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**Trithorax
translocation
leukaemia**

**DNA from
dental remains**

**Nephrogenic
diabetes
insipidus**

**Hydrocephalus
and L1CAM**

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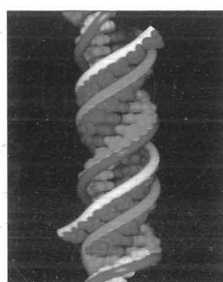
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Cover art: Model of triple helical DNA,
courtesy of BIOSYM Technologies.

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normal and abnormal subunits, only 25% of the channels (those with two normal subunits) would function properly. This would explain how one altered allele could have a severe effect upon chloride conductance. The discovery of this mutation in chloride channels does not rule out the involvement of sodium channels in some families with MC; one form of the disease has been genetically linked to the sodium channel¹⁸.

HYPP, PMC and myotonia congenita in other families are tightly linked to the sodium or chloride channel but do not seem to have any of the published mutations. Thus additional sodium and chloride channel mutations await discovery. Since potassium and calcium channels have a predicted secondary structure similar to sodium channels, it seems inevitable that point mutations in each of these channels will also cause human disease. Moreover, ion channels belong to multigene families,

as illustrated in Table 1 for sodium channels. Five full length and two partial sodium channel sequences have been published, and unpublished reports of additional partial sequences indicate several more genes. Thus, the rat genome probably contains at least ten sodium channel genes, which may all possess a homologue in humans. All of the mutations in Fig. 1a occur in a single

gene, the one expressed in adult skeletal muscle. Many of the other human sodium channel genes are expressed in the nervous system. Mapping these genes will allow linkage studies to be done in families with nervous system disorders, and will help determine whether mutations in these genes conceivably produce epilepsy or other more subtle mental defects. □

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Breast cancer genes: how many, where and who are they?

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Two papers in this issue of *Nature Genetics* add two pieces to the puzzle that will eventually reveal the genes responsible for inherited breast cancer and very likely breast cancer among women in the general population as well. One report on page 128, suggests that the breast cancer gene *BRCA1* on chromosome 17q may act as a tumour suppressor¹; the other report on page 132, demonstrates that a mutation in the androgen receptor gene on the X chromosome can cause male breast cancer, as well as androgen insufficiency². How do these quite distinct findings fit into the evolving story of breast cancer genetics?

The great majority of breast cancers are due solely to acquired mutations. Only about 5% of breast cancer patients have inherited mutations leading to the disease, although this fraction is much higher among younger patients (perhaps 40% of breast cancer diagnosed before age 30 involves inherited alterations)³. However, these inherited mutations may alter the same genes that are the sites of acquired mutations and

hence be critical to breast cancer development in the population as a whole. Furthermore, the inherited mutations clearly exist for decades in a woman's life before the tumours appear, so are early events in the tumorigenesis. The inherited mutations are also worth pursuing for their own sake. Inherited breast cancer is a common genetic disease: 5% of a disease affecting one in ten women over the life span means that roughly one in 200 women will develop breast cancer by reason of inherited susceptibility. Therefore, as an inherited trait, breast cancer is one of the most common genetic diseases in the industrialized world.

Not all inherited breast cancer is due to alterations of the same gene. By far the largest proportion of inherited breast cancer has been attributed to the still-uncloned gene *BRCA1*, on chromosome 17q21 (refs 4,5). Perhaps 60% of families with at least three breast cancer patients, and nearly all families with multiple cases of both breast and ovarian cancer, trace susceptibility to *BRCA1* (ref. 6).

(Many of the remaining 40% of families may represent coincidental occurrence of breast cancer in relatives, rather than inherited predisposition, given the very high rate of purely "acquired" breast cancer.) Gene mapping in families with breast cancer, and often ovarian cancer, has narrowed the region that must contain *BRCA1* to a few centiMorgans (cM), flanked by the markers *THRA1* and *Mfd188* (*D17S250*)^{7,8}. Genes thereby excluded by position from being *BRCA1* include *HER2/neu/erbB2*, the thyroid hormone receptor, *WNT3*, *HOX2*, prohibitin⁹, collagen I (A1) and *NM23*. Perhaps the most biologically plausible candidate gene within the linked interval is that for 17- β hydroxysteroid dehydrogenase, although presumably another hundred or genes lie in this region as well. The use of more than 20 ordered polymorphic markers in this small region and multiple families with informative recombinants, should permit *BRCA1* to be localized to roughly 1 cM by gene mapping. It will

be tedious, but straightforward, to identify all the transcripts in the smallest definable linked interval, and to compare sequences of these genes among susceptible versus not susceptible relatives.

Analysis of tumours of breast and ovarian cancer patients in families with disease linked to 17q suggests that *BRCA1* may be a tumour suppressor gene. The evidence is the observation that the tumours from patients who have inherited mutant *BRCA1* have often lost all or a portion of chromosome 17q. When deletions in tumours are observed, the lost 17q chromosome is invariably the chromosome with the normal (nonmutant) allele of *BRCA1*. This suggests either that *BRCA1* is a tumour suppressor, so that the normal allele must be lost or altered for tumour development; or alternatively that *BRCA1* is a dominant predisposing gene very near a still-unknown tumour suppressor, with acquired alterations in the tumour suppressor associated with selection for retention of the mutant *BRCA1* in the tumour. Once *BRCA1* is identified, these two hypotheses can be easily distinguished.

Other genes responsible for inherited breast cancer have been identified. As demonstrated by Wooster *et al.*², a point mutation in the androgen receptor gene on the X chromosome can lead to breast cancer and androgen insufficiency among males. In other families, susceptibility to male breast cancer appears to be transmitted from father to son and

appears with breast cancer in related females⁴. Breast cancer in at least some of these families is not linked to either X or 17q, indicating the existence of at least one other gene associated with breast cancer in males.

The first gene identified for inherited breast cancer was p53, which is responsible for the Li-Fraumeni syndrome¹⁰. In addition to breast cancer among adult women, these families have extremely high rates of brain tumours, sarcoma and adrenocortical cancers among children with mutant p53. Other cancers also appear among adults. About 1% of women diagnosed with breast cancer before age 30 have germline mutations in p53.

In many families with multiple patients with breast cancer, the disease is clearly not linked to any of these genes. Breast cancer in most families has been diagnosed at older ages, so many cases may be due entirely to acquired mutations, rather than inherited susceptibility¹¹. However, there are certainly families in which breast cancer is attributable to inherited alterations at as-yet-unidentified loci. Cancers of the colon, prostate, uterus or thyroid appear at high frequency in some of these families, as occasionally does breast cancer in males. Searches for the genes critical to inherited susceptibility in these families focus now on chromosomal regions frequently deleted in the tumours observed¹².

Identification of the genes for inherited breast cancer will only be

the end of the beginning of the story: attention will turn to biology and epidemiology. What are the normal and mutant products of the genes? What are the different mutations at each locus and how do they differ in site and severity? What proportion of breast and ovarian cancers in the general population are attributable to acquired mutations at these loci? How do alterations at the heritable sites interact with acquired alterations of *HER2/neu/erbB-2*, p53, cyclin D1, *NM23* and so on? Clinically, it will be important to determine which compounds are most effective against each tumour genotype. Perhaps most usefully, identifying mutations that occur early in tumorigenesis should enable the development of molecular approaches for much earlier diagnosis, when tumour size can be measured in centiMorgans rather than centimetres. □

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