New Colon Cancer Gene Discovered

Genetic linkage studies have identified a new gene for colon cancer susceptibility that may have a novel way of acting—by destabilizing the genome

Physicians have long known that some kinds of cancers, including such common ones as breast and colon cancer, tend to run in families. That observation suggests that although diet and other environmental factors influence the development of cancer, susceptibility to the disease can be inherited. Over the past few years the genes that might cause those susceptibilities have become among geneticists' most intensely sought targets. Now, work described in this issue of *Science* provides evidence for what could be an important new gene for susceptibility to colon cancer, the second leading cause of cancer deaths (see pages 810, 812, and 816).

The hope is that the new gene, by serving as a tool for identifying high-risk individuals before they get colon cancer, might eventually help reduce the toll the disease takes—currently 55,000 people die every year in the United States from colon cancer. The co-discoverers of the susceptibility gene, Albert de la Chapelle of the University of Helsinki, Finland, and Bert Vogelstein of Johns Hopkins University School of Medicine estimate that it's carried by as many as one person in every 200 in Western populations, a frequency more than 10 times greater than those of the genes causing more conventional genetic diseases such as cystic fibrosis. "That would certainly make this [gene] one of the most common causes of inherited disease—if not *the* most common," says de la Chapelle.

What's more, the colon cancer susceptibility gene may have a novel way of acting. The de la Chapelle-Vogelstein group and at least two other teams, one including Stephen Thibodeau and his colleagues at the Mayo Clinic and the other led by Manuel Perucho of the California Institute of Biological Research in La Jolla, have shown that cells from some colon cancers display a high degree of genetic instability, marked by numerous mutations throughout the genome. The implication is that the susceptibility gene causes the instability. While mutations in several genes have been associated with the development of both hereditary colon cancers and the much larger numbers of "sporadic" cancers not thought to have a heritable origin, none of these acts in quite the same way (also see table). In fact, the genomic instability that the new gene apparently creates may underlie at least some of the other gene changes seen in colon cancers.

Because of what it might mean for colon cancer, both in clinical practice and in the lab, the discovery is already winning plaudits from other researchers, even though the gene itself has not yet been isolated. "It's pretty spectacular. These papers will make quite an impact," says Francis Collins, who's just taken over as head of the National Center for Human Genome Research at the National Institutes of Health. Molecular geneticist Eric Lander of the Whitehead Institute in Cambridge, Massachusetts, agrees, hailing the discovery as "the most exciting development in human genetics in the past year." That's no mean feat, given that the year also includes the discovery of such important genes as those causing Huntington's disease and an inherited form of amyotrophic lateral sclerosis (Lou Gehrig's disease).

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Gene trackers. Albert de la Chapelle *(left)* and Bert Vogelstein have genetic evidence for a new type of colon cancer susceptibility gene.

A long and winding road

The path that led de la Chapelle and Vogelstein to the year's "most exciting development in human genetics" was a long one, beginning about 4 years ago. Vogelstein is well known for his work in tracing the gene changes that contribute to colon cancer development. He is, for example, a co-discoverer of the gene that causes a hereditary disposition to colon cancer known as familial adenomatous polyposis (FAP).

Patients with this disorder develop numerous colon polyps, some of which go on to form full-fledged cancerous tumors. But FAP is rare, accounting for only about 1% of colon cancer patients. Much more common, contributing perhaps 15% of the cases, are families in which the disease strikes frequently, even though the members do not have polyps or other clear signs of a predisposition. The family members are also prone to other cancers, including cancers of the uterine lining, ovary, and kidney. That tendency seemed to point to an inherited susceptibility in those families, but the idea has been somewhat controversial because family members would also share diets and other environmental factors that could be responsible instead. In 1989, Vogelstein and de la Chapelle agreed to collaborate to try to show that such families do indeed have an inherited susceptibility in a way that could leave no doubt—by identifying the gene.

They began by doing genetic studies aimed at determining whether the colon and other cancers in the family members could be linked to any of the genes already known to contribute to colon cancer development. Among these were the p53 and DCC genes, as well as the APC gene, which causes FAP. These linkage studies came up empty. "There wasn't [any linkage to these genes]. One after another was excluded," says de la Chapelle. And things got even more frustrating, he says, when the researchers expanded their search, combing the entire genome for markers that might be consistently present in family members who get colon or the other cancers, but absent from those who don't. If such a clear linkage between a marker and the disease could be found, it would mean that the marker was at, or very near, the site of the causative gene.

For these studies, the researchers focused in particular on two large families, one from North America and the other from New Zealand. De la Chapelle, Vogelstein, and their colleagues surveyed 250 markers—and again found nothing. "At that time we really began to question whether we were on the right track," says Vogelstein. Then a 27-year-old family member got colon cancer. That's very young for the disease to develop, says Vogelstein. "It gave us encouragement that

there was a real genetic component to [the cancers] of those families."

At about that time, says de la Chapelle, crucial new tools became available: a set of new probes developed by Jean Weissenbach's group at Généthon in Paris, France, and by James Weber of the Marshfield Medical Research Foundation in Marshfield, Wisconsin. These detect so-called "microsatellite DNA"—short, repetitive DNA sequences that are interspersed throughout the genome. These sequences can vary greatly in length from one individual to another, which makes them highly informative as markers for genetic linkage studies. Finally, after testing a total of 345 markers in all, the researchers hit paydirt: They linked a microsatellite marker located on chromosome 2 to the familial colon cancer. That was unexpected, notes cancer geneticist Curt Harris of the National Cancer Institute, because "until now there hasn't been a suspicion" of a colon cancer gene in that locality.

