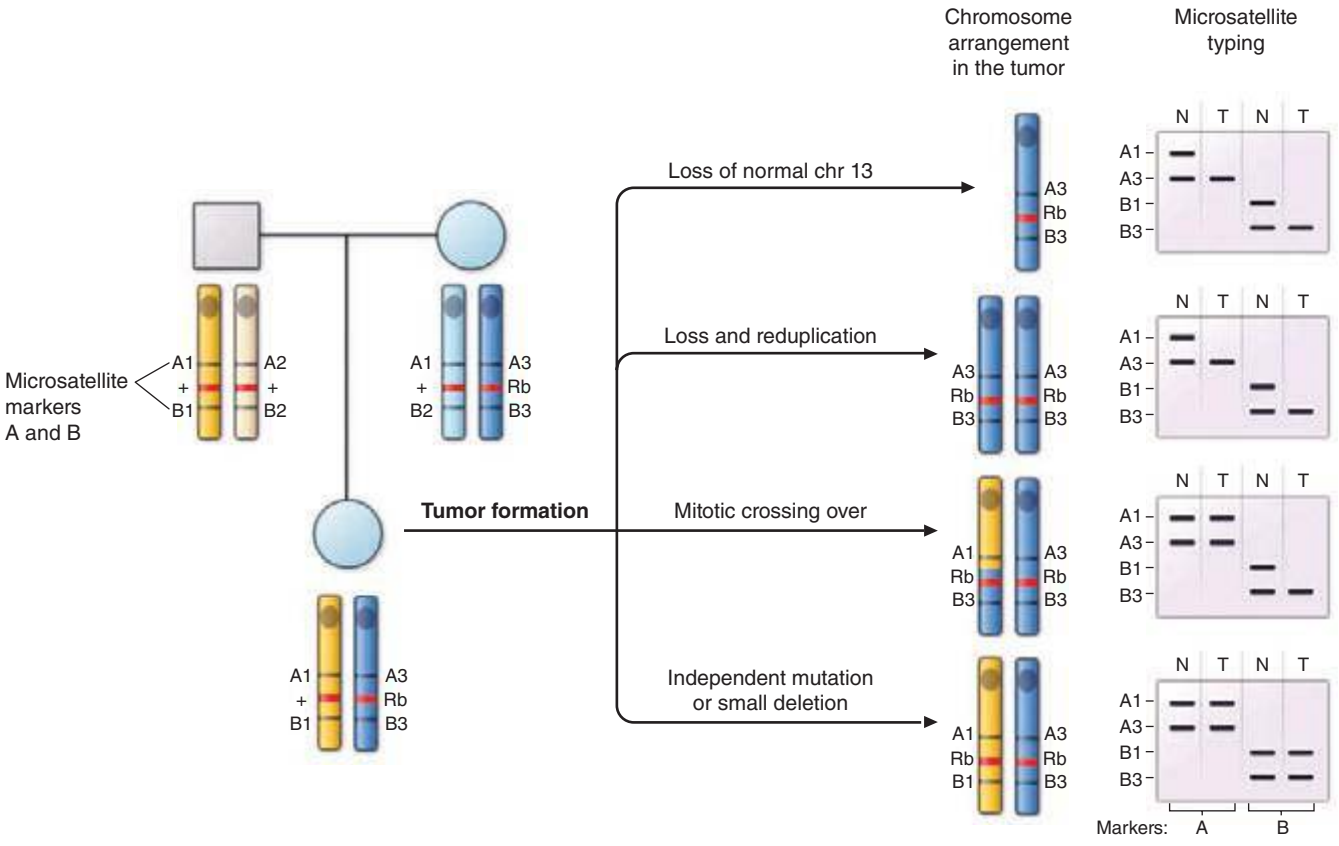

FIGURE 101e-4 **Diagram of possible mechanisms for tumor formation in an individual with hereditary (familial) retinoblastoma.** On the left is shown the pedigree of an affected individual who has inherited the abnormal (Rb) allele from her affected mother. The normal allele is shown as a (+). The four chromosomes of her two parents are drawn to indicate their origin. Flanking the retinoblastoma locus are microsatellite markers (A and B) also analyzed in this family. Markers A3 and B3 are on the chromosome carrying the retinoblastoma disease gene. Tumor formation results when the normal allele, which this patient inherited from her father, is inactivated. On the right are shown four possible ways in which this could occur. In each case, the resulting chromosome 13 arrangement is shown, as well as the results of PCR typing using the microsatellite markers comparing normal tissue (N) with tumor tissue (T). Note that in the first three situations, the normal allele (B1) has been lost in the tumor tissue, which is referred to as loss of heterozygosity (LOH) at this locus.

similar lessons can be applied to many of the cancer syndromes listed in Table 101e-3. In particular, the study of inherited colon cancer will clearly illustrate the difference between two types of tumor-suppressor genes: the *gatekeepers*, which directly regulate the growth of tumors, and the *caretakers*, which, when mutated, lead to genetic instability and therefore act indirectly on tumor growth.

Familial adenomatous polyposis (FAP) is a dominantly inherited colon cancer syndrome due to germline mutations in the adenomatous polyposis coli (*APC*) tumor-suppressor gene on chromosome 5. Patients with this syndrome develop hundreds to thousands of adenomas in the colon. Each of these adenomas has lost the normal remaining allele of *APC* but has not yet accumulated the required additional mutations to generate fully malignant cells (Fig. 101e-2). The loss of the second functional *APC* allele in tumors from FAP families often occurs through loss of heterozygosity. However, out of these thousands of benign adenomas, several will invariably acquire further abnormalities and a subset will even develop into fully malignant cancers. *APC* is thus considered to be a gatekeeper for colon tumorigenesis: in the absence of mutation of this gatekeeper (or a gene acting within the same pathway), a colorectal tumor simply cannot form. Figure 101e-5 shows germline and somatic mutations found in the *APC* gene. The function of the APC protein is still not completely understood, but it likely provides differentiation and apoptotic cues to colonic cells as they migrate up the crypts. Defects in this process may lead to abnormal accumulation of cells that should normally undergo apoptosis.

