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Breast cancer on the brink

According to James Watson, "there is no more exciting story right now in medical science", and who would disagree? He refers to the search for the gene responsible for hereditary breast and ovarian cancer, whose localization was first described by Mary-Claire King three years ago this month. Since then, groups from around the world have been scrutinizing more than 250 families with a high incidence of the disease to refine that localization on the long arm of chromosome 17 and eventually clone the defective gene. Progress has been rapid. Both King and Francis Collins, with whom her group is now collaborating, believe that the gene will be found by someone before the end of the year. Before that happens, however, there will undoubtedly be many promising candidates and inevitable false leads. On page 151 of this issue, Yusuke Nakamura and colleagues from Tokyo's Cancer Institute describe an interesting gene in the vicinity of *BRCA1*; into which category it falls remains to be seen, but it would seem to merit further investigation.

Since the hereditary breast cancer locus (*BRCA1*) was linked to the marker, *D17S74*, in 1990, hopes have risen that its eventual isolation would represent a landmark in the diagnosis and perhaps the treatment of breast cancer. Although hereditary forms of breast cancer are thought to constitute only 5% of all cases, lesions in *BRCA1* probably play a significant part in the far more common sporadic forms of breast cancer. Depending on the ultimate identity of the gene product, it might become an invaluable tumour marker, perhaps leading to a 'molecular mammogram' for women.

Indeed, it would be bitterly disappointing if that were not the case. Recognition of the horrific casualties being claimed by breast cancer has come late, but this epidemic is finally receiving vital attention from governments and the scientific community. In the United States at least, breast cancer is now singled out for special treatment; the US Army, for example, is looking for ways to spend its recent $210 appropriation for breast cancer research. The issue has rightly also attracted the notice of the mass media: from feminist publications such as *Ms.* to fashion magazines including *Vogue*, the risks and fatalities associated with breast cancer are now firmly engraved in the minds of all women: the lifetime risk of acquiring breast cancer is put at one in nine. In the United States, 46,000 women die each year of breast cancer, with more than 180,000 new cases diagnosed annually. In Britain, which has the highest incidence of breast cancer in the world, those statistics are 12,000 and 25,000 respectively. And while mortality rates are stagnant, the incidence is growing, a rise that is only partially attributable to improved detection by mammography. An urgent priority must be to define the role of diet in provoking breast cancer once and for all.

Although hereditary breast cancer accounts for only a small proportion of the total number of breast cancer cases, it ranks as one of the most common of all genetic diseases. Recent estimates suggest that the rogue *BRCA1* allele is carried by

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about one in 200 women and imparts an 85% chance of contracting the disease[3]. King's initial linkage discovery[2] showed that hereditary breast cancer is distinctive in affecting women relatively early, before menopause. This localization was soon confirmed by Gilbert Lenoir and colleagues[4], who also noted that *BRCA1* is faulty in families with breast *and* ovarian cancer. In fact, new results strongly suggest that *BRCA1* is responsible for all cases of hereditary breast and ovarian cancer (and possibly some instances of prostate cancer), but only about half of the familial forms of breast cancer alone[3]. Identifying *BRCA1* therefore will not be the last word in the genetics of breast cancer.

The molecular basis of some extremely rare forms of breast cancer has recently been clarified. The p53 tumour suppressor gene, on the short arm of chromosome 17, is commonly mutated in sporadic forms of breast cancer, and germline mutations in p53 account for the familial Li-Fraumeni syndrome[5], in which patients are predisposed to many tumours including cancer of the breast. And there have been reports of mutations associated with male breast cancer; the second documented mutation within the X-linked androgen receptor gene is described on page 109 of this issue[6].

Meanwhile, researchers have been edging ever closer to *BRCA1*, ruling out a number of candidate genes as they go. As is standard practice, the key to minimizing the critical region that harbours the gene is to detect meiotic recombination events, or crossovers, within the cluster of markers known to be linked to the disease gene. Several examples have been reported within the past few months, with the result that *BRCA1* has been confidently assigned[3] to the region between the thyroid hormone receptor gene, *THRA1*, and *D17S579*; all the known genes near *BRCA1* have now been excluded, either by mapping beyond this critical region or by direct sequencing. (The last of these, the gene for estradiol 17β-hydroxysteroid dehydrogenase II, was recently ruled out by Steven Narod and colleagues, who also placed slightly narrower limits on the *BRCA1* interval[7].)

Nakamura and coworkers[1] have chosen to concentrate on one end of the 4-centiMorgan region defined by linkage between *THRA1* and *D17S579* (also termed mfd188) — the distal portion of about 500 kilobases that overlaps with a region defined by the loss of heterozygosity in sporadic tumours. The new gene from this region described by Nakamura's group[1] will have many neighbours, of course, but is intriguing for at least two reasons. First, in a survey of more than 600 sporadic breast cancer DNA samples, a couple of rearrangements were found, including partial amplifications of certain exons. But no rearrangements were seen in 50 ovarian tumours, and the true significance of such somatic variations is unclear. An earlier candidate called prohibitin that was mapped by Nakamura's group to chromosome 17q21 and shown to contain somatic mutations in sporadic breast cancers[8] has since been excluded.

The second interesting feature of this gene is that it bears several different regions of homology to known genes. The full sequence predicts a protein of 524 amino acids having similarities to the metalloprotease/disintegrin family of snake venom haemorrhagic proteins as well as a cysteine-rich C-terminal domain (the gene has thus been named *MDC*). The C-terminal third of the protein is 38% identical to the guinea-pig sperm surface protein, PH-30β. Thus, the highly conserved MDC protein may function as a ligand for a cell-surface integrin. The one thing that the new report does not contain, sadly, is an analysis of familial breast cancer samples. Breast cancer is far less common in Japan than in other developed countries, affecting only about 1 in 60 women, but more important, for cultural reasons it is also much more difficult for some Japanese researchers to gain access to patient DNA samples for some hereditary diseases.

Many other groups are isolating and sequencing their own candidate genes from the crucial region of 17q21, and not all will share the Japanese group's faith in somatic loss of heterozygosity data for detecting a familial cancer gene. But regardless of its precise location, the imminent isolation of *BRCA1* promises to usher in a new era in breast cancer research and it must be hoped that the same energy that has been spent on tracking down the gene will be channelled into devising new therapies once it is revealed. □

References

1.Emi, M. *et al. Nature Genet.* **5**, 151–157 (1993).
2.Hall, J.M. *et al. Science* **250**, 1684–1689 (1990).
3.Easton, D.F. *et al. Am. J. hum. Genet.* **52**, 678–701 (1993).
4.Narod, S.A. *et al. Lancet* **338**, 82–83 (1991).
5.Malkin, D. *et al. Science* **250**, 1233–1238 (1990).
6.Sultan, C. *et al. Nature Genet.* **5**, 109–110 (1993).
7.Simard, J. *et al. Hum. molec. Genet.* **2**, 1193–1199 (1993).
8.Sato, T. *et al. Cancer Res.* **52**, 1643–1646 (1992).