segment may be inserted either in the same

orientation as its original one or in an inverted orientation. If the segment stays in the same arm of a chromosome, it is called a paracentric insertion; if it is inserted into the other arm of the same chromosome, it is a pericentric insertion (Fig. 16.5). Paracentric insertions, like paracentric inversions, do not change the position of the centromere. They became detectable only with the development of precise banding methods (reviewed by Madan and Menko, 1992).

Some insertions are large enough to be detected by chromosome banding or FISH analysis. Tandemly repetitive rRNA genes are sometimes moved from the short arm of an acrocentric chromosome to an interstitial site on another chromosome, presumably as a result of having two breakpoints within a single rRNA gene cluster and one elsewhere (Guttenbach et al., 1998). Many insertions are submicroscopic, requiring molecular cytogenetic methods to detect. They usually involve a transposable element (Chapter 5). One mechanism by which this occurs is that a cDNA copy of a cytoplasmic mRNA is made, using reverse transcriptase, and is inserted back into the genome. These genes or pseudogenes are easily recognized because they have no introns; these are removed from the RNA transcript before it leaves the nucleus. Since integration occurs at random and may disrupt the gene into which the element integrates, this is one cause of mutation.

Complex and Multiple Rearrangements

The occurrence of three or more chromosome breaks can lead to complex rearrangements involving multiple chromosomes. Q-banding enabled Allderdice et al. (1971) to recognize one of the first of these, involving chromosomes 6, 14, and 20 in the mother of a mentally retarded, chromosomally unbalanced girl; without banding, the girl appeared to have a novel D-group trisomy. More than 100 such complex rearrangements, involving two to six chromosomes, have been reported (reviewed by Batanian and Eswara, 1998). A phenotypically abnormal child with five structurally aberrant chromosomes, 1, 4, 7, 12, and 15, was born to a woman who developed malignant melanoma during pregnancy but was not treated during the pregnancy (Fitzgerald et al., 1977). The same unknown agent may have been responsible for both the malignancy in the mother and the chromosome aberrations in the child, because chromosome aberrations predispose to malignancy (Chapter 26).

A specific chromosome segment can be involved in nonreciprocal rearrangements via a common breakpoint as a result of instability of the repaired site. This

can lead to multiple rearrangements and complex mosaicism (Lejeune et al., 1979) or to jumping Robertsonian translocations that produce a succession of different Robertsonian translocations in an individual (Gross et al., 1996). The nomenclature of ISCN (1995) is useful for providing an unequivocal description of all these complex karyotypes.

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