# 24

# Chromosome Instability Syndromes

Several mutant genes are known that greatly increase the incidence of chromosome aberrations and have striking clinical effects. The most extensively studied of these autosomal recessive disorders are *Bloom syndrome* (BS), *Fanconi anemia* (FA), and *ataxia telangiectasia* (AT). The risk of cancer is enhanced in such individuals: one-fourth of BS patients, one-eighth of AT patients, and about one-eighth of FA patients develop cancer, frequently at an early age. The great interest in BS, FA, and AT might seem out of proportion to their rare occurrence. However, their study has shed light on chromosome structure and function, providing insights into the role of disturbed DNA replication and repair in causing chromosome breaks, mutator phenotypes, and cancer.



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

# Bloom Syndrome

This autosomal recessive disease is characterized by low birth weight, stunted growth, sun sensitivity, facial erythema (dilation of blood vessels), immunodeficiency, and a greatly increased risk of cancer (German, 1993). There is a high frequency of chromosome aberrations in BS patients, as first noted in 1965 by German. These are of two types. In the first, random breaks lead to fragments or to reciprocal translocations between nonhomologous chromosomes. The second type is found almost exclusively in BS and consists of a greatly enhanced tendency to have homologous exchanges. All the breakage probably takes place in S–G2 (Therman and Kuhn, 1985). The increased tendency towards exchanges between homologous chromatids expresses itself in a 10- to 20-fold increase in the number of sister chromatid exchanges (SCEs) (Chaganti et al., 1974; Fig. 24.1) and in a 50- to 100-fold increase in the number of quadriradial configurations indicative of mitotic crossing over (Fig. 24.2; Therman and Kuhn, 1981). Spontaneous cell fusion is sometimes seen in BS cells and in malignant cells, but otherwise occurs only in normally differentiating bone, muscle, and trophoblast (Chapter 23).

The high SCE frequency seen in BS fibroblasts in culture is reduced to normal by fusing BS cells with normal cells or by microcell-mediated transfer of a normal chromosome 15 into BS cells (McDaniel and Schultz, 1992). The BS gene, called *BLM*, is genetically very closely linked to *FES*, which has been mapped more precisely to 15q26 (Mathew et al., 1993). Lymphoblastoid BS cells also show a high SCE frequency, but subcultures sometimes revert to a normal frequency. Genetic marker studies showed that the revertant lines all showed loss of heterozygosity (LOH) for 15q markers distal to the *BLM* locus, presumably as a result of somatic crossing over between homologous chromosomes each carrying a different BLM mutation. Thus, one of the daughter chromosomes has the recombined *BLM* gene with both point mutations, while it homologue has a normal copy of the gene. Mapping the presumptive crossover point led to isolation and cloning of the *BLM* gene (Ellis et al., 1995). Interestingly, the 1417-amino-acid protein product predicted by the DNA sequence of *BLM* belongs to the RecQ family of DNA helicases (unwinding enzymes), and this may account for the well-known retardation of DNA chain elongation during replication in BS cells. Another of these helicases is mutated in Werner syndrome (WS), as described below.

