CANCER GENETICS

Homing In On a Prostate Cancer Gene

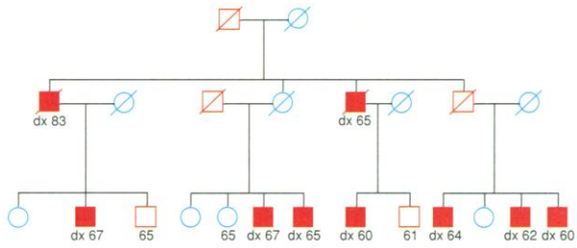
Molecular biologist Jeffrey Trent of the National Center for Human Genome Research (NCHGR) knew he was taking a big risk when he and 22 collaborators decided to search for a gene for the familial form of prostate cancer. The cancer's characteristics have complicated efforts to identify such a gene. For example, it is very common—newly affecting some 340,000 men each year in the United States alone—making it hard to tell whether multiple cases in a family are really due to a susceptibility gene or simple chance. And because prostate cancer usually strikes late in life, the multiple-generation families needed to follow the inheritance of a gene are scarce. Indeed, while others had looked, no one had yet found a susceptibility gene. "It's one of the most difficult cancers to analyze in this way," notes molecular biologist Alfred Knudson, of the Fox Chase Cancer Center in Philadelphia.

Nevertheless, NCHGR geneticists, working with prostate cancer experts from Johns Hopkins University, the University of Michigan, and Umeå University in Sweden, have beaten the odds. On page 1371, they report the results of a family study showing that somewhere in a small region of chromosome 1's long arm is a gene that substantially increases the risk of prostate cancer when it's altered.

The gene itself has not yet been pinpointed, but even getting this far is impressive, Knudson says: "The fact that they have found something on the first round [of searching] is amazing. I think it means [the gene] is a major contributor" to the risk for prostate cancer. Even though the research team estimates that the gene they are homing in on is involved in only about a third of hereditary prostate cancer cases, or about 3% of the total, it may also play a role in prostate cancers that don't run in families. Consequently, once the gene is in hand, it should not only lead to a test for prostate cancer risk in men with a family history of the disease, but also help researchers learn more about the cancer generally, says team co-leader William Isaacs, a molecular biologist at Johns Hopkins.

The team drew on a database of 2500 families, collected over the past decade by Johns Hopkins urologist Patrick Walsh. All the families had two or more affected members. But to help avoid any that had multiple cases by chance, the group focused first on 66 families that had at least three males with prostate cancer.

The researchers analyzed the genomes of various members of the families for some 341 "markers," variable DNA sequences whose chromosomal locations are known, looking for any variations that were consistently inherited with the prostate cancer—an indication that the markers are located near a susceptibility gene. Their analysis revealed a marker on chromosome 1 that did seem to travel together with cancer risk. Confirmation, and a more precise location of the gene, came when the researchers looked at other chromosome 1 markers in their original 66 families plus another 25, including a dozen from Sweden.



SOURCE: W. ISAACS

Inherited risk. The many prostate cancer cases (■) in this family are linked to the chromosome 1 gene (dx is age of diagnosis).

Because the gene, which will be called *HPC1*, for hereditary prostate cancer 1, has not yet been cloned, its function is unknown, although there are hints that it might be a cancer-promoting oncogene rather than a tumor suppressor. Other researchers have found that prostate cancer cells sometimes contain extra copies of the chromosome 1 region that contains the gene. That suggests that what leads to this cancer is increased activity of the gene rather than loss or inactivation of it, as would be expected of a tumor-suppressor gene. And the area does contain some known oncogenes, including the *ski*, *abl2*, and *trk* genes.

Still, it could take years to see if any of these, or some as-yet-unknown gene, is a prostate cancer susceptibility gene. To find it, researchers will have to scour a lot of DNA—up to 10 million base pairs—looking for genes that are mutated specifically in males with the cancer. "There's a substantial element of luck involved [in this search]," points out Isaacs.

The effort will be worthwhile, says Walsh, because "identifying the gene may give us insight into the prevention and treatment" of this disease. The gene might be used, for example, to assess whether a male in a prostate cancer family has a mutated version that puts him at high risk of getting this disease even before other indicators, such as prostate-specific antigen, are detectable. And because prostate cancer, like many others, can be treated effectively if discovered early, this prospect "is quite exciting," says Trent.

–Elizabeth Pennisi

NEUROSCIENCE

Illusion Reveals Pain Locus in Brain

WASHINGTON, D.C.—Illusions can be keys to the workings of the brain. Now, a century-old illusion has helped scientists pinpoint the part of the brain that responds to pain from extreme temperatures. The findings, presented a week ago at the Society for Neuroscience annual meeting here and in this week's issue of *Nature*, also help scientists understand the phantom pain endured by many stroke and spinal cord injury victims.

In 1896, scientists reported a strange phenomenon: When a subject placed his hand on a grill with alternating warm and cool bars, he felt a burning sensation like the pain that accompanies severe cold. Neurobiologist Bud Craig of the Barrow Neurological Institute in Phoenix and his colleagues thought that by comparing the brain areas involved in the illusion with those that respond to real temperature extremes, they could pinpoint where thermal pain arises.

The researchers used positron emission tomography to measure blood flow in the brains of subjects whose hands were resting on a set of temperature-controlled bars. Their results show that the anterior cingulate cortex has relatively high blood flow—indicating neural activity—when the bars are painfully cold (5° Celsius), painfully hot (45°C), or when alternating bars are cool (20°C) and warm (40°C). The region is inactive when the bars are uniformly cool or warm.

Besides pointing to the anterior cingulate cortex as the pain locus, says Craig, the findings are consistent with other work by his group suggesting that the illusion arises from an unmasking effect. Under normal conditions, nerves that respond to temperature changes send pain-inducing signals to the brain even at comfortably cool temperatures, but other nerves override those signals until the cold becomes dangerous. When the hand is placed on the alternating bars, Craig proposes, the warm bars suppress the signal overriding the cool sensation, triggering a pain response.

Craig's group postulates that in patients who suffer from central pain syndrome, which is often felt in an upper limb after neurological injuries, the nerve pathway that normally overrides the pain signals is damaged. Their latest study gives pain researchers a target for developing treatments for central pain syndrome, says Kenneth Casey, a clinical neurologist at the University of Michigan: "It gets at the root cause."

–Gretchen Vogel