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Damage report for *BRCA1*

Three groups have together uncovered more than 20 distinct mutations in families with hereditary breast and ovarian cancer, offering important clues about the function of *BRCA1*.

Two months ago, on 7 October, a beautiful article by Mark Skolnick and 44 colleagues describing the long awaited discovery of the gene for hereditary breast and ovarian cancer, *BRCA1*, was published in *Science*[1]. That same day the complete nucleotide sequence of *BRCA1* was unveiled in the public databases. Instantly, several groups began designing their own oligonucleotide primers to analyse *BRCA1* in high-risk families using the polymerase chain reaction. The results of some of this frenetic activity can be found in three papers[2–4] in this month's issue of *Nature Genetics*. Together, they provide a considerable amount of new information about this infamous gene.

The initial evidence for *BRCA1* having been cloned hinged on the discovery of five inherited mutations in high-risk families[1], coupled with the presence of four germline mutations in a series of other cancer patients who were not known to have an extensive family history of the illness[5]. Just as for cystic fibrosis five years ago, the main priority for breast-cancer researchers has been to compile a comprehensive list of mutations, with two main goals in mind: to shed light on the function of *BRCA1* by discerning a pattern in the genetic lesions in different families, and to estimate how many different aberrations in *BRCA1* can cause cancer, which has obvious implications for screening other high-risk families.

In the new findings, three groups, led by Barbara Weber (University of Pennsylvania), Steven Narod (McGill University) and Mary-Claire King (Berkeley) screened a total of 100 families with multiple cases of breast (and often ovarian) cancer for signs of mutations in *BRCA1*, and were successful in 31 cases. This rate may seem low until one recalls that the recently mapped *BRCA2* locus also gives rise to a considerable number of hereditary cancers, and current methods of gene screening are not 100 per cent accurate, especially for large multi-exon genes such as *BRCA1*.

Also in this month's *Nature Genetics*: the gene for X-linked Emery–Dreifuss muscular dystrophy; mutations in a metalloproteinase inhibitor (TIMP3) in Sorsby's fundus dystrophy; assembly of dystrophin-associated proteins in transgenic mice; imprinting of the *mas* oncogene; and 'searching for shared segments' — a linkage disequilibrium approach to gene mapping.

Of these 31 mutations, 22 are distinct, constituting a complex array of frameshift and missense mutations scattered along the length of the gene[2–4]. Most result in the premature truncation of the gene product, although whether these act in a recessive or a dominant-negative manner is not yet known. Narod's group found two mutations in patients from four separate Canadian breast-cancer families. These families are not thought to be related, but they do share common haplotypes around *BRCA1*, suggesting a possible founder effect in some cases[3]. Efforts to seek a correlation between genotype and phenotype are probably premature, but already there are some curious offerings. In one of King's families, for example, a nonsense mutation[4] crops the last 11 amino acids from the C terminus of the *BRCA1* gene product out of a total of 1,863). On the face of it, this might be considered to be a relatively mild change, and yet women in this family have developed breast cancer at a very early age, in their 20s and 30s.

A handful of *BRCA1* mutations switch one amino acid for another, but although these tend not to reveal much about the function of the protein, there seem to be two prominent exceptions[2,4]. The only recognizable domain in the BRCA1 protein is a C3HC4 zinc-finger domain close to the N terminus. Two substitutions (one of which occurs in two unrelated families) replace one of the last two cysteine residues in this motif, indicating that this is a functionally important part of the protein and fuelling speculation that the protein encoded by *BRCA1* acts as a transcription factor.

But the most sobering aspect of these results is the sheer volume of mutations that can destroy BRCA1, which will make screening women on a large scale, if and when this becomes appropriate, a technically demanding feat. Recently, several academic and advocacy groups, including the National Breast Cancer Coalition and the American Society for Human Genetics[6], have gone on record against large-scale *BRCA1* screening, until much more is understood about the biology of *BRCA1* and the consequences of diagnosis and counselling.

Elsewhere in this month's issue, Doug Marchuk and colleagues at Duke University present solid evidence to implicate a transforming growth factor-β (TGF-β) binding protein, endoglin, in a vascular disorder called hereditary haemorrhagic telangiectasia (HHT)[7]. Patients with HHT are susceptible to frequent bleeding episodes, especially in the nose and gut, but some patients develop pulmonary arteriovenous malformations that can lead to aneurysms and strokes.

Earlier this year, the HHT locus was mapped by two groups to the long arm of chromosome 9 (refs 8, 9). Marchuk's group soon turned its attention to the endoglin gene, and has now described three different deleterious mutations in endoglin in HHT patients. Endoglin is an integral membrane glycoprotein which, in the presence of ligand, associates with the endothelial TGF receptor. Marchuk and colleagues suggest that this signalling process is impaired in HHT patients, leading to abnormal vascular remodelling in response to injury, for example, although the precise cellular mechanism remains to be determined.

Finally, researchers at the Rice Genome Research Program in Tsukuba, Japan, have compiled the most detailed genetic map so far of the 12 chromosomes that make up the 450-million-base-pair rice genome[10]. There are many incentives for studying the rice genome, not least of which is the undisputed importance of the plant in forming the staple diet of about half of the world's population. But in addition to developing thorough genetic and expression maps to aid the isolation of genes controlling disease resistance, growth and other agronomically important traits, rice also promises to serve as an extremely useful model organism for other cereals such as maize and wheat[11]. Of the nearly 1,400 polymorphic DNA markers on the Japanese map, almost 900 are expressed gene fragments, providing an average marker density of one every 300 kilobases. As such, the work serves as an important landmark towards the ultimate goal of determining the complete sequence of the rice genome. **Kevin Davies**

Kevin Davies is Editor of Nature Genetics.

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