On the Trail of a Second Susceptibility Gene

Four years ago when cancer geneticists tracked a breast cancer susceptibility gene to a region of chromosome 17, they quickly realized that this rogue gene could only account for about half of all hereditary breast cancers. In many families in which vulnerability to breast cancer appeared to be inherited, the gene, *BRCA1*, was not linked to the disease. This implied that another, quite separate, breast cancer susceptibility gene was at large.

Now, an international consortium headed by molecular biologist Michael Stratton and genetic epidemiologist Doug Easton at the Institute of Cancer Research in Sutton, Surrey, United Kingdom, and genetic epidemiologist David Goldgar at the University of Utah has dramatically narrowed the search for this gene. In next week's issue of *Science*, the team will publish evidence that it resides on a stretch of chromosome 13. Gene hunters are now gearing up to find the gene, dubbed *BRCA2*, which researchers believe could be implicated in as many cancers as *BRCA1* is—perhaps half of hereditary breast cancers.

Homing in on *BRCA2*. Team co-leader Michael Stratton.

To pin down the new gene's location, members of the consortium—mostly groups trying to track down *BRCA1*, which have refrigerators full of tissue and blood samples from families in which breast cancer is rife—pooled their data. They came up with 15 families, each of which had between two and 25 cases of female breast cancer diagnosed before age 50 that didn't show any linkage with *BRCA1*.

Having identified these non–chromosome 17-linked families, the researchers used standard methods of genetic linkage analysis (see box, p. 1797) to try to find a "marker" sequence that was consistently inherited along with breast cancer, an indication that the marker is physically close to the DNA containing the susceptibility gene. Hoping to short cut their way to the right chromosome, "we first looked at parts of the genome which harbor known cancer-susceptibility genes such as *p53*, or which show abnormalities in sporadic breast cancer," explains Goldgar. But when they didn't turn up anything, they began a systematic search of the whole genome. The Sutton and Utah labs "typed over 200 markers before we found one linked to breast cancer," Goldgar says.

Richard Wooster, a postdoc in Stratton's lab, says "The day we found it was very exciting.... I'd seen a result..., and Mike said he thought he'd found something [too]. We all sat down in a huddle and decided we were 90% sure we'd got it." The teams now have a set of markers linked to *BRCA2* that have placed the gene somewhere within a 6-centimorgan stretch on region q12-13 of chromosome 13. Easton estimates that about 100 genes may lie in that region. As for *BRCA2*'s role in causing cancer, Stratton's first guess is that it, like most other cancer-susceptibility genes, is a tumor suppressor. But proving that will require pinning down its identity.

The race is now on to do just that. Geneticist Bruce Ponder of Cambridge University, one of Stratton's collaborators on the *BRCA2* paper, predicts that the groups who worked on *BRCA1* will now be "ransacking their fridges for forgotten families" that might hold the clue to *BRCA2*. "There are one or two possible candidate genes in the region—we know that from human genome maps," says Ponder. One possible candidate is *BRUSH1*, a gene of unknown function that was partially sequenced earlier this year by Helene Smith's group at the Geraldine Brush Cancer Research Institute in California. This gene is expressed in breast epithelium, and Wooster says "we know it maps to the right location."

Mutations in either *BRCA1* or *BRCA2* appear to result in a similarly high risk of female breast cancer—a woman carrying one defective gene has an 80% to 90% chance of developing the cancer. However, the two gene products seem to act by different mechanisms. *BRCA1* defects, for example, are associated with a much higher risk of ovarian cancer than are *BRCA2* mutations. And families with breast cancer due to *BRCA2* often include a case of male breast cancer, which is not true for *BRCA1* families.

Identification of *BRCA2* is unlikely to be the end of the breast cancer susceptibility gene story. In their *Science* paper, Stratton and his colleagues point out that breast cancer in some families in which the disease seems to be hereditary does not appear to be attributable to either *BRCA1* or *BRCA2*, indicating that there may be yet more breast cancer susceptibility genes to be identified.

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cancer had seemed to follow the classic model of a tumor suppressor at work: In about one half of sporadic, and all familial, cancers, a stretch of chromosome 17 where researchers had been searching for *BRCA1* is lost from tumor cells, suggesting that *BRCA1* mutations play a role in both types of cancer. But the apparent absence of *BRCA1* defects in sporadic tumors suggests otherwise, and could even mean, says Bert Vogelstein of Johns Hopkins University, "that there's another tumor suppressor gene on [the relevant portion of chromosome] 17."

Indeed, genetic epidemiologist Neil Risch of Yale University argues that because the gene fails to show all the predicted features of *BRCA1*, the evidence that it really is the long-sought gene is not completely watertight. Risch calls the work "highly suggestive," but says "the ultimate proof" will require further evidence that the gene is mutated in families with hereditary breast and ovarian cancer, but not in healthy individuals.

Risks and uncertain benefits

Once the gene's sequence is released on 7 October (see box, p. 1797), there will be no shortage of researchers to follow up Risch's suggestion. Assuming they confirm that Skolnick and his collaborators have the correct gene, one of the first tasks will be to get better estimates of the lifetime risk of cancer associated with *BRCA1* defects. The current guesstimate is that a woman who carries a defective copy of *BRCA1* has an 85% chance of developing cancer by age 65. But that could be an overestimate, because it's derived from studies of the families used to track down the gene, which were chosen precisely because so many of their members had been stricken with cancer.

With *BRCA1* in hand, adds King, "we will [also] be able to get some assessment of the risks associated with the different kinds of mutations [in the gene]." Breast cancer experts expect that different mutations will trigger cancer at different ages of onset and will carry different likelihoods of triggering breast or ovarian cancer, or both. However, because of the sheer size of the gene—it's estimated to be a massive 100,000 base pairs