Commentary

# How many more breast cancer predisposition genes are there?

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Next year marks the 10th anniversary of the mapping of the breast–ovarian cancer susceptibility gene *BRCA1* to chromosome 17 [1], and the identification of the *TP53* gene as the cause of the Li-Fraumeni syndrome [2]. As a result of these discoveries, and the subsequent discovery of other breast cancer susceptibility genes, notably *BRCA2* [3], inherited susceptibility has risen from relative obscurity to have a central role in breast cancer research. Understanding the biological mechanisms that underlie the susceptibility genes has become a major research activity, and of course mutation testing is now a major part of clinical genetics practice, with the prospects for improved prevention and treatment of the disease in women at high risk. Thus, it is natural to ask whether there are any more genes to find, what their characteristics might be and how we might go about finding them.

Of the five genes that are, beyond any reasonable doubt, breast cancer predisposition genes, the *BRCA1* and *BRCA2* genes are the most important numerically (Table 1). Mutations in these genes, which cause high risks of breast and ovarian cancer, account for almost all the multiple case breast–ovarian cancer families, and probably around 2% of breast cancer cases overall [4,5]. Germline mutations in the *TP53* gene predispose to a spectrum of cancers known as the Li-Fraumeni syndrome, including childhood sarcomas and brain tumours, as well as early-onset breast cancer [2]; and germline mutations in the *PTEN* gene are responsible for Cowdens syndrome, of which breast cancer is a major feature [6]. Mutations in a fifth gene, the androgen receptor gene, are known to predispose to breast cancer in men [7].

In addition to the five genes mentioned above, there is good, but not conclusive, evidence for two others. Female relatives of ataxia–telangiectasia patients have been shown in a number of studies [8,9] to be at increased risk of breast cancer (and perhaps of some other cancers), suggesting that heterozygous carriers of mutations in the ataxia–telangiectasia gene, *ATM*, are at increased risk of breast cancer. The results from different studies are rea-

**Table1**

**Known or suspected breast cancer genes**

| | | | Cumulative risk by age† | | Contribution to | |
|---|---|---|---|---|---|---|
| Gene | Location | Allele frequency* | 50 years (%) | 70 years (%) | Breast cancer (%) | Familial risk (%) |
| *BRCA1* | 17q | 0.0005–0.002 | 50 | 70‡ | 1–2 | 8 |
| *BRCA2* | 13q | 0.0005–0.002 | 30 | 70‡ | 1–2 | 8 |
| *TP53* | 17p | 0.0001 | ~50 | | <1 | <1 |
| *PTEN* | 10q | <0.0001 | ~30? | | <<1 | <1 |
| *ATM* | 11q | 0.003 | 6 | 18 | 2 | 2 |
| *HRAS1* | 11q | 0.06 | 3 | 10 | 9 | 4 |

*Plausible estimate for large outbred populations. †In the absence of other causes of death; these figures are intended as a guide only. ‡Some studies suggest lower risks for *BRCA1* and *BRCA2*.

sonably consistent, and are confirmed by direct observation of haplotype sharing in breast cancer cases in relatives of ataxia–telangiectasia patients [10]. The residual doubt lies in the fact that, to date, no studies have demonstrated this association in breast cancer case–control studies [11]. There is also evidence that carriers of a certain class of rare alleles of the *HRAS1* minisatellite locus are at increased risk of breast (and other) cancers, the relative risk being approximately twofold [12]. The doubts that surround this association are that the typing of this locus is technically difficult, and has not been attempted on a sufficient number of large case–control studies to be really convincing, and that the mechanistic interpretation of this association remains obscure.

So what evidence is there for the existence of any other susceptibility genes? The most direct way to address this question is to ask whether the known genes can explain the observed familial aggregation of breast cancer. Like most other common cancers, breast cancer exhibits familial aggregation, with the disease being about twice as common in the mothers, sisters and daughters of cases as it is in the general population [13–17]. This 'familial relative risk' rises to around fivefold for cases aged below 40 years [18]. In principle this familial aggregation may be due to either genes or to environmental factors shared within families, but evidence from monozygotic twins of cases (who have approximately twice the risk of first-degree relatives) suggest that genetic factors are mainly responsible [19]. Familial relative risk is a useful measure of overall amount of variation in inherited susceptibility to the disease, and any familial risk 'unexplained' by the known genes provides evidence for other genes [20].

