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[1]. 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[1]. 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[2–4]. 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[5,6], but the association with breast cancer is still unclear[7]. 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[8].

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[9]. 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.

Hypothesis

Association of *CHEK2* variants with breast cancer differs by variant type.

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.

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.

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).

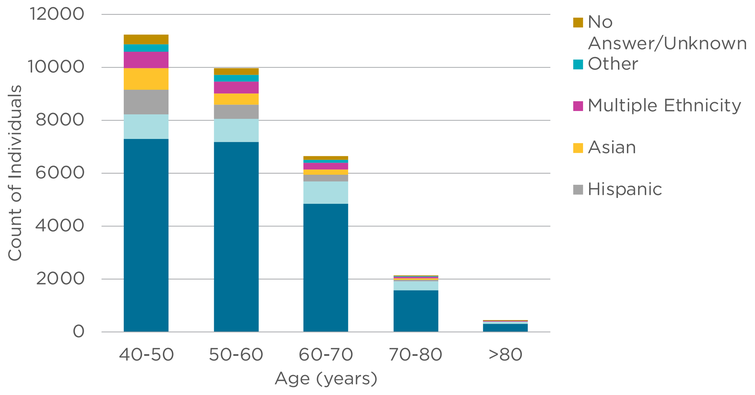

Figure 2: *CHEK2* variants by type

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.

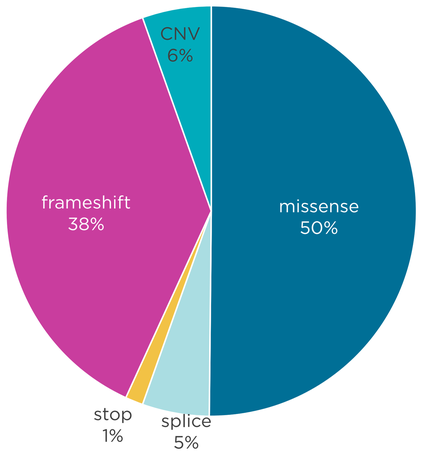

Figure 3: Personal history of breast cancer by *CHEK2* variant type

Percentage of individuals with a personal history of breast cancer among negatives and *CHEK2* positives, stratified by variant type. The average age of breast cancer diagnosis among each group is also shown.

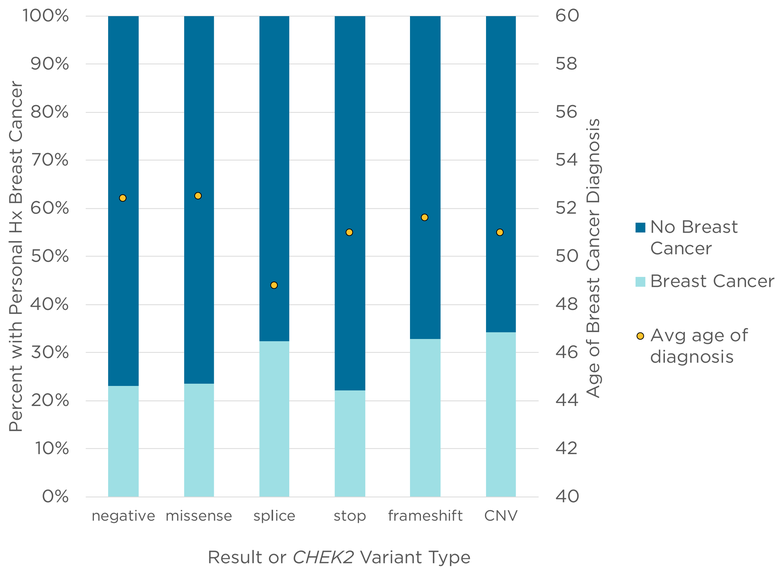

Table 1: Association of *CHEK2* variants with personal history of breast cancer, stratified by variant type

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).

	All *CHEK2*	*CHEK2* Missense	*CHEK2* Truncating/CNV
Odds Ratio	1.31	1.03	1.63
Lower CI (95%)	1.10	0.79	1.27
Upper CI (95%)	1.31	1.33	2.08

References

1. Cybulski, C. et al. Risk of breast cancer in women with a CHEK2 mutation with and without a family history of breast cancer. J. Clin. Oncol. 29, 3747–3752 (2011).
2. Offit, K. et al. Frequency of CHEK2*1100delC in New York breast cancer cases and controls. BMC Med. Genet. 4, 1 (2003).
3. CHEK2 Breast Cancer Case-Control Consortium. CHEK2*1100delC and susceptibility to breast cancer: a collaborative analysis involving 10,860 breast cancer cases and 9,065 controls from 10 studies. Am. J. Hum. Genet. 74, 1175–1182 (2004).
4. Vahteristo, P. et al. A CHEK2 genetic variant contributing to a substantial fraction of familial breast cancer. Am. J. Hum. Genet. 71, 432–438 (2002).
5. Cybulski, C. et al. A deletion in CHEK2 of 5,395 bp predisposes to breast cancer in Poland. Breast Cancer Res. Treat. 102, 119–122 (2007).
6. Bogdanova, N. et al. Association of two mutations in the CHEK2 gene with breast cancer. Int. J. Cancer 116, 263–266 (2005).
7. Muranen, T. A. et al. Patient survival and tumor characteristics associated with CHEK2:p.I157T - findings from the Breast Cancer Association Consortium. Breast Cancer Res. 18, 98 (2016).
8. Shaag, A. et al. Functional and genomic approaches reveal an ancient CHEK2 allele associated with breast cancer in the Ashkenazi Jewish population. Hum. Mol. Genet. 14, 555–563 (2005).
9. NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian Version V2.2018. NCCN.org (2018). Available at: https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf. (Accessed: September 2018)