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RESEARCH ARTICLE

Absence of the CHEK2 c.1100delC mutation in familial breast and ovarian cancer in Colombia: a case-control study [version 1; peer review: 2 approved with reservations]

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Abstract

Background: *BRCA1* and *BRCA2* have been identified as high-penetrance breast cancer predisposition genes, but they only account for a small fraction of the inherited component of breast cancer. To explain the remaining cases, a polygenic model with a large number of low- to moderate-penetrance genes have been proposed; one of these, is the *CHEK2* gene (Checkpoint Kinase 2). The objective of this study was to determine the role of the *CHEK2* gene, specifically the c.1100delC mutation in familial breast cancer susceptibility in Colombian patients.

Methods: We screened 131 high-risk breast and/or ovarian cancer patients (negative for mutations in *BRCA1* and *BRCA2*) and 131 controls for the germline mutation *CHEK2* c.1100delC by allele-specific PCR.

Results: None of the cases or controls showed the *CHEK2* c.1100delC mutation, neither as a homozygote nor as a heterozygote.

Conclusions: Our results suggest that the *CHEK2* c.1100delC mutation is not a risk factor for genetic susceptibility to familial breast or ovarian cancer in the Colombian population. The absence of the *CHEK2* c.1100delC mutation in our population show the importance of considering ethnic background before offering a genetic test.

Keywords

CHEK2, familial breast and ovarian cancer, Colombia, CHEK2 c.1100delC, moderate-penetrance

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Any reports and responses or comments on the article can be found at the end of the article.

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Introduction

Breast cancer (BC) is the most common type of cancer among women¹, and in Colombia, it is the main cause of death by cancer in women¹. Of all cases of BC, approximately 5–10% have a strong inherited component, of which 25% is explained by germline mutations in the genes *BRCA1*² and *BRCA2*^{3,4}. To explain the *BRCA1/2*-negative cases, a polygenic model in which a large number of low- to moderate-penetrance genes as collectively responsible for the disease has been proposed^{5–7}.

CHEK2 has been proposed as a moderate penetrance BC susceptibility gene⁸. This gene controls cell cycle and apoptosis and is activated in response to DNA double-strand breakage⁸. Several mutations in the *CHEK2* gene have been found, being the *CHEK2* c.1100delC mutation the most studied; this is a truncating mutation in exon 10 that abolishes kinase activity of the protein⁹. The role of this mutation in breast cancer was confirmed by Meijers-Heijboer *et al.*⁸, and in several other studies^{10–22}. The mutation *CHEK2* c.1100delC was identified in approximately 5% of families with BC that did not have mutations in either *BRCA1* or *BRCA2* and was estimated to confer moderate risk (20–25%) of developing breast cancer for female mutation carriers²³.

Data on the contribution of moderate- or low-penetrance alleles to BC in South American populations are scarce. In this study, using a case-control design, we studied the *CHEK2* c.1100delC mutation in order to investigate the potential influence of this variant on familial Breast and Ovarian Cancer (BOC) susceptibility in a Colombian cohort.

Materials and Methods

This was a case-control study conducted from 2009 to 2013 with 131 cases and 131 controls, which was carried out to determine the association between the *CHEK2* c.1100delC mutation and increased risk of developing breast cancer. This study was approved by the Ethical Board of the School of Medicine of the University of Valle. Informed consent was obtained from all the participants.

Population Study

Cases

Our study cohort was composed of 131 Colombian familial breast/ovarian cancer (BOC) cases (*BRCA1/BRCA2* negative). The patients were selected from the files of different health/Cancer centers after obtaining permission from each Center to participate in this study. These centers were located in the cities of Cali (Hospital Universitario del Valle, FUNCANCER, Clínica Rafael Uribe Uribe, Hematooncólogos), Armenia (Oncólogos de Occidente), Cartagena (Fundación Hospital Infantil Napoleón Franco Pareja, Fundación mujeres por tus senos) and Bucaramanga (Insustia Oncología e Investigación). The selected cases met, at least, one of the following criteria: at least three family members with breast or ovarian cancer at any age; two first degree family members affected, at least one, with breast cancer before 41 years of age or with ovarian cancer at any age; one breast cancer case diagnosed before 35 years or less; one ovarian cancer case diagnosed before age 31. For all index cases, breast and ovarian cancers were verified by the original pathology report. After the selection of the patients based in the inclusion criteria

(Dataset 1), they were asked to give a blood sample collected by a nurse or technician from each health/Cancer center and then sent to our laboratory.