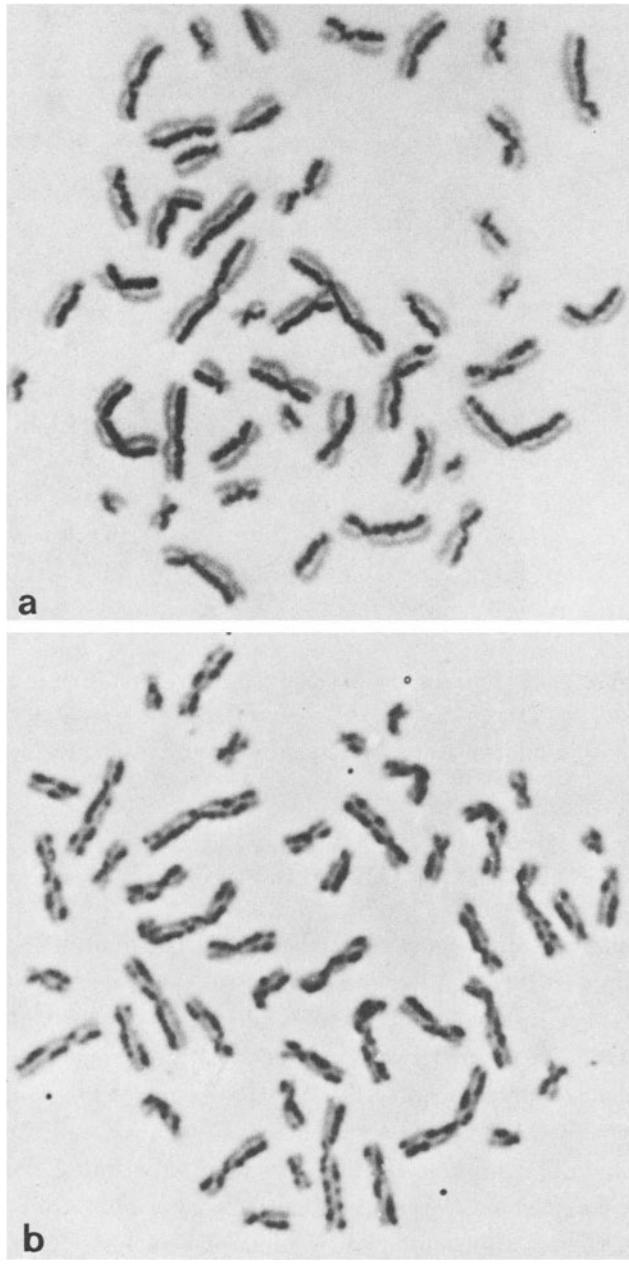


**Figure 24.1.** (a) Sister chromatid exchanges (SCEs) in a normal lymphocyte. (b) Highly increased number of SCEs in a lymphocyte from a patient with Bloom syndrome (courtesy of RSK Chaganti).

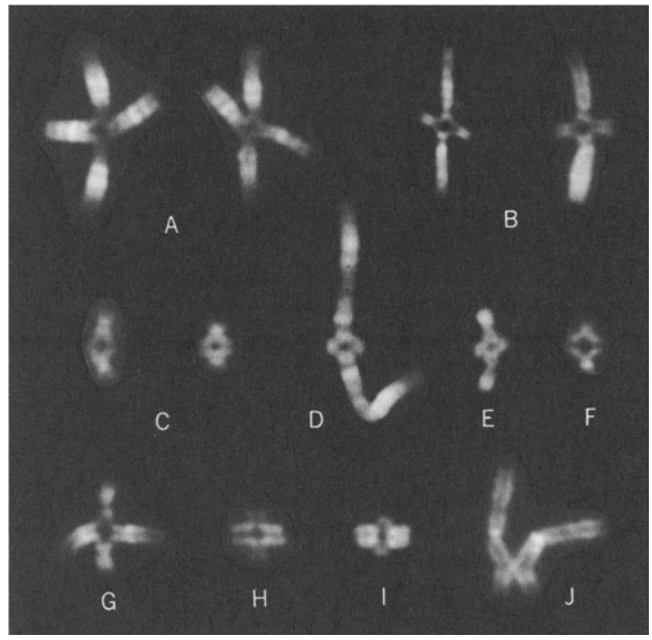


**Figure 24.2.** Quadriradial configurations in chromosomes 1q(A), 6p (B), 19 (C), 1q (D), 20q (E), 22q (F), 12q (G), 18q (H), centric region of 18 (I), and 3p (J), indicative of mitotic chiasmata in Bloom syndrome (Kuhn, 1976).

