obtain surgical samples of the tumors in all of these stages and analyze their gene changes. They found the mutations accumulate gradually over time. "We think that it takes alterations in about five genes to get to the cancer stage," Vogelstein explains. "Small benign adenomas usually only have one recognizable gene change. As they grow in size they acquire three or four more."

The gene changes usually occur in a specific order, but there are exceptions. "It appears that it is the accumulation of changes, not the specific order, that is important for cancer development," Vogelstein says.

One of the genes altered is the *RAS* oncogene, which often undergoes an activating mutation about midway in colon cancer development. (*RAS* is so called because it was first identified in a virus that causes rat sarcomas.) But most of the other gene changes detected by Vogelstein and his colleagues are deletions of specific segments of certain chromosomes, principally num-

One Wilms' Tumor Gene Is Cloned; Are There More?

Cambridge, Massachusetts

A team of investigators has cloned a gene that may be the cause of Wilms' tumor, which accounts for 85% of all kidney cancers in children. The candidate gene, found on chromosome 11, has tumor-suppressing properties; it is only the third such suppressor gene to be identified. The recent cloning, however, does not fully resolve the question of how Wilms' tumor begins, because there is evidence that changes in several other genes (some not even on chromosome 11) may be involved in tumor initiation.

The isolation and characterization of the putative suppressor gene were reported at the recent annual meeting of the American Society of Human Genetics. The work was carried out by a team led by Katherine Call and her colleagues in David Housman's lab at the Massachusetts Institute of Technology, along with Carol Jones at the University of Colorado.

Wilms' tumor is most often diagnosed between the ages of 2 and 5, and the average risk for developing the tumor is about 1 in 8000. Although the prognosis is generally good, among a small subset of patients the death rate exceeds 50%.

The pair of genes seems to suppress tumor formation; when they are missing, a tumor may begin to form.

The Housman group based their identification on a comparison of chromosomes and expression profiles in normal kidney cells and cell lines derived from Wilms' tumor cells. In some tumor-cell lines, the newly identified gene was missing from both copies of the 11p13 region on the short arm of chromosome 11; little or no messenger RNA from the gene was detected in those cells. In normal cells the gene was present in two copies and was expressed. These findings suggest that in normal cells the pair of genes suppresses potential tumor formation; when they are missing, a tumor may begin to form. Since both copies must be altered for the gene to play a role in tumor formation, the Wilms' gene is recessive. The only other known recessive tumor-suppressing gene is the retinoblastoma gene, cloned in 1986. (The second known tumor suppressor gene, p53, seems to behave, at least in some cases, in a dominant fashion [see accompanying story]).

The differences between the retinoblastoma gene and the Wilms' tumor gene, however, may be more striking than their similarities. Only one gene has been implicated in the formation of retinoblastoma, whereas cytogenetic and molecular evidence suggests that the Wilms' gene is only one of several genes associated with that tumor. Grady Saunders and Louise Strong of the M. D. Anderson Cancer Center in Houston have found another sequence in the 11p13 region that may be implicated in Wilms' tumor; other groups have found abnormalities in other regions of chromosome 11 that may also play a role.

There is also evidence that genes on other chromosomes may be involved. Last year, two groups found that in some families with a predisposition to Wilms' tumor there was no apparent linkage to chromosome 11. Strong points out that a gene on another chromosome could initiate the sequence of events leading to Wilms' tumor by acting through a locus on chromosome 11. That other gene "may somehow predispose loss of a gene on 11p13 and/or may otherwise alter its expression," Strong says.

Even independent of its role in tumor formation, the putative Wilms' gene may turn out to be an important stretch of DNA. The partial sequence of the clone obtained by Housman's group shows that it contains a well-formed "zinc finger" region. This motif, named for its fingerlike projections, is thought to be a hallmark of transcription factors: proteins that bind to DNA and either enhance or suppress gene expression. And indeed the sequence already obtained does exhibit homology with other known transcription factors.

Whether the Wilms' gene is a transcription factor or not, its normal function seems to lie in the formation of the kidneys in the developing fetus. Evidence to that effect was presented last month at a meeting in Japan by Nicholas Hastie of the MRC Human Genetics Unit in Edinburgh. Hastie used Housman's gene to probe 7-week and 18-week human fetal tissues and he demonstrated that the gene was transcribed at both those times.

The finding that the Wilms' product is expressed in the developing kidney fits nicely with the histopathology of Wilms' tumors. The majority of these tumors contains a variety of cell types, which suggests, according to Bruce Beckwith of the Denver Children's Hospital, pathologist for the National Wilms' Tumor Study, that tumor induction probably begins during fetal development in a multipotential precursor cell. "Wilms' replicates both normal and abnormal kidney development," Beckwith says, and that is why it has "been referred to as a malignant embryonic kidney."

Beckwith joins other scientists in anticipating that the initiation of Wilms' tumor will not be limited to one genetic locus—or even a few. "It would surprise me," he says, "if only three loci were deranged. Kidney development is such a complex process that a lot of different things can go wrong." With regard to the recently cloned gene, he adds, the fundamental question is, "Does that gene lead to the precursor lesion, or does it activate the gene that does? We need to determine the gene's exact role, whether it's the immediate cause of malignant change or whether it acts prior to malignant change. As yet, either hypothesis could be valid."

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