Absence of *CHEK2* 1100delC mutation in familial breast cancer cases from a South American population

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Dear Editor

The most widely accepted model proposes that familial breast cancer susceptibility is a consequence of a small number of mutations in *BRCA1* or *BRCA2* (*BRCA1/2*) and a much higher proportion of mutations in ethnic-specific genes of moderate and/or low penetrance [1]. *CHEK2* gene, involved in DNA damage and replication checkpoints, has been pointed out as a good candidate. Moreover, a specific variant in this gene, 1100delC, has been found to increase breast cancer susceptibility among familial breast cancer cases not attributable to mutations in *BRCA1/2* [2]. Most of the studies evaluating this mutation as a female breast cancer susceptibility allele have been conducted in European populations, where the prevalence of the variant in controls ranged from 0 out of 400 controls in Spain to 2.8% in the Netherlands (Table 1). This variant has been detected in a considerable higher proportion (4–11%) in patients with a positive family history of breast cancer (usually known to be *BRCA1/2* mutation-negative) from Northern Europe (Table 1) This variant has been estimated to be associated with an approximately 1.5–2.0 fold increased risk in female breast cancer cases with a positive family history [4–6]. *CHEK2* has not been well studied in other ethnic groups.

In our laboratory, we evaluated the 1100delC mutation in 3 Chilean groups: (a) 196 breast cancer patients belonging to high risk Chilean families of which 184 were *BRCA1/2* negatives [21]; (b) a control group of 500 healthy Chilean females with no personal or familial history of breast or other cancer. Cases and controls were matched by age and ethnic background; (c) the third group included 624 healthy Chilean females but with at least two relatives in first or second degree with breast cancer. This study was approved by the Institutional Review Board of the School of Medicine of the University of Chile. Informed consent was obtained from all the participants. No other mutations in the *CHEK2* gene have been studied because it seems that the 1100delC is the only *CHEK2* allele that makes an appreciable contribution to breast cancer susceptibility [22].

Genomic DNA extracted from blood was genotyped for *CHEK2* 1100delC by restriction fragment length polymorphisms (RFLP). PCR was carried out using oligonucleotides 5′ CTTTTGCACTGAATTTTAGAGTA 3′ and 5′ ACCTCCTACCAGTCTGTGC 3′, which specifically amplify exon 10 from the functional copy of *CHEK2* on chromosome 22, relative to the non-functional pseudogenes [16]. The PCR product was digested with *Rsa*I

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Table 1 Frequency of *CHEK2* 1100delC in different populations

Population	Controls (n)	Female Breast cancer cases (n)	Reference
The Netherlands	2.8% (212)	11.4% (237)[b, c]	[3]
	1.3% (460)	2.5% (79)[b, c]	[4]
	1.6% (184)	3.8% (1706)[a]	[5]
Finland	1.4% (1885)	5.5% (507)[b, c]	[6]
	1.1% (447)	2.9% (464)	[5]
Denmark	0.5% (4643)	1.2% (1088)[a, d]	[7]
Russia	0.2% (448)	5.2% (155)[e]	[8]
Germany	–	4.0% (380)[b, c]	[9]
	0.5% (1315)	1.6% (516)[b, c]	[10]
	0.7% (651)	1.4% (71)[b, c]	[11]
	–	2.3% (86)[f]	[11]
	0.25% (401)	1.1% (985)[a]	[5]
Czech Republic	0.3% (730)	0.3% (358)[b, c]	[12]
Basque Country	0.0% (120)	0.9% (214)[a, d]	[13]
Spain	0.0 (400)	0.0% (400)[b, c]	[14]
Italy	0.0% (334)	0.1% (939)[b]	[15]
UK	0.0% (300)	4.0% (68)[b, d]	[16]
USA	0.5% (859)	1.1% (829)[b, d]	[17]
USA (New York)	0.4% (569)	0.0% (67)[b, c]	[18]
USA (California)	–	0.4% (1112)[a, d]	[19]
Canada	0.2% (496)	1.4% (1199)[a, d]	[19]
Australia	–	0.6% (300)[b, c]	[20]
	0.14% (736)	0.7% (1474)[a]	[5]
Ashkenazi	0.3% (1096)	3.0% (33)[b, c]	[18]
Chile	0.0% (1024)	0.0% (196)[b, c]	Present study

[a] Negative family history of breast cancer

[b] Positive family history of breast cancer

[c] BRCA1/2 negative

[d] Non-tested for BRCA1/2 mutations

[e] Bilateral breast cancer

[f] Early-onset breast cancer

restriction enzyme which only digests the wild type allele. A synthetic oligonucleotide containing the 1100delC mutation was used as positive control.

None of the 1320 analyzed samples carried the *CHEK2* 1100delC mutation. This finding suggests that this mutation is not present or is present at an extremely low frequency in Chilean families with familial breast cancer. Therefore this variant has no practical importance for the clinicians of our population.

CHEK2 is the most important breast cancer susceptibility gene to be identified since *BRCA2* was found in 1995. From different articles, it is evident that the contribution of *CHEK2* mutations to the burden of breast cancer varies by ethnic group, and from country to country (Table 1).

The contemporary Chilean population stems from the admixture of Amerindian peoples with the Spanish settlers initiated in the 16th and 17th centuries. Later migrations (19th century) of Germans, Italians, Arabs, and Croatians have had only a minor impact on the overall population (not more than 4% of the total population) and are restricted to the specific locations of the country where they settled [23]. The relationship between ethnicity, Amerindian admixture, genetic markers, and socioeconomic strata has been extensively studied in Chile [24–26].

The highest frequency of *CHEK2* 1100delC has been found in patients from the North and the West of Europe, and the lowest frequency in the South (Italy and Spain) [14, 15]. In Spain, Osorio et al. [14] did not detect the 1100delC mutation in 856 samples analyzed. Martinez-Bouzas et al. [13] reported this mutation in the Basque Country in a 0.93% of the cases with breast cancer, and in none of the control populations. These authors raise the hypothesis of the existence of a 1100delC frequency gradient from the North-West to the South-East of Europe, caused by an ancestral common origin in the North (Table 1). This explains that the first level of *CHEK2* 1100delC incidence in Spain occurs in the Basque Country. The Spanish settlers that arrived to Chile came from the South of Spain, where the 1100delC mutation was not detected [14].

Although we do not have available frequency data of the 1100delC mutation in Chilean Amerindian groups, it is possible to speculate that probably it is also not present in the original Amerindian peoples of Chile, given it was not found in the present admixed Chilean population. A consensus among anthropologists was reached in the sense that Amerindians derived from Mongoloids which, moving from Asia, crossed the Bering Land Bridge [27]. We also raise the hypothesis that the 1100delC mutation is not present in some of those contemporary South American populations that stem from the admixture of Amerindian peoples with the Spanish settlers. Up to date, there are no reports of the *CHEK2* 1100delC mutation in Asian population neither in admixed Amerindian-Spanish populations.

Further studies should be necessary in order to establish the prevalence of *CHEK2* 1100delC mutation in those admixed South American Amerindian-Spanish populations.

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