## Mitotic Recombination or Crossing Over

Chiasmata and genetic recombination occur at high frequency in meiosis (Chapter 9) but far less often in mitosis. The most striking feature of the chromosome instability in Bloom syndrome is the marked tendency for mitotic chiasmata to form between homologous chromosomes to give distinctive quadriradial configurations (Figs. 20.1, 24.2). An interesting example of mitotic recombination (MR) arising by exchange between homologues is the transfer of a distinctive Q-bright satellite from one acrocentric chromosome to another (Therman et al., 1981). Cytological evidence of MR in BS cells (Chaganti et al., 1974) has been confirmed by molecular analyses (Groden et al., 1990). MR occurs far more frequently in Bloom syndrome than in normal cells, in which the rate of mitotic recombination is generally about 1–10 per 100,000 cells (Gupta et al., 1997), with marked individual variation of unknown origin (Holt et al., 1999). Mitotic crossing over leads to LOH (homozygosity) for all loci

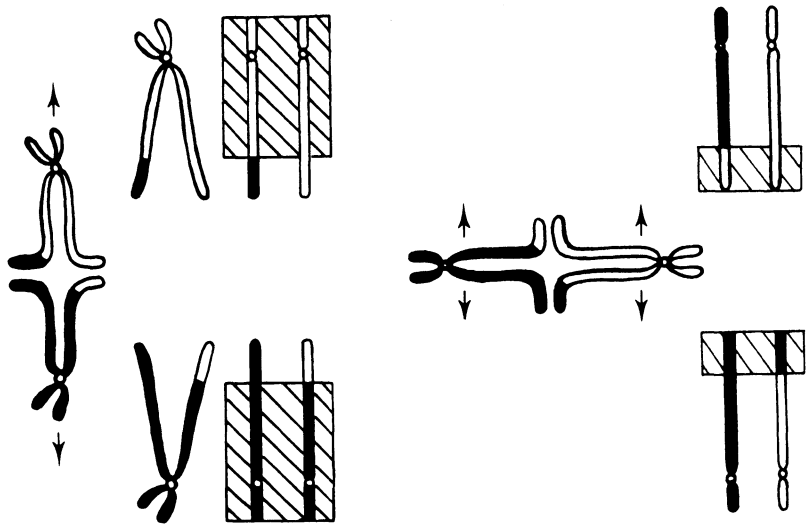

**Figure 24.3.** Segregation after crossing over in a meiotic bivalent (left) and a mitotic chiasma (right). The chromatids distal to a meiotic chiasma are nonsisters, but those distal to a mitotic chiasma are sister chromatids. Note the loss of heterozygosity (LOH) with homozygosity of markers distal to the mitotic crossover point (Therman and Kuhn, 1981).

distal to the breakpoint (Fig. 24.3), as seen in BS lines that have reverted to a normal SCE frequency. Loss of heterozygosity is a major mechanism of carcinogenesis in general (Chapter 28), and it may account for the high incidence of cancer in BS, because many chromosome segments can become homozygous via the abundant SCEs (Therman and Kuhn, 1981). In this regard, the highly nonrandom distribution of mitotic chiasmata in BS may be relevant. Although about one-sixth of the chiasmata are in centromeric heterochromatin, there are also specific hotspots in distal 1p, 3p21, 6p21, 11q13, 12q13, 17q12, and distal 22q (Kuhn, 1976), some near tumor suppressor genes.

