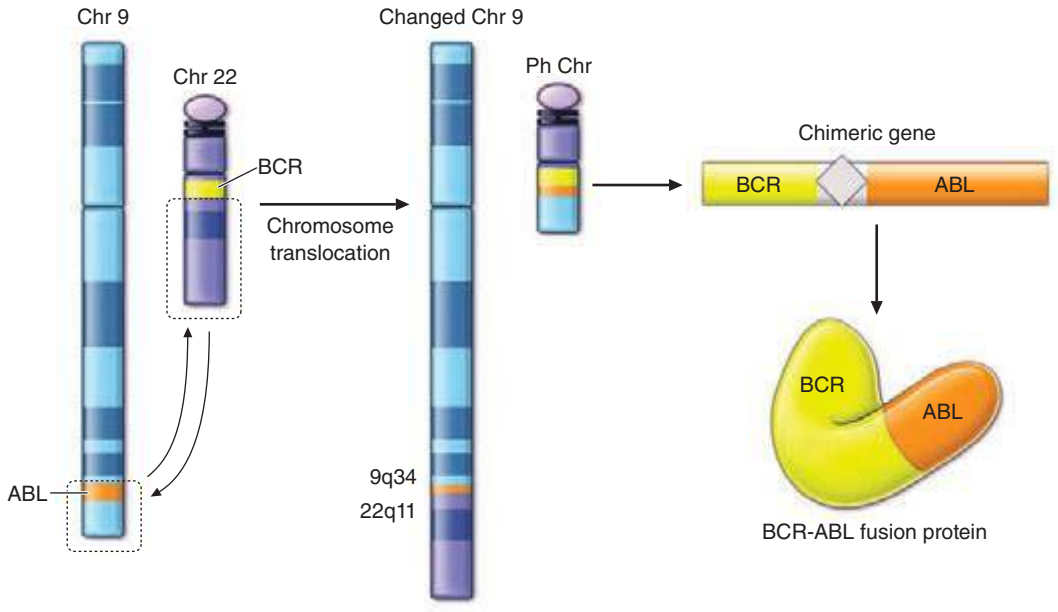

FIGURE 101e-3 Specific translocation seen in chronic myeloid leukemia (CML). The Philadelphia chromosome (Ph) is derived from a reciprocal translocation between chromosomes 9 and 22 with the breakpoint joining the sequences of the *ABL* oncogene with the *BCR* gene. The fusion of these DNA sequences allows the generation of an entirely novel fusion protein with modified function.

in tumors will likely be a formidable task, considering that several hundred genes are thought to control the mitotic checkpoint and other cellular processes ensuring proper chromosome segregation. Regardless of the mechanisms underlying CIN, the measurement of the number of chromosomal alterations present in tumors is now possible with both cytogenetic and molecular techniques, and several studies have shown that this information can be useful for prognostic purposes. In addition, because the mitotic checkpoint is essential for cellular viability, it may become a target for novel therapeutic approaches.

TUMOR-SUPPRESSOR GENE INACTIVATION IN CANCER

The first indication of the existence of tumor-suppressor genes came from experiments showing that fusion of mouse cancer cells with normal mouse fibroblasts led to a nonmalignant phenotype in the fused cells. The normal role of tumor-suppressor genes is to restrain cell growth, and the function of these genes is inactivated in cancer. The two major types of somatic lesions observed in tumor-suppressor genes during tumor development are *point mutations* and *large deletions*. Point mutations in the coding region of tumor-suppressor genes will frequently lead to truncated protein products or otherwise nonfunctional proteins. Similarly, deletions lead to the loss of a functional product and sometimes encompass the entire gene or even the entire chromosome arm, leading to loss of heterozygosity (LOH) in the tumor DNA compared to the corresponding normal tissue DNA (Fig. 101e-4). LOH in tumor DNA is considered a hallmark for the presence of a tumor-suppressor gene at a particular chromosomal location, and LOH studies have been useful in the positional cloning of many tumor-suppressor genes.

Gene silencing, an epigenetic change that leads to the loss of gene expression and occurs in conjunction with hypermethylation of the promoter and histone deacetylation, is another mechanism of tumor-suppressor gene inactivation. (An *epigenetic modification* refers to a change in the genome, heritable by cell progeny, that does not involve a change in the DNA sequence. The inactivation of the second X chromosome in female cells is an example of an epigenetic silencing that prevents gene expression from the inactivated chromosome.) During embryologic development, regions of chromosomes from one parent are silenced and gene expression proceeds from the chromosome of the other parent. For most genes, expression occurs from both alleles or randomly from one allele or the other. The preferential expression of a particular gene exclusively from the allele contributed by one parent is called *parental imprinting* and is thought to be regulated by covalent modifications of chromatin protein and DNA (often methylation) of the silenced allele.

The role of epigenetic control mechanisms in the development of human cancer is unclear. However, a general decrease in the level of DNA methylation has been noted as a common change in cancer. In addition, numerous genes, including some tumor-suppressor genes, appear to become hypermethylated and silenced during tumorigenesis. *VHL* and *p16INK4* are well-studied examples of such tumor-suppressor genes. Overall, epigenetic mechanisms may be responsible for reprogramming the expression of a large number of genes in cancer and, together with the mutation of specific genes, are likely to be crucial in the development of human malignancies. The use of drugs that can reverse epigenetic changes in cancer cells may represent a novel therapeutic option in certain cancers or premalignant conditions. For example, demethylating agents (azacitidine or decitabine) are now approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with high-risk myelodysplastic syndrome (MDS).

FAMILIAL CANCER SYNDROMES

A small fraction of cancers occur in patients with a genetic predisposition. In these families, the affected individuals have a predisposing loss-of-function mutation in one allele of a tumor-suppressor gene. The tumors in these patients show a loss of the remaining normal allele as a result of somatic events (point mutations or deletions), in agreement with the two-hit hypothesis (Fig. 101e-4). Thus, most cells of an individual with an inherited loss-of-function mutation in a tumor-suppressor gene are functionally normal, and only the rare cells that develop a mutation in the remaining normal allele will exhibit uncontrolled regulation.

Roughly 100 syndromes of familial cancer have been reported, although many are rare. The majority are inherited as autosomal dominant traits, although some of those associated with DNA repair abnormalities (xeroderma pigmentosum, Fanconi's anemia, ataxia telangiectasia) are autosomal recessive. Table 101e-3 shows a number of cancer predisposition syndromes and the responsible genes. The current paradigm states that the genes mutated in familial syndromes can also be targets for somatic mutations in sporadic (noninherited) tumors. The study of cancer syndromes has thus provided invaluable insights into the mechanisms of progression for many tumor types. This section examines the case of inherited colon cancer in detail, but