Gene Linked to Commonest Cancer

Mutations in the human version of *patched*, a gene first identified in a fruit fly developmental pathway, cause a hereditary skin cancer and may contribute to sporadic skin cancers, too

The lowly fruit fly, *Drosophila melanogaster*, has proven itself an adept teacher of genetics, instructing us about a host of genes that play key roles in many organisms. This week's lesson is on the cause of the most common human cancer, basal cell carcinoma of the skin, which afflicts some 750,000 people every year in the United States alone.

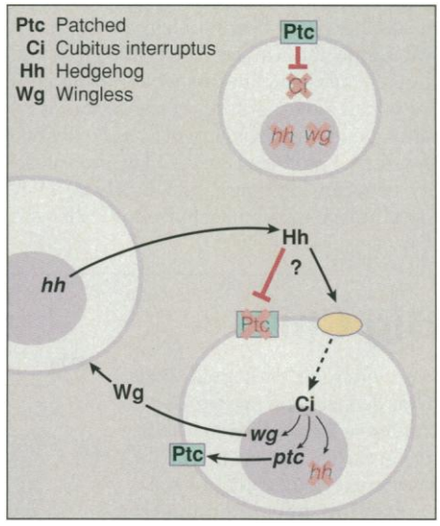
Two groups, one led by Matthew Scott of Stanford University School of Medicine and the other by Allen Bale of Yale University School of Medicine, have just identified the gene at fault in a rare inherited disease, called Gorlin's or basal cell nevus syndrome, which occurs in about one in 100,000 people and predisposes its victims to both developmental abnormalities and a variety of cancers, especially basal cell carcinoma. The errant gene turns out, once again, to be one that was first identified in the fruit fly: the human version of a gene called *patched*, a member of a key developmental control pathway that helps determine how different tissues are laid out in the embryonic fly.

What's more, both groups found that *patched* is mutated in some of the much commoner basal cell carcinomas that are apparently not hereditary. Taken together, the Scott team's work, which is described on page 1668 of this issue, and that of the Bale team, which appears in the 14 June issue of *Cell*, indicate that *patched* is a new tumor suppressor, a gene whose loss or inactivation contributes to the excessive growth of cancer cells.

Development genes are well suited to playing a role in cancer because they control cell growth and specialization. Indeed, two other members of the *patched* pathway, known as *GLI* and *Wnt1*, when mutated, lead to certain cancers. But neither has been linked to a human cancer as common as basal cell carcinoma. And because scientists already know a great deal about *patched* and the genes it interacts with from the fruit fly work, cancer researchers hope the discovery will clarify how basal cell carcinoma develops and perhaps lead to better ways to treat it as well. The new work "is a wonderful example of how *Drosophila* research can have an impact on human biology," says Stephen Katz, director of the National Institute of Arthritis and Musculoskeletal and Skin Diseases in Bethesda, Maryland.

The two teams came to their discovery from opposite directions. Scott, a fruit fly geneticist, wasn't thinking about cancer when his group first cloned the fly *patched* gene in 1989. He was investigating how it works with other so-called "patterning" genes, including the well-studied *hedgehog*, to determine where cells wind up in the fully formed insect and what structures they become part of.

But as researchers soon learned, humans and other mammals have their own versions of *patched*, *hedgehog*, and the other genes with which they interact. In 1994, for example, Lisa Goodrich and Ronald Johnson in Scott's lab detected *patched* in mice; then, using the mouse *patched* gene as a probe, the researchers went on to clone the human gene. Stanford gene mappers Richard Myers and David Cox determined that it lies on the long arm of chromosome 9, very near the site where genetic linkage studies showed that the gene for basal cell nevus syndrome should be.



Identity instructions. The diagram shows some of the proteins (their genes are in italics) that communicate cell-fate signals between cells during development.

At this point, the researchers joined forces with dermatologist Ervin Epstein Jr. of the University of California, San Francisco, who had long been searching for that same gene, to see if it might in fact be *patched*. Demonstrating that proved more difficult than the researchers expected, however. When they first looked for altered *patched* genes in families with the disease, they found no large differences, "a discouraging result," Johnson recalls. But then the team eventually discovered a single base difference in a sporadic basal cell carcinoma, a tumor from someone who did not have Gorlin's syndrome. Moreover, it was not mutated in normal cells from the patient. "That was the first indication that we had the right gene," Johnson adds.

