Association of breast cancer by pathogenic CHEK2 variant type

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Introduction

The CHEK2 gene codes for a protein kinase that is activated in response to DNA damage and is involved in cell cycle arrest. Germline pathogenic and likely pathogenic (P/LP) variants in CHEK2 have been associated with a range of cancer types, including breast cancer. P/LP variants may increase the risk of breast cancer by 1.5 to 3-fold, however, these estimates vary based on family history and variant type. One founder allele, the truncating variant c.1100delC, was first reported as a cause of breast cancer in Eastern and Northern Europe with an allele frequency of 0.2-0.4%; numerous studies have confirmed this association. Another founder allele, the missense variant p.I157T, has a wider geographic distribution and has been associated with breast cancer in Poland, Finland, Germany, and Belarus, but the association with breast cancer is still unclear. More recently, the presence of another missense variant, p.S428F, was shown to increase breast cancer risk by approximately 2-fold among Ashkenazi Jewish women.

However, previous studies of the association of CHEK2 variants with cancer risk are limited by enrichment for people who met insurance criteria for genetic testing, and therefore have a strong personal and/or family history of cancer. Current screening guidelines for individuals found to have a P/LP variant in CHEK2 specifically state that risk data is for frameshift P/LP variants and that the risk conferred by P/LP missense variants is still unclear. We address this ascertainment bias by examining a broader population that underwent panel testing for hereditary cancer risk to determine if variant type impacts association.

Methods

The cohort consisted of over 30,000 females who received a 19- or 30-gene panel for hereditary cancer risk by provider order, and reported if they had a personal history of cancer. Included in this analysis were females, >40 years old, who tested and had a P/LP variant identified only in CHEK2 (positives), or had a negative result (negatives).

Analysis was limited to CHEK2 variants with a consensus classification of LP or P in ClinVar, defined as having at least 2 P/LP classifications reported and at least 2/3 consensus on the classification. Family history of cancer was not analyzed.

Results

Figure 1: Ethnicity of Participants by Age

Overall, 70% of the cohort reported Caucasian ethnicity, followed by 10% reporting Ashkenazi Jewish ethnicity. The average age at testing not different for positives (56.7 years, n = 644) vs negatives (55.1 years, n = 29,794) (p < 0.01, two-tailed t-test).

Figure 2: CHEK2 variants by type

Of the 644 P/LP variants with consensus classification in ClinVar identified in the cohort, half (50%, n = 323) were missense variants. 204 were CHEK2 p.I157T and 81 were p.S428F. The next most frequent were frameshift variants (38%, n = 243), 205 of which were CHEK2 c.1100delC.

Table 1: Association of CHEK2 variants with personal history of breast cancer, stratified by variant type

When combining all P/LP CHEK2 variants, there was a slight association with breast cancer (OR=1.31 95% CI: 1.10-1.56), likely owing to aggregating truncating (nonsense and frameshift) and CNV variants where an association was seen, compared with missense variants where an association was not seen.

Missense variants (the majority of which were p.I157T and p.S428F) did not show an association (OR=1.03, 95% CI: 0.79-1.33).

Truncating (the majority of which were c.1100delC) and copy number variants (CNVs) did show a modest association (OR=1.63, 95% CI: 1.27-2.08).

Conclusions

- When all CHEK2 P/LP variant types are considered in aggregate, they did have a slight association with a personal history of breast cancer.
- When variants were segregated by type, the data support that truncating variants and CNVs are moderately associated with breast cancer risk and missense variants are not associated with breast cancer risk.
- This finding lends to the potential for genotype-phenotype correlations based on CHEK2 variant type, and may be useful for future cancer screening and management recommendations.

References