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Frequency of *CHEK2*1100delC* in New York breast cancer cases and controls

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Abstract

Background: The *1100delC CHEK2* allele has been associated with a 1.4–4.7 fold increased risk for breast cancer in women carrying this mutation. While the frequency of *1100delC* was 1.1–1.4% in healthy Finnish controls, the frequency of this allele in a North American control population and in North American breast cancer kindreds remains unclear.

Methods: We genotyped 1665 healthy New York volunteers and 300 cases of breast cancer for the *CHEK2*1100delC*.

Results: The overall frequency of the *1100delC* was 3/300 (1.0%) among all cases with either a family history of breast cancer (n = 192) or a personal history of breast cancer (n = 108, of which 46 were bilateral, 46 unilateral, and 16 were male breast cancer cases), compared to a frequency of 5/1665 (0.3%) in healthy controls (p = 0.1). There was no difference in allele frequency among Ashkenazi and non-Ashkenazi controls.

Conclusion: The relatively low breast cancer penetrance of this allele, along with the low population frequency, will limit the clinical applicability of germline testing for *CHEK2*1100delC* in North American kindreds.

Background

In response to DNA damage, the cell-cycle checkpoint kinase *CHEK2* can be activated by *ATM* kinase to phosphorylate *p53* and *BRCA1*, which are involved in cell-cycle control, apoptosis, and DNA repair [1,2]. A germline mutation *1100delC* truncates the *CHEK2* protein and was first observed in families exhibiting Li-Fraumeni syndrome [3]. To address the possibility that this allele contributes to increased susceptibility to breast cancer, two recent studies have investigated the frequency of

*CHEK2*1100delC* in cancer cases and controls. Vahteristo et al. [4] reported that the *1100delC* protein-truncating mutation of *CHEK2* was observed in 5.5% of 507 patients with a family history of breast cancer and no detectable *BRCA* mutation compared to 1.4% of 1,885 healthy Finnish controls. The *CHEK2*-Breast Cancer Consortium observed a 5.1% frequency of this allele in 1071 individuals with breast cancer derived from multiple-case families in which no mutations in *BRCA1* or *BRCA2* were detected, compared to a 1.1% of 1,620 healthy (mostly Northern European) controls [5]. These two groups also reported an increased frequency of *CHEK2*1100delC* in kindreds with male breast cancer or bilateral breast cancer. We report here the frequency of *CHEK2*1100delC* in North American breast cancer patients and controls.

Methods

We have analyzed a North American sample of healthy controls participating in the New York Cancer Project, and two series of cases: those enrolled in a genetic counseling clinic as well as a separate series of cases unselected for family history ascertained at Memorial Sloan-Kettering Cancer Center. The cases and controls self-identified themselves as Jewish or non-Jewish and reported their ancestor's countries of origin. The population control samples were derived from the New York Cancer Project, an ongoing cohort study enrolling healthy volunteers. Of the 569 non-Ashkenazi controls participating in this study, 62 were African-American, 37 Hispanic, 20 Asian, 18 Other/Unknown, and 432 Caucasian. All individuals in this study provided informed consent for future DNA analysis. Genomic DNA was extracted and amplified utilizing *CHEK2* external PCR primers:

9Fe 5' CTGTCATCTCAAGAAGAGGACT and

10R 5' ATTTGTGACTTCATCTAATCACCTCC

and internal PCR primers:

9F 5' TGGCAAGTTCAACATTATTCCC and

10Re 5' GAATAACTCCTAAACTCCAGC

Genotyping was performed by dHPLC (Transgenomics, USA) or Pyrosequencing (Pyrosequencing, Inc. Sweden); all mutations were confirmed by both of these methodologies. Non-Ashkenazi individuals were screened by DNA sequencing for mutations in the entire *BRCA1* and *BRCA2* coding sequence and Ashkenazi individuals were screened for the three founder alleles that account for >95% of mutations in this ethnic group [6].

Results

We observed *CHEK2*1100delC* in 5/1665 (0.3%) of healthy New York City controls, significantly lower than the frequency in controls reported by Vahteristo et al. ($p = 0.0004$, Fisher's Exact test) or by the *CHEK2* Consortium ($p = 0.006$). Within our sample, 3/1096 (0.3%) individuals of Jewish (predominantly Ashkenazi) descent carried this allele, a rate comparable to the 0.4% frequency (2/569) observed in individuals of non-Ashkenazi descent. We detected *CHEK2*1100delC* in 1/100 index cases from multiple-case breast cancer families in which mutations in *BRCA1* or *BRCA2* were not detected. As noted in Table 1, the one case heterozygous for the *1100delC* was an individual of Ashkenazi descent seen at our Center who was previously included in the report by the *CHEK2*-Breast Cancer Consortium. Of these 100 families, 33 were of Ashkenazi descent and 67 were of non-Ashkenazi origin. *CHEK2*1100delC* was detected in 0/16 male individuals with breast cancer without mutations in *BRCA2*, and in 1/46 (2.2%) of clinic-ascertained bilateral breast cancer cases in individuals with a family history of breast cancer who were also of Ashkenazi Jewish descent compared to 0/46 clinic-ascertained unilateral breast cancer cases matched by age, ethnicity and family history. In a separate series of bilateral breast cancer cases unselected for family history, 0/46 carried *CHEK2*1100delC*, compared to 1/46 unilateral breast cancer cases matched to the bilateral cases by age and ethnicity. Taking all of the breast cancer cases combined, the frequency of the *1100delC* was 3/300 (1.0%) compared to the population frequency of 5/1665 (0.3%) ($p = 0.10$).

