

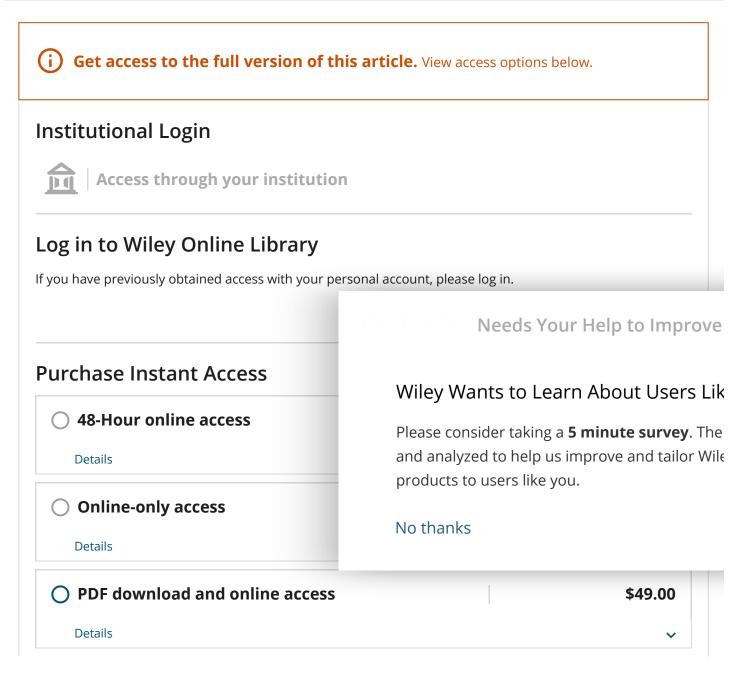
RESEARCH ARTICLE

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

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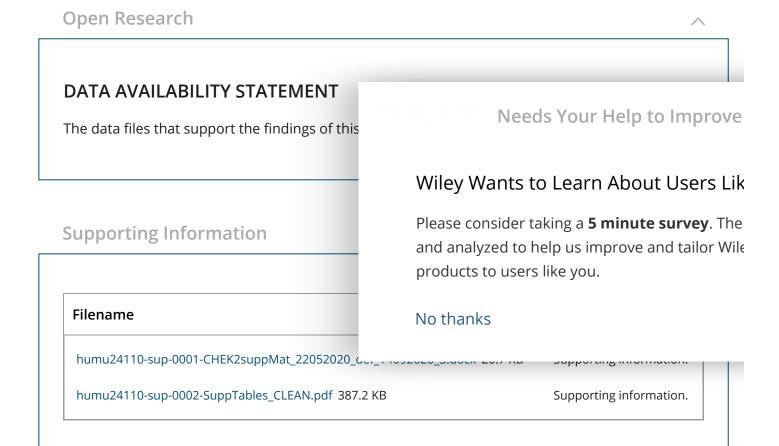
Gardenia Vargas-Parra and Jesús del Valle contributed equally to the work and share first authorship.



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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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