## Fanconi Anemia

This autosomal recessive disease is marked by bone marrow failure (pancytopenia), skeletal anomalies (such as absence of the thumb or radius), hyperpigmentation of the skin, reduced fertility, and an increased incidence of cancer (Alter

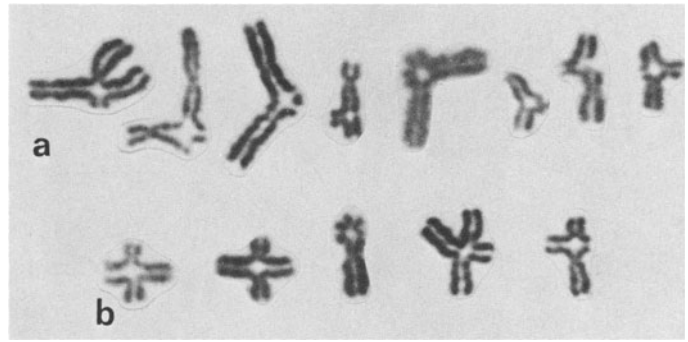


**Figure 24.4.** Chromosome abnormalities in lymphocytes of a patient with Fanconi anemia. (a) Adjacent quadriradials. (b) Alternate quadriradials (courtesy of EM Kuhn).

and Potter, 1983). Cultured FA cells have a decreased rate of DNA replication, a prolonged G2 phase, increased spontaneous chromosome breakage, and increased sensitivity to bifunctional alkylating agents like diepoxybutane (DEB) and mitomycin C (MMC) because the DNA interstrand crosslinks they induce cannot be repaired. The most characteristic chromosome anomalies in FA are translocations between nonhomologous chromosomes (Fig. 24.4), which were first described by Schroeder et al. (1964). Although the proportion of lymphocytes with aberrations may be as high as 30%, there is no increase in intrachromosomal interchanges, as indicated by a normal SCE frequency (Chaganti et al., 1974). The greatly increased chromosome breakage induced by DEB facilitates both prenatal and postnatal diagnosis (Auerbach et al., 1989), but more effective molecular diagnostic tests are becoming available as the various mutant genes causing FA are identified.

Pairwise fusion of FA cells from unrelated patients produces hybrid heterokaryons (Chapter 23) whose sensitivity to a crosslinking agent is reduced to normal only if different mutant genes are present in the two patients, so that the fused cell contains some normal product of each gene. Such analyses have shown that cells from unrelated patients with FA fall into at least eight complementation groups (FA-A to FA-H), indicating that mutations in as many as eight different genes may cause FA (Joenje et al., 1997). The proteins of all eight complementation groups may bind to each other to form a giant complex that carries out an important but still unknown functiion in DNA replication or repair. Three of these genes have been cloned. The normal FAA and FAC protein prod-

Table 24.1. The Genetic Basis of Some Chromosome Instability Syndromes

| Syndrome | Gene | Location | Product or function |
|---|---|---|---|
| Bloom | *BLM* | 15q26 | RecQ DNA helicase |
| Fanconi A | *FANCA* | 16q24.3 | DNA repair |
| Fanconi C | *FANCC* | 9q22.3 | DNA repair |
| Fanconi D | *FANCD* | 3p22–p26 | DNA repair |
| Fanconi E | *FANCE* | 6p21–p22 | DNA repair |
| Fanconi G | *FANCG* | 9p13 | Postreplication repair |
| Ataxia telangiectasia | *ATM* | 11q22–q23 | Cell cycle checkpoint |
| Nijmegen breakage | *NBS1* | 8q21.3 | Nibrin: DNA DSB repair |
| Werner | *WRN* | 8p11–p12 | RecQ DNA helicase |
| Roberts | *RS* | | DNA repair? |

ucts of two of these genes, *FANCA* and *FANCC*, bind to each other, but mutant FAC fails to bind to FAA, suggesting a mechanism for the phenotypic effect of the mutation (Kupfer et al., 1997). The third cloned gene, *FANCG*, maps to 9p13 and is identical to *XRCC9*, which may be involved in DNA postreplication repair or cell cycle checkpoint control (Winter et al., 1998). *FANCD* has been mapped to 3p22–p26. *FANCE* has been mapped by *homozygosity mapping* (Table 24.1). This technique involved screening the entire genome with closely spaced, highly polymorphic (and thus informative) genetic markers. The affected individuals in three families showed a single 18.2-cM region of 6p21–p22 in which all the marker alleles were homozygous, thus mapping the gene to this region (Waisfisz et al., 1999). About 40% of the mutations in the large *FANCA* gene are large intragenic deletions that remove up to 31 of the 43 exons (Morgan et al., 1999).