Discussion

Our current findings do not exclude the possibility that the *CHEK2*1100delC* variant increases the relative risk for breast cancer in North Americans. Because this variant occurs significantly less commonly in healthy New York controls compared to Northern European controls, the low frequency of this allele in multiple-case families, bilateral cases, and male breast cancer cases could still be compatible with a relative risk in the range of 3.5–12 as reported by Vahteristo et al. and the *CHEK2*-Breast Cancer Consortium.

A prior attempt to analyze the entire *CHEK2* gene in a northern European cohort was unable to detect mutations in exons 10–14, including the *1100delC*, in 79 *BRCA1/2*-negative individuals from Finnish families with three or more cases of breast cancer [7]. The relative size of the population control samples in our studies was comparable to prior studies (1,620 population controls in the *CHEK2*-Consortium, 1,885 in Vahteristo et al, and 1,665 in the current study). We evaluated 100 *BRCA* mutation-negative breast cancer families, compared to 216 in the report by Vahteristo et al, and 718 in the Consortium study.

Table 1: *CHEK2*1100delC* in breast cancer cases and healthy controls

	Positive for *CHEK2**1100delC (%)
Controls	
Jewish (New York)	3/1096 (0.3%)
Non-Jewish (New York)	2/569 (0.4%)
Total	5/1665 (0.3%)
BRCA1/2-negative individuals of mixed ethnicity with breast cancer from families with 3 or more cases of breast cancer	0/67 (0.0%)
BRCA1/2 Ashkenazi founder mutation-negative individuals with breast cancer from families with 3 or more cases of breast cancer	1/33# (3.0%)
BRCA2-negative[i] individuals of mixed ethnicity with male breast cancer	0/16 (0.0%)
Individuals with bilateral breast cancer of mixed ethnicity unselected for family history	0/46 (0.0%)
Individuals with unilateral breast cancer unselected for family history matched for age, ethnicity	1/46 (2.2%)
Clinic-ascertained individuals of Ashkenazi Jewish descent with bilateral breast cancer	1/46 (2.2%)
Clinic-ascertained individuals of Ashkenazi Jewish descent with unilateral breast cancer matched for age, family history	0/46 (0.0%)

#This case previously reported in *CHEK2* Breast Cancer Consortium [5].

However, our report also utilized the hypothesis proposed by Begg et al [8], of an "enrichment" of germline carriers of cancer predisposition alleles in individuals with bilateral breast cancer. Our series analyzed 92 cases of bilateral breast cancer and 92 controls, compared to 33 bilateral breast cancer cases included in the report by Vahteristo et al. While no enrichment was noted in our bilateral cases compared to unilateral cases, this may also reflect the lower population frequency of the allele in our population.

Further study of the frequency of the *CHEK2*1100delC* allele in North American breast cancer kindreds is warranted, however, the relative rarity of this allele in our population, plus the relatively low breast cancer penetrance reported for this allele, limit the clinical relevance in North American kindreds of *CHEK2*1100delC* as a cancer-predisposing allele.

Conclusions

The 0.3% frequency of the *1100delC CHEK2* allele in a New York population is significantly lower than the 1.1–1.4% rate observed in Northern European populations. This allele was infrequent in *BRCA*1/2 wild-type cases with family history of breast cancer or in cases with a personal history of unilateral or bilateral of breast cancer. The relatively low breast cancer penetrance, along with the low population frequency, limit the clinical relevance in North American kindreds of *CHEK2*1100delC* as a cancer predisposing allele.

Competing interests

None declared.

Authors' contributions

KO designed the study and wrote the final draft of the paper; HP helped in the design and coordinated specimen collection; TK, KN, and PK performed genotype analysis and wre supervised by NE who also participated in study design; BR wrote the first draft of the manuscript and coordinated data collection; PK and SG oversaw collection of control samples and participated in study design; OY ascertained the familial breast cases and helped with study design; HH helped with data collection and analysis, JS provided biostatistical analysis; MR and LS participated in study design and analysis.

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