Kidney cancer affects nearly 28,000 Americans each year and is responsible for 12,000 deaths annually in the United States. Kidney cancer can occur as localized, locally advanced, or advanced disease. Little is known about the specific cause of kidney cancer, although as with smoking, a number of associations have been noted. Kidney cancer can occur in both a hereditary as well as a nonhereditary sporadic form [1]. When two or more members of the same family are found to have kidney cancer, screening of other at-risk individuals in the family is recommended.

Studies to locate the site of a potential kidney cancer gene detected a consistent segment loss on chromosome 3 in tumor tissue from patients with clear-cell kidney cancer. Further analysis detected a potential location of a kidney cancer gene on chromosome 3 [2].

To localize the gene for clear-cell kidney cancer further, scientists initiated studies of a hereditary form of renal carcinoma associated with von Hippel-Lindau (VHL) disease [3,4]. Genetic linkage analysis was used to localize the VHL gene to the short arm of chromosome 3. Subsequent genetic and physical mapping identified the VHL gene at the 3p25 locus on chromosome 3 [5]. Inactivating mutations in the VHL gene have been detected in the germline of affected individuals [6,7].

The VHL gene mutations were detected in a high percentage of tumors from patients with clear-cell renal carcinoma [8,9]. VHL gene abnormalities have not been detected in papillary renal carcinoma. These findings provide the basis for a molecular genetic classification of kidney cancer (ie, papillary vs clear-cell), with clear-cell renal carcinoma being characterized by a mutation in the VHL gene. In addition, VHL gene abnormalities have been detected in formalin-fixed tissues and in tissue aspirates [10,11].

Hereditary papillary renal carcinoma (HPRC) is an autosomal-dominant hereditary cancer syndrome in which patients inherit a predisposition to develop bilateral, multifocal papillary renal carcinoma [12,13].

Genetic linkage studies performed at the National Cancer Institute identified a locus on the long arm of chromosome 7 as the site for the HPRC gene. Subsequently, the MET gene was identified as the HPRC gene. Although the VHL gene has the characteristics of a classic tumor-suppressor gene of the Knudson model, the MET gene fits the characteristics of an oncogene. Mutations in the tyrosine kinase domain of the MET gene have been detected in the germline of affected individuals [14]. It is thought that mutations in the MET gene, which is the receptor for the ligand hepatocyte growth factor, result in the development of the papillary renal carcinomas detected in these patients.
Recently, five families have been identified in which two or more members are affected with renal oncocytoma. Affected individuals, who may be asymptomatic, are likely to develop bilateral, multifocal oncocytoma. These findings raise the possibility that there may be a genetic basis for the predisposition to develop renal oncocytoma [15]. Studies are currently in progress to identify such a genetic basis for familial renal oncocytoma.

### CANCER GENES

#### Hereditary Forms of Kidney Tumors

- VHL
- HPRC
- FRO

#### Cancer Genes

- Tumor suppressor gene
- "Two-hit" hypothesis
- Inactivation of both copies
- Resulting in loss of growth inhibition
- Oncogene
- "Single" hit
- Activating mutation
- Resulting in gain of growth advantage

#### Kidney Cancer Genes

- **VHL gene**
  - Tumor suppressor gene (loss of function)
  - VHL, HRCC
  - Sporadic clear-cell renal carcinoma
- **MET gene**
  - Proto-oncogene (gain of function)
  - HPRC
  - Sporadic papillary renal carcinoma

#### Clinical Features of von Hippel-Lindau Disease

- Bilateral kidney tumors, cysts
- Cerebellar or spinal hemangioblastomas
- Retinal angiomas
- ELST
- Pancreatic cyst, tumors
- Pheochromocytoma
- Epididymal cystadenoma

### FIGURE 3-1. Hereditary forms of kidney tumors. Kidney cancer, like prostate cancer, bladder cancer, colon cancer, and breast cancer, occurs in both a hereditary and a nonhereditary sporadic form. There are three forms of hereditary renal cancer: von Hippel-Lindau (VHL), hereditary papillary renal carcinoma (HPRC), and familial renal oncocytoma (FRO) [1,12,15].

### FIGURE 3-2. Cancer genes. There are two basic types of cancer genes, both of which are found in kidney cancer. A tumor-suppressor gene is a cancer gene in which transformation (cancer) may occur after both copies of the tumor-suppressor gene are inactivated. Inactivation of both copies of a tumor-suppressor gene results in loss of growth inhibition (ie, unregulated growth). This is the basis of the Knudson "two-hit" model in which both copies of a gene, such as the retinoblastoma gene or the von Hippel-Lindau gene, are inactivated in retinoblastoma or clear-cell kidney cancer, respectively [16,17]. An oncogene is a dominantly acting gene in which a "single hit" mutation activates the gene, resulting in a gain of growth advantage that is characteristic of a cancer cell.

### FIGURE 3-3. Kidney cancer genes. The **VHL** gene is a tumor-suppressor gene of the classic Knudson model. **VHL** gene mutations are found in the germline of affected individuals with von Hippel-Lindau disease and in nonhereditary, sporadic clear-cell renal carcinoma [1,9,18]. The **MET** gene is a dominantly acting (gain of function) oncogene that is mutated in the germline of patients with hereditary papillary renal carcinoma and in some forms of sporadic papillary renal carcinoma [14]. HPRC—hereditary papillary renal carcinoma; HRCC—hereditary renal cell carcinoma.

### FIGURE 3-4. Clinical features of von Hippel-Lindau (VHL) disease. VHL disease is a hereditary cancer syndrome in which affected individuals are at risk for developing bilateral, multifocal, early-onset renal tumors. Affected individuals are also at risk for developing tumors in a number of organs including cerebellar or spinal hemangioblastomas, retinal angiomas, endolymphatic sac tumors (in the inner ear), pancreatic cysts and tumors, pheochromocytomas, and epididymal cystadenomas [19]. ELST—endolymphatic sac tumors.