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A common missense variant in *BRCA2* predisposes to early onset breast cancer

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Abstract

Introduction Mutations in the *BRCA2* gene are one of the two major causes of hereditary breast cancer. Protein-truncating mutations of BRCA2 are usually deleterious and increase the risk of breast cancer up to 80% over a lifetime. A few missense mutations in *BRCA2* are believed to have a similarly high penetrance, apart from more common neutral polymorphisms. It is often difficult to classify a particular sequence variant as a mutation or a polymorphism. For a deleterious variant, one would expect a greater allele frequency in breast cancer cases than in ethnic-matched controls. In contrast, neutral polymorphic variants should be equally frequent in the two groups.

Methods We genotyped 3,241 cases of breast cancer diagnosed at under 51 years of age, unselected for family history, from 18 hospitals throughout Poland and 2,791 ethnic-matched controls for a single *BRCA2* C5972T variant.

Results The variant was present in approximately 6% of the Polish population. In the study, 13 women (11 cases and two controls (OR = 4.7; p = 0.02)) were homozygous for the variant allele. The overall odds ratio for breast cancer in women with a single copy of the *BRCA2* C5972T variant was 1.1 (p = 0.7); however, the effect was significant for patients diagnosed at or before age 40 (OR = 1.4; p = 0.04). We reviewed the association between the *BRCA2* variant in different histologic subgroups and found the effect most pronounced in women who had ductal carcinoma *in situ* (DCIS) with micro-invasion (OR = 2.8; p < 0.0001).

Conclusion The *BRCA2* C5972T allele is a common variant in Poland that increases the risk of DCIS with micro-invasion. The homozygous state is rare but increases the risk of breast cancer five-fold.

Introduction

There are several approaches to identifying low-penetrance candidate genes for breast cancer. In one approach, it is assumed that missense variants of genes for which truncating mutations are clearly pathogenic might also be deleterious. If the missense allele demonstrates high penetrance (i.e. like truncating mutations), then it will be relatively straightforward to establish the association when allele frequency is high. If the penetrance of the missense variant is low, however, then the association may be missed if only a small number of cancers is studied and the variant may falsely be classified as a neutral polymorphism. We are in the process of establishing a large database of breast cancer cases and ethnic-matched controls in order to evaluate the pathogenicity of the common founder alleles of the most important cancer susceptibility genes. Several deleterious founder alleles have been identified in *BRCA1*, but to date, no founder mutation in *BRCA2* has been identified [1-3]. There are a few common variant alleles in *BRCA2* in Poland; one of these (C5972T) changes the amino acid sequence of BRCA2 from threonine to methionine at codon 1915. It lies within the range of the BRC encoded by exon 11 that are thought to be involved in binding to RAD51 [4]. We sought to determine whether this common missense BRCA2 variant plays a role in breast cancer susceptibility.

Materials and methods

Study subjects

The study population included prospectively ascertained cases of invasive breast cancer diagnosed at 50 years of age or less at 18 treatment centers throughout Poland between

DCIS = ductal carcinoma *in situ*; LOH = loss of heterozygosity; OR = odds ratio; RFLP-PCR = restriction fragment length polymorphism polymerase chain reaction.