## Ataxia Telangiectasia: A Cell Cycle Checkpoint Disorder

This autosomal recessive disease is characterized by progressive cerebellar ataxia, telangiectasia of eyes and skin, growth retardation, elevated serum alpha-fetoprotein, severe immunodeficiency, premature aging, and a greatly increased risk of developing solid or lymphoid tumors (Shiloh, 1995). Surprisingly, even heterozygotes show some increased risk of cancer (Swift et al., 1991). Ataxia

develops between 3 and 6 years of age, and the patients usually die of pulmonary infections or cancer. AT patients have a greatly increased sensitivity to ionizing radiation and radiomimetic chemicals (Gatti and Hall, 1983).

Chromosome aberrations are less frequent in AT than in BS or FA. Random breakage often leads to cell clones with a translocation, most commonly involving chromosome 14 (Kaiser-McCaw et al., 1975). SCEs are not increased. There is, however, a striking finding: frequent telomere-telomere fusions. These, like the premature aging, may be due to the greatly elevated rate of telomere shortening seen in AT cells (Metcalfe et al., 1996). There is also a marked increase in intrachromosomal recombination; this could account for the abnormal rearrangements of immunoglobulin and T-cell receptor genes that lead to immunodeficiency in these patients (Meyn, 1993).

The AT gene, called *ATM*, maps to 11q22–q23 (Gatti et al., 1988). It has been cloned and sequenced (Savitsky et al., 1995). Its deduced protein product is similar to the signal-transducing phosphatidylinositol-3 kinases (PI-3Ks). The ATM protein is involved in meiotic recombination (Keegan et al., 1996). It also functions as an early signal in the activation of the G1 checkpoint, which blocks entry of cells into S until any DNA damage is repaired (Chapter 2). AT cells can move into S despite DNA damage, resulting in unrepaired DNA strands, chromosome breaks and rearrangements, or cell death. Normally, in cells exposed to a DNA-damaging agent such as ionizing radiation, a phosphate group is first removed from the serine residue in position 376 of the p53 protein, which is then able to bind 14-3-3 proteins and become active (Waterman et al., 1998). There is a coordinate rise in both the p53 tumor suppressor protein and the growth arrest and DNA damage inducible protein 45 (GADD45) protein, which both act in the signal-transducing pathway that activates the G1 checkpoint discussed in Chapter 2. However, in AT cells, no increase in either protein occurs in response to radiation, indicating that the ATM protein is essential for cell cycle arrest following DNA damage (Kastan et al., 1992). The importance of this for carcinogenesis is discussed in Chapter 26.

## Related Disorders with Chromosome Instability

Nijmegen breakage syndrome (NBS) is a rare autosomal recessive disorder that was initially considered to be a variant of ataxia telangiectasia because of their

virtually identical phenotypes: growth retardation, hypersensitivity to ionizing radiation, chromosomal translocations arising at sites of V(D)J rearrangements, immunodeficiency, gonadal failure, and increased risk of cancer. However, the gene for NBS is at a different location: 8q21.3 rather than 11q22–q23. Positional cloning has identified the *NBS1* gene, which is transcribed in all tissues (Matsuura et al., 1998; Varon et al., 1998). A shorter transcript is expressed at high levels in the testis, suggesting that the NBS1 protein is involved in meiotic recombination. If this is also true in the female germline, it could account for the presence of ovarian failure in NBS. Mutations of the gene are often submicroscopic deletions, identifiable by molecular analysis; a 5-bp deletion is common. The *NBS1* gene product is nibrin (Varon et al., 1998), part of a multiprotein complex that also contains the human MRE11, RAD50, and BRCA1 proteins, in keeping with its role in DSB repair during meiotic recombination (Carney et al., 1998; Zhong et al., 1999; see also Chapter 10). MRE11 maps to 5q23–q31, a region that is frequently altered in myeloid leukemia.

