CANCER RESEARCH

# New Gene Forges Link Between Fragile Site and Many Cancers

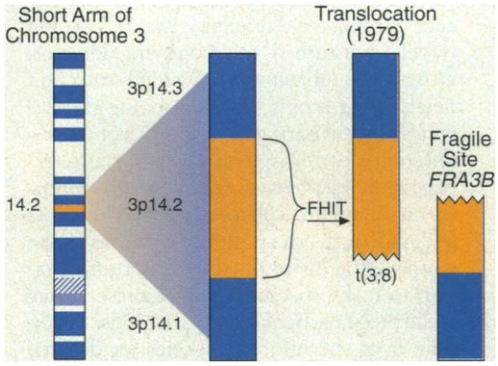
For years, cytogeneticists have known that the chromosomes are riddled with weak points, known as fragile sites, that break or appear to form gaps very easily, at least in cells in lab culture. They've wondered whether chromosomal breakage at the fragile sites might somehow contribute to the genetic abnormalities that are a hallmark of aggressive tumor growth. Linking the fragile sites to cancer has proved difficult, but now there may have been a break in the case.

In work reported in just the past few months, cancer gene experts Carlo Croce, Kay Huebner, and their colleagues at the Kimmel Cancer Center in Philadelphia have discovered a gene, called *FHIT*, that is located at one of the most common fragile sites. *FHIT*, they find, is either completely or partially missing in a wide variety of common cancers, including colon, breast, and lung. That suggests it may be an important tumor suppressor, a gene whose loss or inactivation contributes to the runaway growth of cancer cells. The possibility that a chromosomal change at a fragile site is inactivating this gene is also "spurring new interest in fragile sites," says Thomas Glover, a human geneticist at the University of Michigan Medical School in Ann Arbor. "This is the first molecular evidence tying the instability of fragile sites in with cancer."

Because *FHIT* lies in an easily disrupted area of the genome, it may be a ready target for carcinogens, such as those in tobacco smoke, believed to cause the early gene mutations leading to cancer. *FHIT* gene disruption may turn out not to be the initiating event in tumor growth, as some suggest, but it may still prove to be an indicator of cancer in the making that could be used for early diagnosis, Glover says.

The race to find a tumor-suppressor gene on chromosome 3 began in 1979 after a family with several members who got kidney cancer at an unusually early age turned out to have a particular chromosomal abnormality: a "translocation" in which part of chromosome 8 became attached to the short arm of chromosome 3 near its fragile site, which is called *FRA3B*. Thinking that this translocation might have helped cause the early cancers by disrupting a suppressor gene, Croce, Huebner, and their colleagues spent the past decade looking for candidate genes in the area. Their first find proved to be the wrong gene, but with *FHIT*, they appear to have the one they wanted. In the 23 February issue of *Cell*, they reported that not only does *FHIT* cross the exact spot where the extra bit of chromosome 8 becomes attached, but that the gene is missing completely or lacking coding sections in 50% of the esophageal, stomach, and colon cancers studied.

Its effects may not be limited to digestive system cancers. In the 5 April *Cell*, the same team reported that the gene is missing in 80% of small cell lung carcinomas, and in 40% of two other types of lung cancer. And last week, at the annual meeting of the American Association for Cancer Research (AACR),* they added breast cancer to this growing list: About 30% of several dozen breast tumor samples lacked a normal *FHIT* gene, says Croce, while healthy breast tissue from the same individuals showed no such abnormalities. "Clearly the gene seems to be involved in some of the most common human cancers," Croce concludes.




**Finding *FHIT*.** A translocation in chromosome 3's fragile site helped pinpoint *FHIT*.

*FHIT*'s location at a fragile site may be what makes it so susceptible to damage, notes Glover. Other researchers have shown that many substances, including a chemical in tobacco smoke, can induce fragile sites. And Glover himself described another way the damage can be done in the February issue of *Human Molecular Genetics*. There, Glover's group reported that a human papillomavirus, which has been linked to cervical cancer, inserted its genes into the chromosome 3 fragile site of cells in a cervical tumor, knocking out a piece of the DNA, including the *FHIT* gene.

Such disruptions may be an early event that sends a cell down the road to cancer, say cancer geneticists. Cells from bronchial tissue that show signs of abnormal growth, but are not yet cancerous, for example, often lack a piece of the short arm of chromosome 3, as do early head and neck cancers. "[That alteration] could be coincidence, but I believe that is very unlikely," says Lee Mao, a geneticist at the M. D. Anderson Cancer Center in Houston.

But even though a great deal of evidence links *FRA3B* disruption to cancer, researchers note that the evidence that *FHIT* is the important gene in the region is not airtight. Glover and David Smith of Wayne State University in Detroit have found that the fragile site extends 500,000 base pairs—big enough to contain several other genes besides *FHIT*. "There's a huge region that's unstable," says Michelle Le Beau of the University of Chicago, although she notes that she and her collaborators did in fact find breaks in *FHIT* in lung tumor cells.

At the AACR meeting, Harry Drabkin, Robert Gemmill, and their colleagues from the University of Colorado Cancer Center in Denver also reported that while DNA is missing from the chromosome 3 fragile site in some breast, cervical, colon, and lung cancers, a different part was deleted in other lung cancers. And some researchers, including Michael Lerman at the National Cancer Institute laboratory in Frederick, Maryland, think this different part of this chromosome is really key to the initiation of lung cancer, while the genes elsewhere may play a lesser role. "I don't believe the *FHIT* gene is causing lung cancer," Lerman says.

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There's skepticism, too, because no one has shown when the FHIT protein is produced or how it works, although Croce says those studies are under way. The only clue to its function is its amino acid sequence, about 69% of which matches that of a yeast enzyme, a hydrolase, which breaks down a chemical in cells called diadenosine tetraphosphate. Some evidence suggests that when this chemical accumulates in the cell, it induces new DNA synthesis, triggering cell division. If the FHIT protein has a role similar to the hydrolase, it's possible to imagine how inactivation of the gene could lead to the excess growth of cancer. Thus, if, say, a tobacco carcinogen causes breakage at the fragile site and the cell fails to make the FHIT protein as a result, the growth stimulator might build up and eventually stimulate replication.

None of this has yet been demonstrated, however, nor have researchers shown that restoring *FHIT* function prevents tumor growth—a necessary step to proving a gene acts as a tumor suppressor. Until that can be done, Gemmill concludes, "they have an interesting candidate gene, but the story is not complete."

**–Elizabeth Pennisi**

* The meeting was held in Washington, D.C., from 20 to 24 April.