Controls

The sample of healthy Colombian controls (n=131) consisted of unrelated individuals, with no personal or familial history of cancer, these individuals were interviewed and informed as to the aims of the study and who gave their informed written consent for anonymous testing. This control cohort was recruited in the same cities where the study cases were collected and also matched by age, sex and socioeconomic strata.

Genotyping

Genomic DNA was extracted from the blood samples of 131 the BC cases and the 131 healthy controls, for both groups the blood samples were collected specifically for this study. Samples were analyzed using allele-specific PCR (ASPCR)²⁴ to detect the presence of *CHEK2* c.1100delC, using the primers reported by Rashid *et al.*²⁵. The products of the ASPCR were visualized by electrophoresis on an 8% polyacrylamide gel. The expected results were a band of 200 base pairs (bp) for the deletion of cytosine 1100 or a band 534 bp when the deletion is not present; if the sample showed both bands, it meant the presence of a heterozygote.

Dataset 1. Raw data for "Genotype and type of cancer present in the studied patients and their families"

<http://dx.doi.org/10.5256/f1000research.13368.d207084>

Results

A total of 262 samples (131 study cases and 131 matched-controls) were analyzed for the presence of the *CHEK2* c.1100delC mutation. The clinical characteristics of the families included in this study are listed in Table 1 (Also see Dataset 1). After allele-specific PCR analysis, none of the cases or controls showed the *CHEK2* c.1100delC mutation. All the samples showed only the heavier band (534bp) (Supplementary Figure 1). This indicates that all the samples were homozygotes for the normal allele.

Discussion

This is the first study conducted in the Colombian population for *CHEK2* c.1100delC mutation. Our results have shown that none of the 262 analyzed samples carried the *CHEK2* c.1100delC mutation, suggesting that the frequency of this mutation is extremely low (or not present) in the Colombian population.

Similar results have been reported for populations in other South American countries. Although studies are scarce, in the few populations that have been evaluated for the presence of this variant, it has not been found in Chile²⁶ and Mexico²⁷, or has been found at very low frequencies in Brazilian population^{10,22,28,29}.

Worldwide, *CHEK2* c.1100delC is absent in Spain^{30–31} and all Asian populations studied to date, including those in India³², Japan³³, China³⁴, Korea³⁵, Singapore³⁶, the Philippines²², Pakistan³⁷ and Malaysia³⁸. The mutation is present in populations of Galicia

Table 1. Distribution of breast and/or ovarian cancer cases included in this study according to inclusion criteria.

Selection Criteria	Family n (%)
≥ 3 family members with breast cancer, at least one with ovarian cancer	13 (9,9%)
≥ 3 family members with breast cancer	37 (28,2%)
2 family members with breast cancer, at least one with ovarian cancer	9 (6,9%)
2 family members with breast cancer	36 (27,5%)
1 family member with breast cancer and at least one with ovarian cancer	12 (9,2%)
Single affected individual with breast cancer ≤ age 35	21 (16,0%)
Single affected individual with Ovarian cancer ≤ age 31	3 (2,3%)
Total	131 (100%)

(northwest Spain)^{39–41}, 1.4% of the Northern European countries including Finland, the UK and the Netherlands^{8,11,42} and the United States^{43–45}.

An explanation for this variability, proposes *CHEK2* c.1100delC as an allele whose frequency is distributed along a population-gradient, which would have originated in populations of Northern Europe (with high frequencies) and decreasing towards the regions of Southern Europe (Basque Country, Spain and Italy)³⁹. This may explain the absence of the allele in the Colombian population., which is a mixture, in different proportions, of European-Spanish, African and Native American ancestry⁴⁶. Hence, the probability that the allele would have reached our population is low. As reported in several studies, it is evident that the contribution of *CHEK2* c.1100delC mutation to the burden of cancer varies according to the ethnic group, and from country to country⁴⁷.

We found that the *CHEK2* c.1100delC mutation is not present or is present at an extremely low frequency in familial BOC cases and controls in our Colombian cohort.

Based on our findings, we suggest that genotyping of the *CHEK2* c.1100delC mutation in genetic testing for breast cancer susceptibility in the Colombian population should not be recommended. However, further studies are required to confirm the contribution of this variant in the Colombian population.

The study of *CHEK2* mutations in the Latin American population has been focused mainly in the c.1100delC mutation. However, databases like ExAC (Exome Aggregation Consortium) showed

the presence of other germline mutations in the *CHEK2* gene in Latin American samples that could generate cancer susceptibility⁴⁸.

Accordingly, it would be important to examine other mutations in the Colombian population and its association with the development of familial BOC.

