Human Mutation
Variation, Informatics, and Disease
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RESEARCH ARTICLE

Comprehensive analysis and ACMG-based classification of *CHEK2* variants in hereditary cancer patients

Gardenia Vargas-Parra, Jesús del Valle, Paula Rofes, Mireia Gausachs, Agostina Stradella, José M. Moreno-Cabrera, Angela Velasco, Eva Tornero, Mireia Menéndez ... See all authors

First published: 09 September 2020
https://doi.org/10.1002/humu.24110

Gardenia Vargas-Parra and Jesús del Valle contributed equally to the work and share first authorship.

Abstract

CHEK2 variants are associated with intermediate breast cancer risk, among other cancers. We aimed to comprehensively describe *CHEK2* variants in a Spanish hereditary cancer (HC) cohort and adjust the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG-AMP) guidelines for their classification. First, three *CHEK2* frequent variants were screened in a retrospective Hereditary Breast and Ovarian Cancer cohort of 516 patients. After, the whole *CHEK2* coding region was analyzed by next-generation sequencing in 1848 prospective patients with HC suspicion. We refined ACMG-AMP criteria and applied different combined rules to classify *CHEK2* variants and define risk alleles. We identified 10 *CHEK2* null variants, 6 missense variants with discordant interpretation in ClinVar database, and 35 additional variants of unknown significance. Twelve variants were classified as (likely)-pathogenic; two can also be considered “established risk-alleles” and one as “likely risk-allele.” The prevalence of (likely)-pathogenic variants in the HC cohort was 0.8% (1.3% in breast cancer patients and 1.0% in hereditary nonpolyposis colorectal cancer patients). Here, we provide ACMG adjustment guidelines to classify *CHEK2* variants. We hope that this study would be useful for variant classification of other genes with low effect variants.

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DATA AVAILABILITY STATEMENT

The data files that support the findings of this

Supporting Information

Filename		
humu24110-sup-0001-CHEK2suppMat_22052020_		
humu24110-sup-0002-SuppTables_CLEAN.pdf	387.2 KB	Supporting information.

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