Werner syndrome (WS) is a rare autosomal recessive disorder marked by growth retardation and premature aging. Both chromosome structural aberrations and the risk for cancer are increased (Salk et al., 1981). Gene mutations also occur at a high frequency. Three-fourths of them are due to submicroscopic deletions, with half of the deletions more than 20 kb long (Fukuchi et al., 1989). The initiation of DNA replication is impaired in WS cells, and the locus-specific mutation rate is increased 50-fold. The WS gene, called *WRN*, has been cloned and sequenced (Yu et al., 1996). The gene product has been shown to be an active DNA helicase of the RecQ family (Gray et al., 1997). Helicases are involved in DNA replication and repair but also in transcription. Molecular studies have shown that the gene is expressed only in nonepithelial cells, which is probably the reason that only nonepithelial tumors are common in this disorder.

The xeroderma pigmentosum (XP) group of autosomal recessive diseases is not associated with an increased rate of spontaneous chromosome breakage but shows very high susceptibility to sunlight (UV)-induced skin cancers. Complementation analyses (Chapter 23) and follow-up studies have shown that mutations of at least eight different genes, *XPA–XPG* and *XPV* (variant), produce the XP phenotype, although only those of *XPA*, *XPB*, *XPD*, and *XPG* are associated with progressive neurological degeneration (Cleaver and Kraemer, 1995). *XPV* encodes DNA polymerase η, which carries out error-free replication of UV-damaged DNA by bypassing UV-induced thymine dimers (Masutani et al., 1999). The XPB and XPD proteins, like BLM and WRN, are RECQ DNA heli-

**Table 24.2.** Genes for Eight Complementation Groups of Xeroderma Pigmentosum

| Gene | Location | Function in excision repair of UV-damaged DNA |
|---|---|---|
| *XPA* | 9q34.1 | Binds UV-damaged DNA preferentially |
| *XPB* | 2q21 | RecQ DNA helicase |
| *XPC* | 3p25.1 | ? |
| *XPD* | 19q13.2* | RecQ DNA helicase |
| *XPE* | ? | ? |
| *XPF* | 16p13 | Component of a nuclease† |
| *XPG* | 13q32–q33 | Endonuclease |
| *XPV* | ? | DNA polymerase η |

*The ERCC1 gene is also at 19q13.2

†ERCC1 and XPF encode components of the same nuclease

cases. All four of these proteins bind to the p53 protein and reduce p53-mediated cell killing, or *apoptosis* (reviewed by Spillare et al., 1999). This contributes to the mutator phenotype (see below) of these disorders. More generally important in XP is the error-prone replication of DNA in individuals homozygous for a mutation in any one of the XP genes. All eight of them are required for excision repair of DNA that has been damaged by UV or certain other agents (Table 24.2).

Bloom, Werner, and xeroderma pigmentosum syndromes are good examples of *mutator phenotypes*: Inactivation of a mutator locus by deletion or mutation greatly increases the risk of mutation at other loci throughout the genome. The importance of mutator phenotypes as causes of cancer is discussed further in Chapter 26. Given the complexity of DNA replication and repair and the still incomplete understanding of the many proteins (and thus genes) involved, it would not be surprising if other genotypes are found that predispose to increased chromosome aberrations. In fact, a number have already been reported. One intriguing report involved a girl with craniosynostosis, microcephaly, birdlike facies, and mental retardation. Her lymphocytes showed a high frequency of spontaneous chromosome breakage, endomitosis, endoreduplication, and hypersensitivity to alkylating and radiomimetic agents. Her parents were consan-

guineous, supporting the notion that this may be a newly recognized rare recessive disorder (Tommerup et al., 1993).