Data availability

Dataset 1: Raw data for “Genotype and type of cancer present in the studied patients and their families” [10.5256/f1000research.13368.d207084](https://doi.org/10.5256/f1000research.13368.d207084)⁴⁹

Competing interests

The authors declare no conflicts of interest.

Grant information

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Supplementary Material

Supplementary Figure 1: Allele specific PCR products for the *CHEK2* c.1100delC mutation.

Polyacrylamide gel electrophoresis at 8% (29:1 acrylamide:bisacrylamide) of allele specific PCR products for the *CHEK2* c.1100delC variant for cases and controls. Lanes 1 - 5 show the amplified product of Colombian patients with breast and/or familial ovarian cancer; lanes 7-11 show the amplified product of healthy controls; Lane 6: molecular weight marker of 100 base pairs. all individuals show an amplified product of 537 bp which corresponds to the normal genotype. The letters “p.b.” in the picture are the spanish initials for base pairs (“*pares de bases*”).

[Click here to access the data.](#)

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Rivera-Herrera *et al.* reported the analysis of CHEK2 c.1100delC in a population selected following the NCCN criteria, very well detailed in table 1. The MS is clearly written and thus, easy to follow.

Specific comments:

1. The actual nomenclature for this variant is of CHEK2 c.1100del.
2. It might be important to have the information of the ethnic origin of the probands analyzed since this pathogenic variant is common in Northern-European countries and to make a population conclusion it is critical.
3. The number of patients analyzed is low based on the expected frequency in the northern countries that may have the highest, 0.5-1,16%, while it is expected based on the databases 100 times lower in Latin populations¹. Although in Brazil it is reported 1.76%, based in 1 out of 59 probands analyzed, a number still low to analyze a cohort of 131 patients and extrapolate to a population frequency.
4. The above comment does not deny the importance of the testing since the family diagnosis is always very valuable for the counselling the relatives.
5. In methods it is very necessary to show the capacity to detect a positive mutation for CHEK2 c.1100del since a few reasons could account for a false negative result. The authors should include the DNA sequence profile for this positive control, in the case it was done.
6. A brief explanation of the method used for *BRCA1/2*, as the patients were selected for not

being a carrier of a mutation in those genes.

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Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Diagnostic laboratory, genes sequencing

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.

Reviewer Report 04 April 2019

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Rivera-Herrera et al. report a carefully designed study on the occurrence of a moderate-

penetrance breast cancer-susceptibility mutation CHEK2: c.1100delC. The paper is well written and the methods and results clearly articulated.

c.1100delC is a founder mutation enriched in certain Northern-European populations. The two-to threefold increased risk associated with the mutation and the relatively high population carrier frequency (0.5-1.5%) e.g. in the United States, United Kingdom, The Netherlands, Germany, and Finland has prompted the inclusion of the mutation in the panels used for genetic counselling. However, in countries, where the c.1100delC frequency is very low (less than 0.1%), testing for the mutation may not be cost-effective. On the other hand, since c.1100delC is a causal mutation with verified risk effect, independent of the genetic background or ethnicity, even in countries with admixed population and very low carrier frequency the positive carrier status is informative for the rare mutation carriers and their families.

The report of Rivera-Herrera et al. serves well in the building of an overall view of breast cancer risk mutations present in Hispanic populations and would thus deserve visibility in the scientific community. However, they should address the limitations of their study and report the genotyping conditions in more detail. There are two issues:

1. In genotyping, they should use a positive control, i.e. a DNA sample from a c.1100delC carrier, to ensure proper performance of the assay. Referring to conditions and assays used in previous studies is not enough, because the assay ought to be optimized on site. If the authors had included a positive control, they should indicate it in the text.
2. The authors should discuss the power of their analysis. Assuming underlying carrier frequency of 1.16% (as in Couch et al. 2017, *JAMA Oncology*¹) in Colombian breast cancer families, the probability of by chance not detecting any carrier in 131 probands would be 21.7%, which is rather high for a conclusion that the mutation is not present in the country. The authors refer to other studies in Latin-American countries and claim that the c.1100delC mutation is absent or has very low frequency. These studies are also quite small. Furthermore, in the Brazilian studies the mutation frequency in families appeared comparable to the frequency in Couch et al.¹, and thus should not be referred to as very low.

References

1. Couch FJ, Shimelis H, Hu C, Hart SN, et al.: Associations Between Cancer Predisposition Testing Panel Genes and Breast Cancer. *JAMA Oncol.* 2017; **3** (9): 1190-1196 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No source data required

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cancer genetics, breast cancer

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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