

Rare, intermediate penetrance breast cancer susceptibility genes

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Introduction

Less than 30% of familial risk in breast cancer is attributed to known genes. BRCA 1/2 were identified over a decade ago. Therefore there is a need to identify which genes are causing breast cancer in families without a BRCA1/2 mutation.

At least 3 categories of breast cancer susceptibility genes are known to exist:

- **Rare, high penetrance genes** such as BRCA1/2. No similar genes have been found from linkage analysis studies in BRCA1/2 negative families. Therefore if further high penetrance mutations do exist they are likely to be very rare and only contribute to breast cancer in a very small number of families.
- **Rare, intermediate/low penetrance genes** which are the subject of this study
- **Common, low penetrance genes** (see summary of presentation given by Alison Dunning).

Rare intermediate penetrance genes

A problem with identifying this type of gene is that because they are rare (population prevalence <1%) and conferring a low risk (2-4 fold) it is hard to prove their association with a particular disease. A very large number of cases and controls are required. In this study a familial case vs. control design was applied. Screening a particular gene in familial cases rather than non-familial increases the power of the study by approximately 4 fold. The use of BRCA1/2 negative cases enriched for other breast cancer alleles.

This method has been used to identify the rare intermediate breast cancer genes Chek2, ATM, PALB2 and BRIP1.

Chek2 1100delC mutation

The truncating Chek2 1100delC mutation had been reported in breast cancer cases from a number of different families. The Chek2 gene was screened in 1,000 familial cases and the 1100delC mutation found to be present in 5% of cases compared to approximately 1% of controls. The relative risk (RR) conferred by this Chek2 mutation is approximately 2. Chek2 is intimately connected with BRCA1 and involved in DNA repair.

ATM

Biallelic ATM mutations cause the disease ataxia telangiectasia (AT). Female relatives of AT cases have a 2-4 fold increased risk of breast cancer. The full ATM gene was screened in 443 familial breast cancer cases (BRCA1/2 negative) and 521 controls. Twelve truncating AT causing mutations were found in the breast cancer cases and 2 in controls. The RR of ATM is 2.37 (which is the same as predicted by its epidemiology). Therefore ATM mutations that cause AT are low penetrance breast cancer susceptibility alleles.

ATM mutations have a similar prevalence to Chek2 1100delC mutations and are thought to make a similar contribution to breast cancer. These 2 genes were essentially proof of principle for the familial case vs. control design method since they were already implicated in breast cancer from previous studies.

Fanconi Anaemia (FA) and breast cancer

FA is a rare heterogeneous (at least 14 different genes implicated) autosomal recessive disorder. All FA proteins are involved in DNA repair. When DNA is damaged host FA proteins form a complex that leads to the ubiquitination of another FA protein, D2. Monoubiquitinated D2 gets translocated to DNA repair foci where it cooperates with other proteins to repair DNA.

i. PALB2

In 2002 biallelic BRCA2 mutations were shown to cause the FA-D1 subtype. This was the first link between FA and breast cancer. The FA-D1 subtype causes a specific severe phenotype of FA with childhood solid tumours. Cases with this particular phenotype were screened and patients lacking a BRCA2 mutation identified. This suggested that at least one other gene was giving rise to FA with the same phenotype as the BRCA2 subtype.

PALB2 was shown to be associated with BRCA2 and knockout results in mitomycin C (a DNA crosslinking agent) sensitivity which is a cellular hallmark of FA. Screening of FA cases not due to BRCA2 but with the same

phenotype revealed 7/82 with bilallelic truncating PALB2 mutations (none present in controls). Therefore bilallelic PALB2 mutations cause FA.

Following this the full PALB2 gene was screened in 923 familial breast cancer cases (BRCA1/2 negative). Ten cases were found to have a truncating PALB2 mutation (none present in 1,084 controls). The RR of breast cancer conferred by PALB2 mutations is 2.3.

ii. BRIP1

BRIP1 encodes a BRCA1 interacting protein. Bilallelic mutations in BRIP1 have been shown to cause the FA-J subtype. The full gene was screened and 9/1,212 truncating mutations were found in familial breast cancer cases and 2/2,081 in controls. BRIP1 confers a RR of 2.0.

Links between FA and breast cancer

None of the FA proteins that form the core complex upstream of D2 has been associated with breast cancer to date. Downstream of D2 PALB2, BRCA2 and BRIP1 have all been identified as both FA genes and as conferring an increased risk of breast cancer. It is not known whether D2 is a determining factor in the link between FA and breast cancer but the information provides a route to explore this further.

There are many underlying complexities between the genes and phenotypes that are not yet understood – for example in bilallelic cases BRCA2 and PALB2 have very similar (FA) phenotypes but in heterozygotes they are dissimilar (BRCA2 heterozygosity confers a 10-fold risk of breast cancer compared to 2-fold with PALB2).

Conclusion

Chek2, ATM, BRIP1 and PALB2 are all examples of rare intermediate penetrance breast cancer genes conferring a RR of 2-3. Together they account for approximately 2.3% of the familial RR of breast cancer. Clinical use of this knowledge is the ultimate aim of research but remains a very complex process.

Nearly 70% of familial breast cancer risk is currently unexplained. DNA repair genes, particularly those related to the known breast cancer susceptibility genes, remain good candidates.

It is thought that at least of this remaining familial risk will be explained by more of these types of genes – multiple truncating mutations that are each associated with small risks rather than high risks. With current technologies and sample sizes it is difficult to identify them. Without familial enrichment (or a founder effect) the associations summarised here could not have been proven.

References

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