A number of studies have now tested for *BRCA1* and *BRCA2* mutations in population-based series of breast cancer cases, and these allow one to estimate directly the contribution of these genes to familial aggregation, providing there are also good data on family history and an estimate of mutation sensitivity. In the largest study published to date, Peto *et al* [5] found a total of 30 mutations in 617 breast cancer patients diagnosed below age 46 years. When the family histories of these 30 mutation carriers were examined, it was found that only five of their mothers or sisters had had breast cancer, compared with 64 in the relatives of the 587 noncarriers. After allowing for the number of breast cancers that would be expected at population rates, and assuming a mutation sensitivity of 64% [4], this would equate to approximately 16% of the observed familial risk being due to *BRCA1* and *BRCA2*. This observation fits well with linkage results derived by the Breast Cancer Linkage Consortium [4]. Over 80% of families with six or more cases of breast cancer were found to be linked to either *BRCA1* or *BRCA2* (even in the absence of ovarian cancer in relatives), but the proportion dropped to 40% in families with four or five cases.

Mutations in the *TP53* and *PTEN* genes are very rare and are probably responsible for less than 1% of familial breast cancer. The importance of *ATM* can only be assessed indirectly. On the basis of the best available estimates of allele frequency (about 0.002) and relative risk (about fourfold), *ATM* would be expected to cause a familial relative risk, on its own, of about 1.02, or about 2% of the observed familial risk, although this could possibly be as high as 6 or 7%. On the basis of risks given by Krontiris *et al* [12], *HRAS1* would be expected to explain a further 4% of the familial risk. Taking all of these effects together, it appears that the known susceptibility genes can only account for around 20–25% of the familial risk.

What types of gene might underlie the remaining 75–80% of familial breast cancer? In principle, it ought to be possible to address this using segregation analysis, based on families without *BRCA1* or *BRCA2* mutations. Previous segregation analyses (eg [21]) were quite successful at identifying a major gene component responsible for a subset of cases, consistent with the effects of *BRCA1* and *BRCA2*. Unfortunately, however, segregation analysis tends to be weak at discrimating models unless there is a clear major gene component. Antoniou *et al* (personal communication), using mutation and family history data from a large population-based series of breast cancer patients from East Anglia, UK, have shown that a variety of both single gene and polygenic models can give an adequate fit once *BRCA1* and *BRCA2* are allowed for.

Nevertheless we can draw some general conclusions about the likely characteristics of other susceptibility genes:

(1) There are several genes involved. The genomic linkage searches that mapped *BRCA1* and *BRCA2* would have had adequate power to map a third gene, had it been responsible for most or all of the remaining families, but in fact no further loci have emerged. (Linkage to the oestrogen receptor on chromosome 6p [22] and to chromosome 8p [23,24] have been suggested in some families, but to date these have not been confirmed in other studies.)

(2) There are no further genes with penetrances comparable to those of *BRCA1* or *BRCA2*, or at least if there are, the predisposing mutations in these genes must be very rare. In the Breast Cancer Linkage Consortium analysis of Ford *et al* [4], there were 78 families with six or more patients breast cancer younger than 60 years old. Of these, all but nine either had a *BRCA1* or *BRCA2* mutation, or had clear linkage evidence in favour of one of these loci, and only one (reported by Seitz *et al* [24]) actually had strong evidence against linkage to either locus (LODs $< -1$).

(3) Some of the genes show age-specific effects. The trend in familial relative risk with age, which is consistently observed in epidemiological studies, cannot be accounted for by *BRCA1* or *BRCA2* alone, and there-

fore other genes must also confer relative risks that decrease with age. (For this reason, early onset breast cancers remain more informative for both linkage and association studies than late-onset disease.)

(4) A rare recessive gene model is unlikely, because the large population studies give very similar sibling and parent–offspring risks [13–17]. A model involving a gene or genes with common recessive alleles would, however, be quite possible.

(5) The genes do not (on the whole) confer substantial risks of any other cancer. The relatives of breast cancer patients have not been consistently shown to suffer significant risks of any other cancer except ovarian cancer, and this association can be explained by *BRCA1* and *BRCA2* [25].

(6) There is some suggestion that lobular breast cancer and lobular carcinoma *in situ* show bigger familial risks than other histological types of breast cancer [26,27]. This effect does not appear to be due to *BRCA1* or *BRCA2* so it does suggest that other genes may predispose preferentially to lobular carcinoma [28]. Non-*BRCA1/2* familial breast cancer also tends to be of lower grade than breast cancer in *BRCA1* or *BRCA2* carriers, and perhaps than 'sporadic' breast cancer as well [28].

