

<https://doi.org/10.29289/259453942025V36S11058>

1058 – Reclassification of variants of uncertain significance in genes associated with hereditary breast cancer in patients treated at referral hospitals in the state of Goiás

Bruno Eduardo Feitosa Nascimento, Igor Marques Cesario Calassa, Luiz Henrique Alves Costa, Hellen Rocha Luz, Andréa Moreira dos Santos, Rosemar Macedo Sousa Rahal, Paula Francinete Faustino da Silva, Elisângela de Paula Silveira Lacerda

¹Hospital das Clínicas – Goiânia (GO), Brazil.

²Universidade Federal de Goiás, Instituto de Ciências Biológicas – Goiânia (GO), Brazil.

³Universidade Federal do Amazonas, Programa de Pós-graduação em Biotecnologia – Manaus (AM), Brazil.

⁴Universidade Federal de Goiás – Goiânia (GO), Brazil.

Introduction: Breast cancer is the most common malignancy among women, with 5–10% of cases arising from hereditary predisposition, driven by pathogenic variants in DNA repair genes such as BRCA1/BRCA2, as well as moderate-risk genes, including ATM, CHEK2, TP53, BARD1, and BRIP1. Next-generation sequencing improves variant detection but increases the number of variants of uncertain significance (VUS) in underrepresented admixed populations, such as the Brazilian population, where global databases (gnomAD) underestimate local allele frequencies, complicating risk stratification and clinical management.

Methods: In this study, 105 women with breast cancer treated at two referral centers in Goiás, Brazil, between 2020 and 2024 were evaluated. The study was approved by the Research Ethics Committees of Hospital das Clínicas, Federal University of Goiás (CAAE: 50626315.6.0000.5078; approval no. 2,901,648) and the Goiás Cancer Combat Association (CAAE: 50626315.6.3001.0031; approval no. 4,093,502). All participants provided written informed consent. Germline DNA was analyzed under rigorous quality controls, integrating annotations from ClinVar, VarSome, Franklin, gnomAD, ABraOM, and in silico prediction tools. Interpretation strictly followed the American College of Medical Genetics and Genomics guidelines, with reclassification based on population, functional, and clinical evidence, aligned to the hg19 reference genome for analytical consistency.

Results: A total of 13 VUS were identified in seven predisposition genes (ATM, BRCA2, BRIP1, BARD1, BRCA1, CHEK2, TP53) and were present in ten patients (9.5%). After systematic reclassification based on integrated population, functional, and clinical evidence, eight variants (61.5%) were reclassified as benign/likely benign, and five variants (38.5%) remained as VUS, reflecting the lack of national data.

Conclusion: Critically, this approach mitigates overtreatment by reclassifying VUS, minimizing unnecessary prophylactic interventions, familial anxiety, and oncology-related costs. In admixed populations such as Brazil's, integrating local data (ABraOM) corrects bias from under-representative global databases (gnomAD), improving diagnostic accuracy; however, inherent limitations persist, including the scarcity of functional assays for moderate-risk genes and the underrepresentation of rare variants, which perpetuates uncertainty in multifactorial risk stratification.

Ethics: Approved by the Research Ethics Committees of Hospital das Clínicas, Federal University of Goiás (CAAE 50626315.6.0000.5078) and the Association for Cancer Control in Goiás (CAAE 50626315.6.3001.0031).

Keywords: breast neoplasms; genetic predisposition to disease; DNA repair; DNA sequence analysis; variant of uncertain significance.