An even bigger surprise came when the de la Chapelle-Vogelstein team began to delve further into the nature of the genetic defect they were studying. Because the few other genes linked to hereditary cancer susceptibilities, including the APC gene, have been classic tumor suppressor genes, the researchers originally supposed that the new gene would be, too. As their name suggests, such genes normally act to keep cell growth in check; but when they are lost or inactivated by a mutation, that brake on growth is lost, allowing malignant tumors to form. One of the hallmarks of classic tumor suppressor genes is the loss of at least one of the two copies in tumor cells.

But the de la Chapelle-Vogelstein team didn't see any deletions in the region identified by the chromosome 2 marker in colon cancers from their families. Instead, the researchers found a totally different kind of abnormality. The microsatellite DNA at the chromosome 2 marker site varied in length from tumor to tumor, indicating that it had lost or gained nucleotides. Even more intriguing, they saw similar size changes in microsatellite DNA at several other chromosomal sites in almost all the familial tumor samples they analyzed.

Supporting evidence

The de la Chapelle-Vogelstein group is not the only one to find microsatellite instability in colon cancers. Indeed, Mayo's Thibodeau, who did not know about the other group's findings at the time he and his colleagues were doing their own work, reports on page 816 that they've found a high degree of microsatellite variation in 13 of the 90 colon cancers they examined, with another 12 showing much smaller variation. And Perucho confirms that his group is seeing microsatellite instability in colon cancers, too, although he declined to discuss the details because he has a paper in press at *Nature*.

Since the different groups were looking at different collections of microsatellite markers, their results, taken together, show that mutations in the regions are widespread in the genome. "What's really interesting," says Vogelstein, "is that there are literally thousands of changes throughout the genome." This makes it extremely unlikely that they arose independently and indicates that the DNA as a whole is not being copied accurately in the colon cancer cells, apparently because of a gene mutation that causes wholesale errors during DNA replication. As Thibodeau points out: "We're used to thinking of a single event [causing a genetic disease]. But here we could have an event in a single gene causing mutations throughout the genome."

GENES ALTERED IN COLON CANCERS

Gene	Chromosome	Tumors with mutations	Class	Action
"FCC"	2	~15%	?	Maintains DNA replication accuracy
K-Ras	12	~50%	Oncogene	Intracellular signaling molecule
Cyclins	Various	4%	Oncogene	Help regulate cell cycle
neu/HER2	17	2%	Oncogene	Growth factor receptor
myc	8	2%	Oncogene	Regulates gene activity
APC	5	>70%	Tumor suppressor	Unknown
DCC	18	>70%	Tumor suppressor	Cell adhesion molecule
p53	17	>70%	Tumor suppressor	Regulates gene activity

The assumption now is that the colon cancer susceptibility gene at the chromosomal 2 location identified by the de la Chapelle-Vogelstein group and tentatively called "FCC," for familial colon cancer, is the one to blame, at least in the colon cancers known to be of familial origin. And it may also play a role in some supposedly "sporadic" colon cancers as well. The tumors studied by Thibodeau were not known to be of familial origin, and when the de la Chapelle-Vogelstein group looked for microsatellite instability in sporadic colon cancers, they found it in 13% (6 of 46 tumors tested), a percentage similar to the Mayo group's. These results could mean, Vogelstein says, that the tumors with the instability result from a previously unsuspected genetic susceptibility after all.

Indeed, both groups' findings indicate that the presence of microsatellite instability defines a distinct subgroup of colon cancers with a common origin and properties. The clinical features of the established familial tumors and of the sporadic colon cancers in which the de la Chapelle-Vogelstein and Thibodeau groups found the instability are similar. For example, they occur predominantly in the segment of the colon furthest away from the rectum. Thibodeau's work also indicates that they are less likely to be fatal than other colon cancers.

For now, however, the new work has raised far more questions than it has answered. Foremost among them: What is the nature of the chromosome 2 gene and how might it affect the accuracy of DNA replication? De la Chapelle and Vogelstein suggest that it might encode a factor needed for DNA replication. Of course, the only way to find out is to find the gene, and how long that will take is hard to predict. At best, de la Chapelle says, their marker could be right on top of the gene, which would be "an incredible stroke of luck." But then it could be as much as 9 centimorgans—roughly 9 million base pairs—away.

Equally important is the question of how the mutations induced by the gene might lead to colon cancer. One possibility is that they induce the APC or other gene changes already detected by Vogelstein and others in colon cancers. The evidence is still preliminary, but Vogelstein notes that they've found microsatellite instability in a precancerous colon tumor, indicating that the change happens early.

But even before these fundamental questions are answered, the new knowledge can begin to be applied in the clinic. The chromosome 2 marker can be used to identify those members of non-FAP families who have inherited the susceptibility gene and are at high risk of getting colon cancer. Once researchers isolate the gene itself, it may be possible to screen the population at large to see who has inherited it. And that could help cut down the lives lost. As Vogelstein says, "deaths from colon cancer are totally preventable if the cancers are caught early enough."

–Jean Marx