Cancer develops and progresses as the result of accumulated genetic damage or mutations. These mutations are most commonly described as either oncogenes, which positively regulate cell growth, or tumor suppressor genes, which negatively regulate cell growth. When oncogenes are mutated, cell growth signals are enhanced; mutations in tumor suppressor genes lead to a reduction in the level of growth retarding activities. While it was hypothesized that advances in molecular genetics would lead to the identification of specific mutations that cause common solid tumors, progress was relatively slow until approximately 20 years ago. The first genetic mutations were identified in patients with hereditary tumors such as retinoblastoma and familial colonic polyposis. With the development of positional cloning techniques and the discovery of polymerase chain reaction methodology, the identification of genetic mutations in familial tumors increased such that newly identified mutations in familial cancer syndromes are now commonplace. Some of the genetic mutations identified in hereditary cancer are shown in the Table. This review focuses on examples of molecular genetic discoveries in solid tumors, and their importance in the diagnosis and treatment of patients with two malignancies, retinoblastoma and familial colon carcinoma.

<table>
<thead>
<tr>
<th>Cancer/Cancer Syndrome</th>
<th>Gene</th>
<th>Chromosomal Location</th>
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<tbody>
<tr>
<td>Breast and ovarian cancers</td>
<td>BRCA1</td>
<td>17q21</td>
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<tr>
<td>Breast cancer</td>
<td>BRCA2</td>
<td>13q12-13</td>
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<tr>
<td>SBLA/Li-Fraumeni syndrome</td>
<td>p53</td>
<td>17p13</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>RB1</td>
<td>13q14</td>
</tr>
<tr>
<td>HNPCC</td>
<td>MSH2</td>
<td>2p</td>
</tr>
<tr>
<td></td>
<td>MLH1</td>
<td>3p21.3-23</td>
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<tr>
<td></td>
<td>PMS1</td>
<td>2q31-33</td>
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<td>PMS2</td>
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<th>Turcot’s syndrome:</th>
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<tr>
<td>Predominance of glioblastoma multiforme</td>
<td>PMS2</td>
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<td></td>
<td>MLH1</td>
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<thead>
<tr>
<th>Familial adenomatous polyposis</th>
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<th>distal to 5'</th>
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<tr>
<th>MEN 2A, MEN 2B, FMTC</th>
<th>RET</th>
<th>10q11.2</th>
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<tr>
<th>Wilms' tumor</th>
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</table>

HNPCC = hereditary nonpolyposis colorectal cancer
SBLA = sarcoma, breast and brain tumor, leukemia, laryngeal and lung cancer, and adrenal cortical carcinoma
MEN = multiple endocrine neoplasia syndromes
FMTC = familial non-MEN medullary thyroid carcinoma

Retinoblastoma
The tumor retinoblastoma (Rb) develops in the retinal cells and, with rare exception, affects children under 5 years of age. A family history of retinoblastoma is present in 10% of children. In 90% of patients, the tumors appear to be sporadic, even though in 40% to 50% of them, the tumors are bilateral and suggest a new germine mutation. The mutated gene for retinoblastoma is located on chromosome 13q14. The Rb gene spans approximately 200 kb of genomic DNA and consists of 27 exons that code 928 amino acids. Patients who carry constitutional Rb gene mutations are at significant risk for developing second nonocular tumors (usually osteosarcomas or soft-tissue sarcomas) late in life.

The discovery of the Rb gene has markedly altered the management of patients with this disease. In kindreds with hereditary retinoblastoma, family members at risk can be positively identified as genetic carriers of an Rb mutation by direct DNA testing. Whereas the treatment for this disease used to be bilateral resection of the ocular globes, vision is usually saved in these patients if they are identified early and treated with various nonresectional therapies. The history of management of these patients demonstrates some of the complications of various therapeutic regimens and emphasizes the importance of careful life-long follow-up and postoperative evaluation in patients with this complex familial disease.

**Colon Cancer**

Familial adenomatous polyposis (FAP) is a relatively uncommon cancer syndrome that has been recognized clinically for over 100 years. The disease is inherited in an autosomal dominant manner with high penetrance. FAP is characterized by the development of numerous adenomatous polyps throughout the large bowel early in life. If untreated, virtually all of these patients will die of malignancy of the large bowel. Using molecular probes and linkage analysis from numerous FAP families, the disease gene for FAP was isolated in 1991. The gene was named APC for adenomatous polyposis coli, and it resides on chromosome 5q21-22. Current approaches to genetic testing rely on direct identification of DNA mutations or gross alterations.

The clinical utility of a genetic test for FAP is twofold. For those patients with a known family history of FAP and a defined APC mutation, a negative test result means that endoscopic screening can be reduced to three or fewer examinations (to insure against a false-negative test result), thus relieving the financial, practical, and emotional consequences of “watchful waiting.” Those patients who test positive can also benefit from improved management through increased surveillance and timely intervention.

More recently, a new entity entitled Lynch syndrome I or hereditary nonpolyposis colorectal cancer (HNPCC) was described. Patients with this syndrome have an autosomal dominant inherited predisposition to colorectal carcinoma with right-sided predominance and an excess of multiple primary colorectal cancers. The colon carcinomas are commonly of the mucinous type, and even though the histological features indicate an aggressive malignancy, they are less aggressive biologically than colon cancers that occur outside of this specific clinical setting. Patients with HNPCC also develop extracolonic malignancies in various organs, especially the uterus and ovary. The genetic basis for HNPCC results from mutations in various mismatch repair genes (hMSH2, hMLH1, hPMS1, and hPMS2). Defective DNA mismatch repair genes result in a steady accumulation of mutations that ultimately produce microsatellite instability defined as showing replication error (RER) phenotype. The management of patients with HNPCC poses an interesting dilemma for genetic counselors in that the methods of follow-up and the timing of intervention for both the colon and the extracolonic organs at risk for developing malignant disease are not clearly defined. Various strategies for managing these patients have been published.

**References**