The disorders discussed thus far in this chapter are marked by increased rates of both spontaneous and induced chromosome damage. In addition, a few conditions show hypersensitivity to DNA-damaging agents despite the absence of a high rate of spontaneous chromosome damage. One of these is Roberts syndrome (RS), a rare autosomal recessive disease characterized by severe pre- and postnatal growth retardation and symmetrical limb reduction deformities (tetraphocomelia). About half the cases show a striking abnormality (the RS effect): "puffing," or decondensation, of the constitutive heterochromatin and premature separation of the centromeres so that some sister chromatids look straight, or parallel, with no primary constriction (Tomkins et al., 1979). Because a *Drosophila* mutant with a defect in mitotic condensation of heterochromatin was reported to be hypersensitive to cell killing by mutagens, Burns and Tomkins (1989) looked for, and found, a similar hypersensitivity of RS cells to cell killing by mitomycin C (MMC). MMC induces chromosome breaks mostly in the heterochromatin (Shaw and Cohen, 1965). Such breakage, if unrepaired, would produce multiple acentric chromosome fragments, whose loss in succeeding mitoses would lead to deletion of essential genes and thus to cell death. This suggests that there is a defect in the repair of this kind of DNA damage in RS patients. The mechanism of the undercondensation of heterochromatin in RS remains unclear.

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Color Plate V

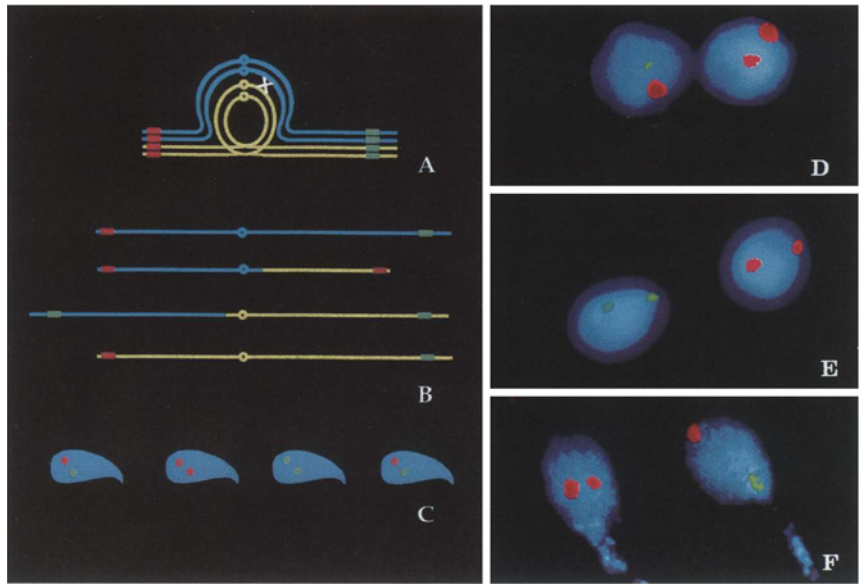


**Figure 16.3.** Recombination within a pericentric inversion, as visualized by two-color FISH. (A-C) Diagrams of a crossover within the inverted segment, the recombinant and nonrecombinant chromosomes, and nonrecombinant (green-red) and recombinant (two red or two green) sperm. (D-F) Images from two-color FISH showing recombinant and nonrecombinant sperm (reproduced from Jarrola et al., Am J Hum Genet 63:218–224, copyright 1998, American Society of Human Genetics, with permission of the University of Chicago Press).

