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1194 – Importance of reclassification of variants of uncertain significance in patients with breast cancer using multigene panel testing

Joanine Fernandes Tavares¹, Paula Francinete Faustino da Silva¹, Bruno Eduardo Feitosa Nascimento¹, Wendyson Duarte Oliveira¹, Elisângela de Paula Silveira Lacerda¹

¹Centro de Genética Humana – Goiânia (GO), Brazil.

Introduction: The increasing use of next-generation sequencing in breast cancer investigation has expanded the detection of variants of uncertain significance (VUS), representing a challenge in clinical practice. The reclassification of these variants is essential for accurate assessment of hereditary cancer risk and for decision-making in mastology.

Objective: To reclassify VUS identified in patients with breast cancer through an integrated bioinformatics approach and according to the American College of Medical Genetics and Genomics (ACMG) criteria.

Methods: This retrospective observational study included 352 patients who underwent next-generation sequencing using a multigene panel. Among them, 27 women with breast cancer presented variants initially classified as VUS in genes associated with hereditary predisposition, including BRCA1, BRCA2, PALB2, CHEK2, ATM, BRIP1, RAD51D, and TP53. Variants were reclassified according to the ACMG criteria using an integrated bioinformatics approach, including population frequency analysis in the Genome Aggregation Database (gnomAD) and the application of artificial intelligence-based tools such as HerediVar, HerediClassify, DeepVariant, and SpliceAI.

Results: VUS were identified in patients with breast cancer, and after reclassification, a subset of variants was categorized as likely pathogenic and likely benign, while others remained classified as VUS. Variants with higher pathogenic potential were highlighted in genes such as BRCA1, TP53, and PALB2, including a BRCA1 deletion (c.542_543del) and a TP53 variant (c.472C>T). The integrated bioinformatics approach enabled greater accuracy in reclassification, despite variability among predictive algorithms.

Conclusion: The reclassification of VUS demonstrated a direct impact on genetic interpretation and risk stratification in patients with breast cancer. The identification of likely pathogenic variants reinforces the importance of appropriate clinical follow-up for patients and their families, enabling surveillance strategies, early diagnosis, timely therapeutic intervention, and disease prevention. These findings highlight the fundamental role of bioinformatics in precision medicine.

Ethics: Research Ethics Committee of Hospital das Clínicas, Federal University of Goiás (UFG), CAAE 50626315.6.0000.5078; Opinion No. 1791010, and by the Research Ethics Committee of the Association for Cancer Control in Goiás (ACCG), CAAE 50626315.6.3001.0031; Opinion No. 4.093.502.

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