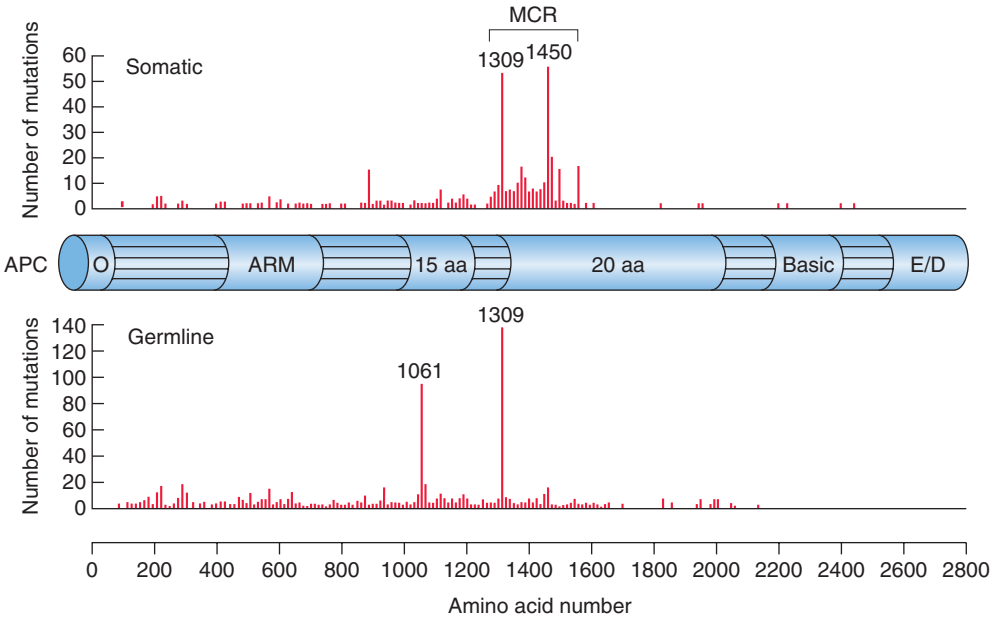

FIGURE 101e-5 Germline and somatic mutations in the tumor-suppressor gene *APC*. *APC* encodes a 2843-amino-acid protein with six major domains: an oligomerization region (O), armadillo repeats (ARM), 15-amino-acid repeats (15 aa), 20-amino-acid repeats (20 aa), a basic region, and a domain involved in binding EB1 and the *Drosophila* discs large homologue (E/D). Shown are the positions within the *APC* gene of a total of 650 somatic and 826 germline mutations (from the *APC* database at *http://www.umd.be/APC*). The vast majority of these mutations result in the truncation of the APC protein. Germline mutations are found to be relatively evenly distributed up to codon 1600 except for two mutation hotspots at amino acids 1061 and 1309, which together account for one-third of the mutations found in familial adenomatous polyposis (FAP) families. Somatic *APC* mutations in colon tumors cluster in an area of the gene known as the *mutation cluster region* (MCR). The location of the MCR suggests that the 20-amino-acid domain plays a crucial role in tumor suppression.

testing is less than 70% (i.e., of 100 kindreds tested, disease-causing mutations can be identified in 70 at most). Therefore, such testing should in general begin with an affected member of the kindred (the youngest family member still alive who has had the cancer of interest). If a mutation is not identified in this individual, then the test should be reported as noninformative (Fig. 101e-6) rather than negative (because it is possible that, for technical reasons, the mutation in this individual is not detectable by standard genetic assays). On the other hand, if a mutation can be identified in this individual, then testing of other family members can be performed, and the sensitivity of such subsequent tests will be 100% (because the mutation in the family is in this case known to be detectable by the method used).

MICRORNAs AND CANCER

MicroRNAs (miRNAs) are small noncoding RNAs 20–22 nucleotides in length that are involved in posttranscriptional gene regulation. Studies in chronic lymphocytic leukemia first suggested a link between miRNAs and cancer when *miR-15* and *miR-16* were found to be deleted or downregulated in the vast majority of tumors. Various miRNAs have since been found abnormally expressed in several human malignancies. Aberrant expression of miRNAs in cancer has been attributed to several mechanisms, such as chromosomal rearrangements, genomic copy number change, epigenetic modifications, defects in miRNA biogenesis pathway, and regulation by transcriptional factors. Somatic mutations of miRNAs have been identified in many cancers, but the exact functional consequences of these changes on cancer development remain to be determined. The SomaMir database (*http://compbio.uthsc.edu/SomamiR*) catalogs somatic and germline miRNA mutations that have been identified in cancer.

Functionally, miRNAs have been suggested to contribute to tumorigenesis through their ability to regulate oncogenic signaling pathways. For example, *miR-15* and *miR-16* have been shown to target the *BCL2* oncogene, leading to its downregulation in leukemic cells and apoptosis. As another example of miRNAs' involvement in oncogenic pathways, the p53 tumor suppressor can transcriptionally induce *miR-34* following genotoxic stress, and this induction is important in mediating p53 function. The expression of miRNAs is extremely specific, and there is evidence that miRNA expression patterns may be useful in distinguishing lineage and differentiation state, as well as cancer diagnosis and outcome prediction.

VIRUSES IN HUMAN CANCER

Certain human malignancies are associated with viruses. Examples include Burkitt's lymphoma (Epstein-Barr virus; Chap. 218), hepatocellular carcinoma (hepatitis viruses), cervical cancer (human papillomavirus [HPV]; Chap. 222), and T cell leukemia (retroviruses; Chap. 225e). The mechanisms of action of these viruses are varied but always involve activation of growth-promoting pathways or inhibition of tumor-suppressor products in the infected cells. For example, HPV proteins E6 and E7 bind and inactivate cellular tumor suppressors p53 and pRB, respectively. There are several HPV types, and some of these types have been associated with the development of several malignancies, including cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancer. Viruses are not sufficient for cancer development, but constitute one alteration in the multistep process of cancer progression.

GENE EXPRESSION IN CANCER

The tumorigenesis process, driven by alterations in tumor suppressors, oncogenes, and epigenetic regulation, is accompanied by changes in gene expression. The advent of powerful techniques for high-throughput gene expression profiling, based on sequencing or microarrays, has allowed the comprehensive study of gene expression in neoplastic cells. It is indeed possible to identify the expression levels of thousands of genes expressed in normal and cancer tissues. Figure 101e-7 shows a typical microarray experiment examining gene expression in cancer. This global knowledge of gene expression allows the identification of differentially expressed genes and, in principle, the understanding of the complex molecular circuitry regulating normal and neoplastic behaviors. Such studies have led to molecular profiling of tumors, which has suggested general methods for distinguishing tumors of various biologic behaviors (molecular classification), elucidating pathways relevant to the development of tumors, and identifying molecular targets for the detection and therapy of cancer. The first practical applications of this technology have suggested that global gene expression profiling can provide prognostic information not evident from other clinical or laboratory tests. The Gene Expression Omnibus (GEO, *http://www.ncbi.nlm.nih.gov/geo/*) is a searchable online repository for expression profiling data.

GENOMEWIDE MUTATIONAL PROFILING IN CANCER

With the completion of the Human Genome Project and advances in sequencing technologies, systematic mutational analysis of the cancer genome has become possible. In fact, whole genome sequencing of cancer cells is now possible, and this technology has the potential to