BREAST CANCER GENE

Many Mutations May Make Test Difficult

The cloning in September of a strong candidate for the breast cancer gene known as *BRCA1* triggered a whirlwind of activity as cancer researchers rushed to verify the finding (*Science*, 23 September, p. 1796 and 7 October, p. 66). A bare 10 weeks later, three articles in this month's issue of *Nature Genetics* have confirmed *BRCA1*'s identity.

But while those articles have nailed *BRCA1*, they've also raised problems that may further cloud the development of the much-anticipated test for susceptibility to breast cancer caused by mutations in *BRCA1* (*Science*, 22 July, p. 464). The articles report that *BRCA1* mutations occur in many different forms, scattered throughout the gene, making it technically challenging to develop an accurate test. What's more, they hint that mutations in the gene may account for fewer cases of hereditary breast cancer than previously thought.

In the *Nature Genetics* papers, teams led by Steven Narod of McGill University in Montreal (a member of the team that isolated *BRCA1*), Barbara Weber of the University of Pennsylvania, and Mary-Claire King of the University of California, Berkeley, describe 22 different *BRCA1* mutations in 31 families. As the *Science* paper describing the cloning of *BRCA1* identified five mutations in the gene, including one also found in the current work, the total number of published *BRCA1* mutations now stands at 26. Because these mutations are scattered throughout the gene, which at about 100,000 base pairs is exceedingly long, development of a test that will detect all mutations with certainty may be difficult. Indeed, Weber calls the results "bad news for testing."

Still, the problem may be less formidable than it looks right now, says Narod. He notes that some mutations have been detected again and again in different families, suggesting that a relatively small number of mutations may account for most *BRCA1*-related cancers, a situation that may help make screening possible. His team, for example, found two mutations, each of which turned up in four Canadian families. In addition, says Narod team member David Goldgar of the University of Utah, who is busy categorizing all known mutations, published or otherwise, the two Canadian mutations have also been detected in families in the United Kingdom and the United States, and several other mutations have been found two or more times.

"We'll probably be able to identify mutations 75% of the time ... and if it turns out that the majority of [*BRCA1*-associated breast cancers] are caused by 10 or fewer mutations, it could still be a relatively simple screening test," says Narod. Such a test, he adds, "will be very helpful" for screening women from families with a high incidence of breast and ovarian cancer, because the mutation can first be sought in a family member with cancer. But, he says, widespread screening of the general population for *BRCA1* defects is not feasible unless all the mutations can be detected, because it would be uncertain whether a negative result could be trusted.

Both Weber and Narod also point out that about two thirds of the *BRCA1* mutants detected so far cause the protein produced by the gene to be shorter than normal, effectively crippling it. Therefore, measuring the length of *BRCA1*'s protein product could be the basis of a rapid screening test for predisposition to breast cancer. Such a test would avoid the technical difficulty of screening for all types of mutations, but it would also miss more subtle—yet equally dangerous—mutations that don't shorten the protein.

But even if detection of *BRCA1* mutations does one day become practical for widespread population testing, its usefulness for predicting susceptibility to breast cancer may be limited. Hereditary susceptibility accounts for up to 10% of the 180,000 breast cancers that occur in the United States each year. But the discovery of a second breast cancer gene, *BRCA2* (*Science*, 30 September, p. 2088), and hints of others, restrict the number of breast cancers that can be attributed to *BRCA1* defects. Moreover, the three groups failed to detect *BRCA1* mutations in 69 breast cancer families, suggesting either that the tests used were too insensitive or that *BRCA1* accounts for fewer breast cancers than expected. "We are already talking about fairly small numbers," says Weber. "If *BRCA1* accounts for even less, it will further limit the clinical usefulness of a test."

–Rachel Nowak

EPIDEMIOLOGY

Yale Arbovirus Team Heads South

As a source of knowledge about the strange and deadly viruses carried by such creatures as ticks and mosquitoes, nothing rivals a small research center tucked away at the Yale University School of Medicine. Since 1964, the Yale Arbovirus Research Unit (YARU) has been the central repository for the world's arboviruses—shorthand for arthropod-borne viruses—and the place that puzzled scientists have sent their samples. In addition, the unit's director, virologist Robert E. Shope, travels the world to lend his expertise on everything from outbreaks of encephalitis in China to the dengue virus now afflicting U.S. soldiers in Haiti.

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Lone Star–bound. Yale's Robert Shope is expected to join new Texas center.

But as of next year, researchers should plan to send their samples to Shope at a new address: the University of Texas Medical Branch at Galveston. Shope, who is retiring from Yale next year, and virologist Robert B. Tesh, a senior scientist with the unit, have decided to leave New Haven to join a new center for tropical medicine at Galveston—and they hope to take the virus collection with them. Tesh and Shope, who were traveling abroad and could not be reached for comment, disclosed their plans 2 weeks ago at a meeting of the American Committee on Arbovirology in Cincinnati. The University of Texas verified the move after a report appeared in *The Hartford Courant*. A Yale spokesperson says officials have confirmed the departure of Tesh but "have had no conversation with" Shope.

Outside scientists say they aren't surprised the two are leaving Yale. Shope has faced "an uphill battle finding money," says Thomas Monath, former director of the Fort Collins, Colorado, vector-borne infectious diseases laboratory run by the U.S. Centers for Disease Control and Prevention (CDC) and now research director for Oravax Inc. in Cambridge, Massachusetts. After researchers paid by the unit's dwindling original endowment from the Rockefeller Foundation began to retire in the late 1970s, says James Meegan, head of the extramural arbovirus program at the National Institute of Allergy and Infectious Diseases and a former YARU scientist, Shope came to rely increasingly on