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The glittering prize

In the words of the front-page report in *The New York Times* announcing the discovery, it was 'a genetic trophy so ferociously coveted and loudly heralded that it had taken on a near-mythic aura'[1]. It was the culmination of a research race that took four agonizing years to complete, mesmerizing hundreds of scientists and consuming millions of dollars. The elusive prize was the gene known as *BRCA1* that is responsible for about half of all hereditary breast cancers. An estimated 600,000 women in the United States alone carry the defective *BRCA1* gene.

First across the finishing line was a team of 45 scientists led by Mark Skolnick, at the University of Utah and Myriad Genetics (a private biotechnology company), and Roger Wiseman of the National Institute of Environmental Health Sciences (NIEHS) in North Carolina. On September 14, the day after the breakthrough was first reported on US television, the director of the National Institutes of Health, Harold Varmus, convened an extraordinary press conference featuring the successful NIEHS scientists to announce the discovery officially. Skolnick and colleagues were unable to attend at such short notice, having headed into the Wasatch mountains near Salt Lake City to celebrate at a 'champagne retreat'. Two papers on *BRCA1* will be published in *Science* this month[2,3]. October is, quite fittingly, 'Breast Cancer Awareness Month' in the United States.

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One down ... Mark Skolnick and Donna Shattuck-Eidens (Myriad Genetics) on the day the cloning of *BRCA1* was announced.

Skolnick and colleagues had narrowly beaten numerous other groups around the world that had eagerly sought the same goal. Many of the competitors hid their deep sense of personal disappointment upon learning that their efforts had fallen just short. Mary-Claire King said the work was 'beautiful' and the scientists 'deserve their success'. Ray White, who had led a separate effort at the University of Utah to find *BRCA1*, praised 'an outstanding discovery'. And Francis Collins, the director of the National Center for Human Genome Research, said that the cloning of *BRCA1* was 'a revolutionary development' in the war against cancer.

The region on chromosome 17q containing *BRCA1* had been reduced to just 600 kilobases (kb) when the gene was finally pieced together. *BRCA1* turns out to sit right in the middle of this critical region[4], spanning the marker *D17S855*. It

was ultimately found using a technique called 'solution hybrid capture', which greatly enriches for cDNAs that map to a specific segment of genomic DNA. Wiseman says the method is 'the closest thing to magic' he has seen in his career. *BRCA1* consists of 21 exons spanning 100 kb, and exhibits a complex pattern of alternative splicing reminiscent of the Wilms' tumour gene. The gene encodes a protein of 1863 amino acids, but, with the exception of a zinc finger domain near its N terminus, shows no resemblance to other known sequences. In addition to the breast and ovary, *BRCA1* curiously shows high expression in thymus and testis, where its significance is unclear at present.

Of the four *BRCA1* mutations that have been uncovered in breast/ovarian cancer families, three occur in the C-terminal half of the protein, and comprise missense (Met1782Arg), nonsense (Gln1320Ter) and frameshift (Gln1763fs) mutations[2]. (The fourth appears to abolish expression of the mutant allele.) Interestingly, at least one carrier of a mutant *BRCA1* allele in each family lived to the age of 80, confirming the less than complete penetrance of the gene and offering a glimmer of hope that ways can be found to combat the deadly consequences of the mutation.

But although the evidence for *BRCA1*'s role in hereditary breast/ovarian cancer is unequivocal, a surprise has emerged from the companion study of sporadic breast and ovarian tumours[3]. One expectation prior to the cloning of *BRCA1* was that the gene would be found to have a central role in sporadic as well as inherited cancers. With that in mind, Futreal *et al.* examined 44 sporadic breast or ovarian tumours exhibiting loss-of-heterozygosity (LOH) for chromosome 17q markers, but found only four cases in which *BRCA1* was damaged. To their surprise, the mutations were present in the germline of each patient; indeed, two were found retrospectively to have family members with breast or ovarian cancer. Thus *BRCA1* seems to have minimal involvement in the onset of sporadic breast and ovarian tumours. While some mutations may have been missed, such sporadic tumours may feature the loss of different tumour suppressor loci. *BRCA1* itself seems to be most important in premenopausal breast and ovarian cancers, and may have an early role in a hypothetical genetic pathway leading to breast tumorigenesis. The search for putative downstream targets of BRCA1 has already become a priority.

While virtually all hereditary ovarian cancers are attributable to *BRCA1* mutations, only about half of all hereditary breast cancers can be blamed on such defects. In another exciting development for breast cancer research, a large collaborative study[5] led by Michael Stratton at the Institute of Cancer Research in Sutton, UK, has mapped the location of a second hereditary breast cancer locus, *BRCA2*, to chromosome 13, close to the original cloned tumour suppressor gene — retinoblastoma. Like its predecessor, *BRCA2* is mutated in a subset of early-onset inherited breast cancers, but by contrast may also have a role in the onset of male breast cancer in affected families. There is probably at least one other hereditary breast cancer gene to be mapped, but the localization of *BRCA2* to a small 6 centiMorgan interval is sure to spark another frantic scramble for the gene.

But the impending research benefits that are likely to be generated by *BRCA1* are of little immediate consequence to women with a family history of breast cancer. If they carry the faulty gene, their lifetime risk of the disease is dramatically increased from about 13% to 90%. Ironically, the large size and spread of mutations in *BRCA1* may prove to be a blessing in disguise, providing a narrow window of opportunity for researchers and clinicians to address the many complex ethical issues that have surfaced so suddenly, while a practical and efficient method of genetically screening potential carriers is devised. Collins stressed: "This is not a time to rush this kind of testing into the general practitioner's office." For women who do test positive for a *BRCA1* mutation, the only hope is to maintain extra vigilance for the first signs of cancer, modifying dietary and other lifestyle factors, while contemplating a hopelessly inadequate set of options. These basically narrow down to the unproven benefits of the drug tamoxifen or a prophylactic mastectomy.

The cloning of *BRCA1* has been lauded as a major breakthrough in the war against breast cancer, even though the lustre of the accomplishment is perhaps not quite as brilliant as had been anticipated. Nevertheless, despite the daunting amount of work ahead to capitalize on the discovery, there can be little doubt about 1994's 'Molecule of the Year'.

1. Angier, N. *The New York Times* September 15, A1 (1994).
2. Miki, Y. *et al. Science* October 7 (1994).
3. Futreal, A. *et al. Science* October 7 (1994).
4. Albertsen, H. *et al. Nature Genet.* 7, 472–479 (1994).
5. Wooster, R. *et al. Science* September 30 (1994).