

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](#) ▾

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

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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 study are available in the following repository: [https://doi.org/10.1002/humu.24110](#)

Supporting Information

Filename

[humu24110-sup-0001-CHEK2suppMat_22052020_clean_10022020_0001.pdf](#) Supporting information.

[humu24110-sup-0002-SuppTables_CLEAN.pdf](#) 387.2 KB Supporting information.

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