nature genetics August

Let's get physical

A complete physical map of the region encompassing the locus for hereditary breast and ovarian cancer should assist the long-awaited cloning of this important gene.

FOR the better part of four years now, researchers the world over have been scouring a steadily diminishing stretch of the long arm of chromosome 17 for an elusive gene, *BRCA1*, responsible for hereditary breast and ovarian cancer. Women who inherit a faulty copy of *BRCA1* have about an 85 per cent risk of developing breast cancer during their lifetime, and together with one or more other loci, *BRCA1* accounts for about 5 per cent of all cases of breast cancer. Given that there are hundreds of thousands of new cases diagnosed around the world each year, the implications for screening families at high risk, and learning more about the molecular basis of both inherited and sporadic forms of the disease, place *BRCA1* firmly at the top of the human geneticist's wanted list.

Yet *BRCA1* is stubbornly refusing to reveal itself. For the past three years, researchers have been studying hundreds of families with inherited breast (and ovarian) cancer to refine the genetic linkage first detected at the end of 1990 (ref. 1). Thanks in large measure to an international consortium of researchers[2], a handful of important meiotic recombination events have been characterized, which in turn have allowed investigators to position *BRCA1* on one side or the other of a particular DNA marker, each time pushing in the boundaries of the so-called critical region. In parallel with these efforts, several groups have been establishing detailed physical maps using yeast artificial chromosomes (YAC), P1 clones and so on, to allow them to begin the tedious task of isolating the dozens of transcripts in the crucial region that should include *BRCA1* itself.

A paper in this month's *Nature Genetics*[3] affords a glimpse at the strategies being employed jointly by two of the larger groups involved in this effort. A little more than two years ago, Ray White in Salt Lake City and Bruce Ponder in Cambridge agreed to pool their resources in their quest for the *BRCA1* gene[3]. The physical map they have constructed consists of more than 130 different clones and embraces more than 3.5 megabases of genomic DNA. As is customary with ventures of this sort, the map is a little tentative in a couple of places (because of gaps or possible YAC rearrangements) but fortunately these are not in the area that really matters. By mapping the two closest (published) DNA markers flanking *BRCA1* that have been shown to be recombinant in key breast cancer families (*D17S78* and *D17S776*)[4,5], they estimate that the interval containing the gene spans no more than 1–2 centimorgans — about one megabase or so.

With classical genetics having just about exhausted its usefulness in localizing *BRCA1*, the next task is to trawl across the region in search of transcripts. Albertsen *et al.*[3] pulled out dozens of complementary DNA clones by screening a fetal cDNA library with purified inserts from a pair of critical YACs, although a number of other techniques, such as exon trapping, are equally valid. Among the new genes described in the current report are relatives of the Rab[5] family, the Ki antigen and a yeast transcriptional factor, GCN5. A rapid screen for mutations in samples from breast cancer patients has excluded some of these sequences, but the search continues apace.

Several other groups have similar physical and transcriptional maps at their disposal, and as more and more candidates are investigated[6] it should not be long before the real culprit is nabbed. Whether the gene will be of immediate use in revealing the celullar process affected in (hereditary) breast cancer remains to be seen, for it is a distinct possibility that *BRCA1* will look quite unlike anything characterized in the public databases. Such has been the disheartening experience for a number of significant genetic discoveries recently, including the defect responsible for Huntington's disease[7], polycystic kidney disease[8] and spinocerebellar ataxia type 1 (see Banfi *et al.*[9] in this month's issue of *Nature Genetics*). On the other hand, perusal of cDNA sequence databases has paid off handsomely with the identification of genes for hereditary non-polyposis colon cancer. And one should not forget that conventional biochemistry can still teach us a trick or two, as was nicely demonstrated just a few weeks ago with the revelation that the gene underlying Miller-Diecker lissencephaly (isolated last year by positional cloning) is that for a subunit of the platelet-activating factor acetylhydrolase in brain[10].

Physical mapping also plays an illuminating role in another paper in this month's issue[11], here in the search for a curious gene on the short arm of the X chromosome (Xp) which has a profound effect on the route of sexual development. In males, the presence of the *SRY* sex-determining gene (on the Y chromosome) is normally sufficient to initiate the development of the male gonads[12]. But in rare individuals with an intact Y chromosome and partial duplications of the short arm of the X, female (or ambiguous) genitalia may develop.

Giovanna Camerino, from the University of Pavia in Italy, and colleagues[11] have studied eight patients with Xp duplications, four of whom showed sex reversal. They found that the duplications in the four sex reversed patients all had different breakpoints, making it most unlikely that their phenotype resulted from the disruption of a single gene. What they had in common, however, was the duplication of a small region estimated to be no larger than 160 kilobases. Presumably, the extra copy of a gene(s) in this interval, which Camerino calls *DSS* (for dosage-sensitive sex reversal), upsets normal testis formation, although interestingly the extent of sex reversal (gonadal dysgenesis) varied among the four patients. By contrast, deletion of this same region in patients with an otherwise normal male (46, XY) genotype does not affect the development of male genitalia, prompting Camerino and colleagues to speculate that *DSS* may represent a link between the ovarian and testicular developmental pathways.

Kevin Davies

Kevin Davies is the editor of Nature Genetics.

Also in this month's *Nature Genetics*: The genes involved in the t(X;18) translocation in synovial sarcoma; interaction of the *Rb* and *p53* genes; a keratin 2e mutational hotspot in icthyosis bullosa of Siemens; and modelling the expansion of the Huntington's disease gene.

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