In contrast to patients with FAP, patients with hereditary nonpolyposis colon cancer (HNPCC, or Lynch's syndrome) do not develop multiple polyposis, but instead develop only one or a small number of adenomas that rapidly progress to cancer. Most HNPCC cases are due to mutations in one of four DNA mismatch repair genes (Table 101e-3), which are components of a repair system that is normally responsible for correcting errors in freshly replicated DNA. Germline mutations in *MSH2* and *MLH1* account for more than 90% of HNPCC cases, whereas mutations in *MSH6* and *PMS2* are much less frequent. When a somatic mutation inactivates the remaining wild-type allele of a mismatch repair gene, the cell develops a hypermutable phenotype characterized by profound genomic instability, especially for the short repeated sequences called *microsatellites*. This microsatellite instability (MSI) favors the development of cancer by increasing the rate of mutations in many genes, including oncogenes and tumor-suppressor genes (Fig. 101e-2). These genes can thus be considered caretakers. Interestingly, CIN can also be found in colon cancer, but MSI and CIN appear to be mutually exclusive, suggesting that they represent alternative mechanisms for the generation of a mutator phenotype in this cancer (Fig. 101e-2). Other cancer types rarely exhibit MSI, but most exhibit CIN.

Although most autosomal dominant inherited cancer syndromes are due to mutations in tumor-suppressor genes (Table 101e-3), there are a few interesting exceptions. Multiple endocrine neoplasia type 2, a dominant disorder characterized by pituitary adenomas, medullary carcinoma of the thyroid, and (in some pedigrees) pheochromocytoma, is due to gain-of-function mutations in the protooncogene *RET* on chromosome 10. Similarly, gain-of-function mutations in the tyrosine kinase domain of the *MET* oncogene lead to hereditary papillary renal carcinoma. Interestingly, loss-of-function mutations in the *RET* gene cause a completely different disease, Hirschsprung's disease (aganglionic megacolon [Chaps. 353 and 408]).