Genetic Defect Identified in Rare Cancer Syndrome

A mutation in the p53 tumor suppressor gene underlies the high cancer rate in members of Li-Fraumeni families

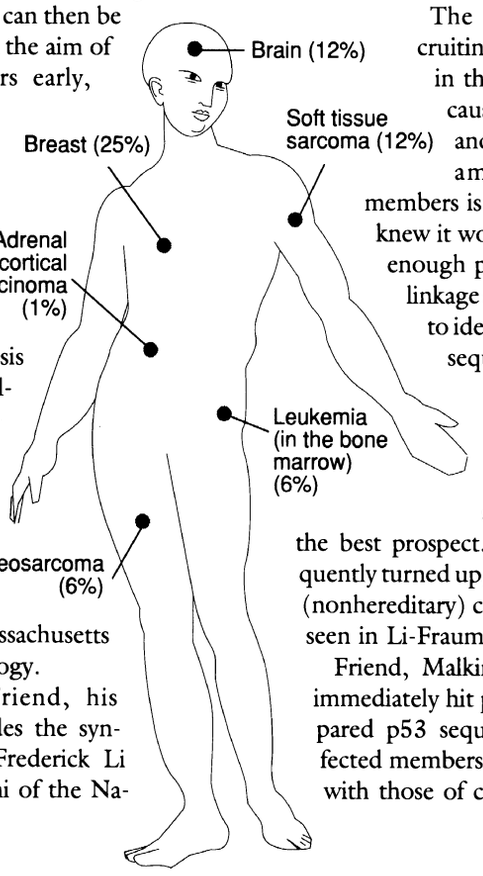
ABOUT 100 FAMILIES AROUND THE WORLD are known to be afflicted with a rare genetic disorder known as Li-Fraumeni syndrome. They provide dramatic evidence that cancer can be inherited. Members of these families are highly susceptible to several malignant tumors—especially breast cancer—often developing the malignancies before they reach their 30th birthdays. Now researchers have discovered the key to this syndrome, and their findings may help to understand cancer generally.

On page 1233 of this issue, Stephen Friend and his colleagues at Massachusetts General Hospital Cancer Center in Boston report that they have found the gene defect underlying Li-Fraumeni syndrome—and it involves a recently discovered tumor suppressor gene known as p53. "It's the first documented inherited change in the p53 gene," says Bert Vogelstein of Johns Hopkins University School of Medicine, a cancer gene expert whose interests include p53.

At the very least, the discovery should make it possible to identify precisely which members of Li-Fraumeni families carry the gene defect and are thus at high risk of getting cancer. They can then be closely watched with the aim of catching the cancers early, when they are most likely to be curable. But researchers also hope that the identification of the p53 defect will help them understand the genetic basis of cancer susceptibility generally. "Li-Fraumeni syndrome could be the tip of the iceberg," says another cancer gene expert, Robert Weinberg of the Massachusetts Institute of Technology.

According to Friend, his group, which includes the syndrome discoverers Frederick Li and Joseph Fraumeni of the National Cancer Institute, as well as David Malkin of Mass General and Louis Strong of M. D. Anderson Cancer Center in Houston, began looking for tumor suppressor gene mutations in Li-Fraumeni families about 2 years ago. At the time, there was already good evidence that such mutations caused two other kinds of hereditary cancers: retinoblastoma, an eye cancer, and Wilms tumor, a kidney cancer. In fact, cancer researchers were beginning to realize that mutations that knock out suppressor genes—effectively taking the brakes off tumor cell growth—could be just as important in causing cancer as the activation of oncogenes, which act positively to make cells cancerous.

But, as Friend points out, Wilms tumor and retinoblastoma are relatively rare cancers that strike in early childhood, and his group wanted to see what role tumor suppressor genes might play in predisposing people to the common adult cancers. So they turned to the Li-Fraumeni families, whose members get a variety of those cancers (see figure). The most common is breast cancer, which is the third leading cause of cancer deaths in the general population.



The researchers began recruiting families for the study in the summer of 1989. Because the syndrome is so rare and the cancer death rate among affected family members is so high, Friend's group knew it wouldn't be able to collect enough people to do the genetic linkage studies traditionally used to identify disease genes. Consequently they decided to look at "candidate" genes—and p53, which several groups had just shown to be a suppressor gene, seemed to be the best prospect. Mutations in p53 frequently turned up, for example, in sporadic (nonhereditary) cancers of the same types seen in Li-Fraumeni families.

Friend, Malkin, and their colleagues immediately hit pay dirt when they compared p53 sequences from cells of affected members of a Li-Fraumeni family with those of cells from members who were free of cancer. Both tumor and normal cells from affected members had a mutation in the codon that specifies amino acid 248 in the p53 protein, but the mutation was not seen in cells of the unaffected relatives.

The presence of the mutation in normal cells as well as in tumor cells indicates that it is passed down through the germ line, and could thus be the cause of the hereditary cancer susceptibility. And Friend says, "We were fortunate to find this as the first mutation because it is a mutation that comes up frequently in the sporadic tumors." The researchers have since detected germ line p53 mutations in affected members of an additional four families.

The discovery raises a lot of interesting questions, Vogelstein says. For one, he observes that even though all the cells of affected family members carry a p53 mutation, the individuals only get one or few cancers. A likely explanation is that mutations may be required in additional genes to convert a susceptible cell to a fully cancerous cell. But Vogelstein raises another possibility. Work with the p53 mutations in the sporadic tumors has indicated that some are more powerful than others, and it may be that only the weaker mutations can be inherited. Weinberg suggests a similar explanation for another "very surprising" aspect of p53 mutant transmission in the germ line—the absence of developmental defects in Li-Fraumeni family members.

Researchers are now trying to find out how widespread hereditary p53 mutations might be. "The suspicion is," Li says, "that the germ line mutation might be present in people who don't have these spectacular family histories." In particular, breast cancer can run in families that don't show the spectrum of other cancers afflicting Li-Fraumeni families. Researchers have already begun looking at some of these breast cancer patients, although with negative results in the few studied so far.

Meanwhile, Li points out that the discovery is raising social and ethical questions as well as scientific ones. He's concerned that the members of Li-Fraumeni families, especially the children, who are diagnosed as having the mutant gene—and the consequent high risk of developing cancers—receive not only close medical attention but also appropriate counseling to help them deal with their uncertain futures. He also worries that they will be discriminated against by insurance companies or potential employers.

These issues have cropped up before for genetic conditions such as Huntington's disease and cystic fibrosis. But for cancer specialists, they are new concerns, and ones that are likely to grow as more cancer susceptibility genes are identified. ■ JEAN MARX