Since March, the researchers have unearthed two mutations in families, including a *patched* mutation consisting of a loss of 15 base pairs in a teenager who is apparently the first in her extended family to have the syndrome. She is also the first to have the deletion, leading the researchers to conclude that it arose in a parent's germ-line. "That's what really clinched it for us that it was the [disease] gene," Johnson says.

Instead of moving from the fly gene to the human disease, as Scott's group did, Bale's followed the more traditional approach of taking off from the disease itself. Their starting point was the chromosomal region where the gene at fault in Gorlin's syndrome had been mapped. They searched the region for candidate genes and then looked to see whether any of them were mutated in patients with the syndrome. And they, too, came up with *patched*.

Bale, working with Brandon Wainwright from the University of Queensland in Australia; Georgia Trench from the Queensland Institute of Medical Research; Rune Toftgard of the Karolinska Institute in Huddinge, Sweden; and Mick Dean from the U.S. National Cancer Institute Laboratory in Frederick, Maryland, found mutations in the gene in six people with the inherited disease and also in two so-called sporadic tumors. "In these two papers, scientifically the content is remarkably similar," notes Bale, a cancer geneticist.

The two groups do not yet know how often *patched* mutations lead to sporadic basal cell carcinoma. But Bale and Scott both note that Gorlin's syndrome patients suffer not only from a high risk of skin cancer but also from developmental abnormalities, including jaw cysts, large heads, abnormal ribs, scoliosis, neural tube defects, and a variety of tumors, that are consistent with *patched* mutations.

And while the exact biochemical mechanism by which *patched* mutations cause the developmental abnormalities and cancer is another problem that needs to be solved, the fruit fly work has provided some clues. The

researchers know, for example, that the protein made by *hedgehog* sets in motion a train of events that ultimately turns on or revs up several genes, *patched* among them. Patched protein builds up until it interrupts transmission of the Hedgehog signal traveling from the cell membrane to the nucleus. By turning off the genes that Hedgehog turned on, the Patched protein keeps the system in check. It's "the balance between these two things that determines what goes on," Scott explains.

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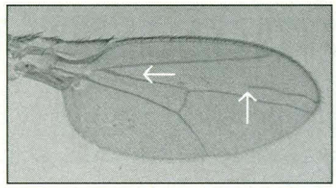
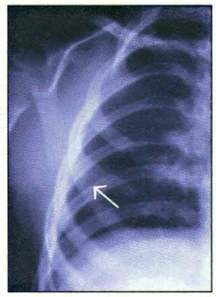




ALLEN BALE

Subtle but significant. In the fruit fly, *patched* mutations cause faulty wing veins *(arrows)*, and in humans they cause defective ribs *(arrow)*, as well as skin cancer.

When *patched* isn't functioning correctly, the genes stimulated by Hedgehog may be abnormally active, possibly prompting cells to continue to proliferate rather than differentiate. "You can wind up with uncontrolled growth," says Konrad Basler, a fruit fly developmental biologist at the University of Zurich in Switzerland.

Indeed, previous work had already suggested that malfunctioning of genes associated with the hedgehog path might lead to cancer. The *Wnt1* gene of mice—a counterpart of the fruit fly *wingless* gene, which codes for a protein that stimulates Hedgehog production in the target cell—can cause mammary tumors when it's overactive. In addition, a human *GLI* gene, which Bert Vogelstein's group at Johns Hopkins University School of Medicine discovered as an oncogene in a rare human brain tumor, is the counterpart of the *cubitus interruptus* gene of the fly. Studies of this gene, which encodes a transcription factor (a protein that turns genes on or off), indicated that it also interacts with *hedgehog* and *patched*, although its role in the path was unclear.

But now in a Research Article in this week's issue, Basler and his colleagues have helped clear up the mystery, also providing more clues about how problems in this pathway can lead to cancer (see p. 1621). When they created fruit flies in which some cells contained a mutant form of the *cubitus interruptus* gene, the Swiss group found evidence that the Ci protein serves as a key intermediary between Hedgehog and Patched. They found, for example, that Hedgehog leads to an increase in the amount of Ci protein, which in turn revs up the expression of genes normally activated by Hedgehog. Conversely, Patched causes a decrease in Ci, which may cause those genes to be turned off.