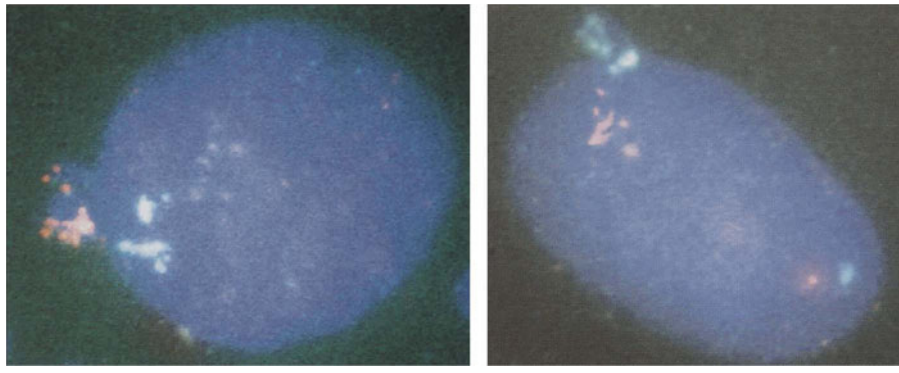

**Figure 25.3.** Preferential segregation of one amplified marker into nuclear blebs containing *P3C4* only (left) or *AMPD3* only (right) (reproduced from Toledo et al., EMBO J 11:2665–2673, 1992, with permission of Oxford University Press).

Color Plate VI

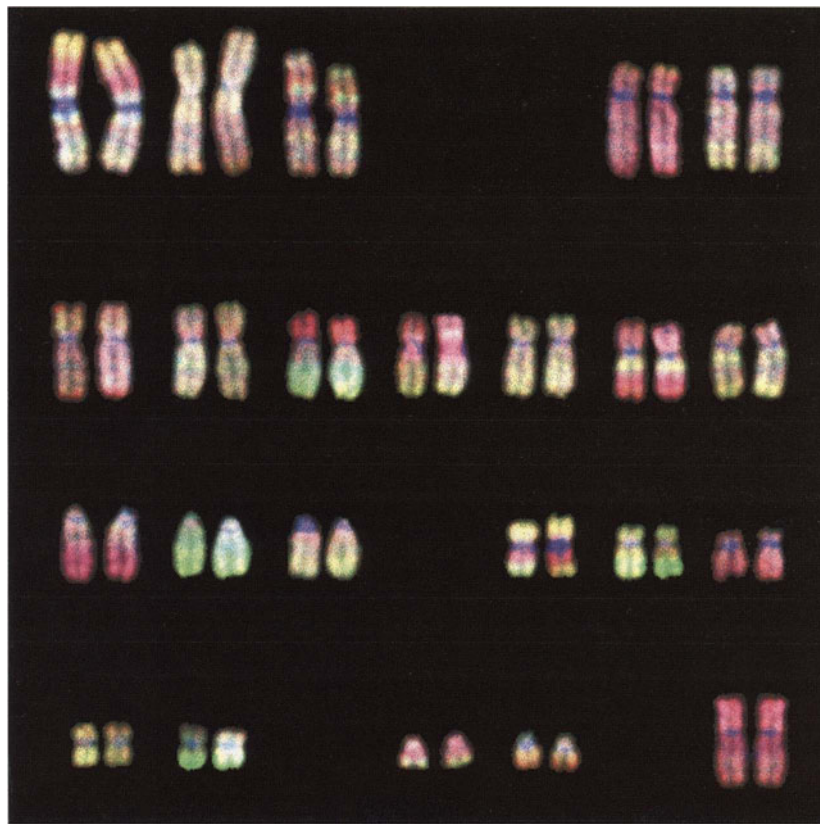

**Figure 26.1.** Analysis of chromosome changes in a breast cancer by comparative genomic hybridization (CGH). Regions that appear green reflect DNA gains and amplification in the cancer (e.g., 8q, 14, 17q22–q24, and 20q). Regions that appear red reflect DNA losses and deletions (e.g., 1p21–p31, 8p, 11q14–qter, and 16q12–q21) (reprinted from Forozan et al., Trends Genet, v13, Genome screening by comparative genomic hybridization, p 408, copyright 1997, with permission from Elsevier Science).