Although the above observations are useful for guiding collections of cases and families, the range of plausible genetic models for the remaining genes is still very wide. At one extreme, there is still room for several genes causing quite substantial relative risks, say 10- to 15-fold. A number of mutations with a combined frequency of 2%, each causing a 10-fold risk of the disease, could adequately explain the familial risks and the many multiple case families not due to *BRCA1* or *BRCA2*. Such a model would be quite plausible given a moderate degree of selection against carriers (for example, if homozygotes were nonviable). Under this model one would expect a substantial degree of allelic heterogeneity, with population-specific mutations, as for *BRCA1* or *BRCA2*. In fact, these genes (which one might expect to call *BRCA3*, *BRCA4*, *BRCA5*, etc) would be qualitatively similar to *BRCA1* and *BRCA2*, but conferring somewhat lower absolute risks (although responsible for a higher fraction of cases overall). One would speculate that they are likely to have inactivating mutations and act as tumour suppressor genes. Such genes ought to be mappable by genetic linkage, providing that the genetic heterogeneity is not too severe. For example, if there were four such genes each responsible for one-quarter of the families, a series of around 400 families with three affected sisters should be sufficient to map them, given a sufficiently dense marker map. This would be a substantial undertaking (at least four-fold larger than the current linkage searches) but would be achievable with international collaboration. Families collected from isolated populations with small numbers of founders, such as French Canadians or Afrikaaners, could be a major advantage here. Such populations are likely to have less genetic heterogeneity, and it may be possible to link families to a common founder, increasing their informativeness.

At the other extreme are 'low-risk' polymorphisms, causing relative risks of less than fivefold. To be of much interest, these polymorphisms need to be quite frequent in the population (hence, we would not normally describe them as 'mutations'). This in turn implies that homozygotes must be viable and that there can be little or no selection against heterozygotes. These polymorphisms are most likely to be single nucleotide polymorphisms leading to amino acid substitutions, although inactivating mutations in nonessential genes (for example, genes coding for certain metabolizing enzymes) and polymorphisms in regulatory sequences may also be important. The human genome contains vast numbers of such polymorphisms; recent surveys suggest around 200 000–400 000 with frequencies of a few percent [29,30], and the majority of genes appear to have at least one polymorphism, so it is reasonable to postulate that a few of these single nucleotide polymorphisms do influence breast cancer risk.

Finding common low-risk polymorphisms related to breast cancer would be almost impossible by linkage analysis, and attention has turned to direct testing in case–control association studies, which are able to detect genes with much lower relative risks. An association study based on 1000 breast cancer cases and 1000 control individuals should be able to detect polymorphisms that cause relative risks as low as 1.5, with allele frequencies of 15% or more. There is room for around 30 such polymorphisms, given the overall familial relative risk of the disease. In this sense, association studies are about one order of magnitude more powerful than linkage studies, which are probably limited to three or four more genes. The total number of polymorphisms related to breast cancer risk could be much larger of course, but polymorphisms with very small effects will not be detectable.

A large number of such association studies have already been conducted, concentrating on polymorphisms in 'candidate genes' that are thought to be relevant to the development of breast cancer. A number of positive associations have been found in individual studies, but few have been replicated. In a recent meta-analysis, Dunning *et al* [31] analysed 17 polymorphisms that had been studied for association with breast cancer by at least two groups. Only one of them, the Ile105 polymorphism in *GSTP1*, was significant when data were combined across all studies, and this was only marginally so. The lack of success of this approach so far may be partly blamed on the small sample size often employed, but it does suggest that the important genes have yet to be examined. Many of the genes tested so far have been involved in steroid hormone

metabolism, and it may be that some other types of genetic variation, for example in DNA repair fidelity, or metabolism of some specific dietary factors, are more important. The major drawback of association studies is that, unlike in linkage studies, it is necessary to guess the gene in advance, and type the causative polymorphism or at least a very tightly linked polymorphism in strong disequilibrium. One is therefore limited by one's existing knowledge of mechanisms. Fortunately, this is set to change over the next few years, as the catalogue of common single nucleotide polymorphisms becomes more complete, and the technology for typing them becomes more rapid and less expensive; ultimately, it may be possible to test all common coding single nucleotide polymorphisms in this way. Even this exhaustive search could miss some important susceptibility genes, for example low-risk genes with substantial allelic heterogeneity (as in the case of *HRAS1*). Overall, the prospects for finding more breast cancer genes over the next few years are good, but a complete enumeration of all important genes may prove more difficult.

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