It all implies, says Philip Ingham of the Imperial Cancer Research Fund in London, that the uncontrolled cell growth of cancer results either when excessive Gli/Ci causes the genes controlled by Hedgehog to become overactive or when a disabled *patched* cannot rein in Ci activity. "Excess Ci is the same as not having Patched," says Ingham. "In fact, with enough Ci, the Hedgehog signal is transmitted even if there's no Hedgehog."

How that translates into different cancers is unclear, but as this picture gets sharper, researchers hope to pick out potential targets for different cancer therapies. Although basal cell carcinoma can be cured surgically, Katz points out that the new understanding suggests a less drastic alternative. Because the skin is so accessible for treatments, it might be possible "to interfere with the adverse effects [of mutated *patched*] chemically."

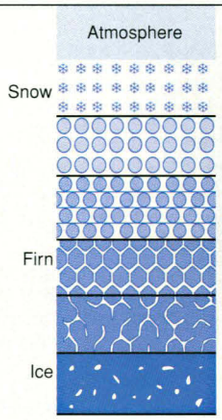
Researchers caution that even with the new information, however, they still don't know everything about how the Hedgehog pathway works. But with these new links to cancer, "all the biochemistry is going to come in floods now," Ingham predicts.

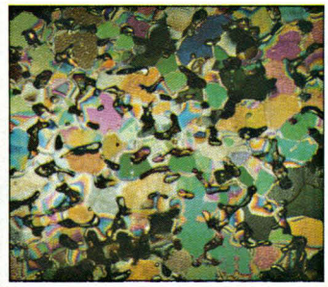
–Elizabeth Pennisi

CLIMATE CHANGE

Ice Bubbles Confirm Big Chill

SOURCE: J. SEVERINGHAUS





R. ALLEY

A deep squeeze. Bubbles trapped in glacial ice *(above*, in polarized light) as snow gradually compacted *(left)* hold climate clues.

Twelve thousand years ago and more, Greenland suffered a series of climate catastrophes. Clues buried in its ice sheet show that during the last ice age the climate repeatedly warmed sharply, only to slide into a renewed chill lasting thousands of years. Just how drastic the warmings and coolings were, and how much of the world they affected, has been a matter of debate. Now, new indicators derived not from the ice itself but from trapped bubbles of ancient gases—nitrogen and methane—show that at least the last of these catastrophes fully deserves the name. Known as the Younger Dryas, this cold snap 12,000 years ago was twice as severe as was thought, and it seems to have gripped much of the world.

"I'm completely in awe of the scale of the change and its speed," says isotope specialist James White of the University of Colorado. Glaciologist Richard Alley of Pennsylvania State University (PSU) adds that the result, presented at last month's meeting of the American Geophysical Union by Jeffrey Severinghaus of the University of Rhode Island (URI) and his colleagues, leaves "no way anyone can argue" that it was only Greenland that suffered the chill, 14 degrees Celsius colder than today: "A big piece of the world's climate was switching to a new mode." That deepens the mystery of these climate swings, but the new indicators in the ice may eventually help researchers home in on a cause.

Existing paleothermometers had been enough to show that Greenland's climate oscillated sharply during the last ice age. The evidence came from the ratio of oxygen isotopes in the deep ice, which preserves the isotopic makeup of ancient snowfalls. The relative abundance of lighter oxygen can serve as a thermometer because the colder it gets, the more water vapor containing the lighter isotope condenses to form snow. But although the oxygen isotopes clearly showed climate swings in Greenland during the last ice age, their magnitude was in doubt. The reason: The oxygen thermometer also reflects temperature far from Greenland, at the source of the water vapor.

Evidence that its readings were off came last fall, when Kurt Cuffey of the University of Washington and his colleagues used the temperatures in deep-ice bore holes to estimate the average chill of the ice age in Greenland. Like a cellar that holds last winter's chill, the deep ice preserves the ice-age cold. From the ancient chill, Cuffey and his colleagues estimated that ice-age Greenland was 20°C colder than today instead of the 10°C suggested by the oxygen isotopes.

The climate shifts that punctuated the last ice age were too brief to show up in the bore hole records, however. To measure them, Severinghaus, Edward Brook of URI, Todd Sowers of PSU, and Alley developed another isotope method that relies on the ratio of nitrogen-15 and nitrogen-14 trapped far below the surface, where snow compacts to ice. That ratio, they knew, would be altered any