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MULTIGENE PANEL TESTING FOR BREAST CANCER PREDISPOSITION IN BRAZILIAN PATIENTS

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Objective: Only 5–10% of breast cancer (BC) is related to inherited genetic variants, and BRCA1 and BRCA2 mutations are responsible for the majority of cases. BRCA1 is more associated with triple-negative and BRCA2 to the luminal subtype. The contribution of other genes of high and moderate risk for BC, such as TP53, STK11, CDH1, PTEN, ATM, CHEK2, and PALB2, are not well defined, and risk estimates to specific BC subtype are lacking, especially for an admixed population like Brazilian. The aim of this study was to evaluate the contribution of the multigene panel in detecting germline mutations in Brazilian BC patients and their relationship with molecular subtypes and predominant ancestry. **Methods:** A 94-gene panel was performed on 321 patients with BC fulfilling NCCN criteria who were referred for BRCA1/2 testing between August 2016 and May 2018. Molecular subtypes were retrieved from medical records, and ancestry-specific variants were obtained from the sequencing data. **Results:** A panel analysis of 321 patients resulted in a total of 83 pathogenic/likely pathogenic (P/LP) variants identified in 81 patients, leading to a positivity rate of 25%. Of the total P/LP variants, 47% were identified in high-risk BC genes (BRCA1/2, PALB2, and TP53) and 17% in moderate-penetrance genes (ATM and CHEK2). The remainders of the variants were identified in low-risk genes and were considered unexpected findings. Variants of uncertain significance were identified in 77.6% of the patients. Regarding the molecular subtype, triple-negative BC had a mutation frequency of 32% (25/79), with predominance in BRCA1 (40%). Among the luminal subtype, 19% (29/155) had P/LP variants, with BRCA1/2 genes contributing to 38% of mutated cases. For the Luminal B HER2-positive subtype, 40% (16/40) had P/LP variants, with a predominance of the ATM gene (37%). Finally, the HER2-enriched subtype presented a mutation rate of 31% (4/13; 1 BRCA2 and 3 non-BRCA1/2). We did not detect any association of ancestry with P/LP variants or molecular subtypes. **Conclusion:** The multigene panel contributed to identify P/LP variants in other actionable genes besides BRCA1/2, increasing 7.2% of the positivity of the genetic test. Additionally, our results highlight the distinct contributions of BC genes in each molecular subtype. These results indicate that women with clinical criteria for hereditary BC may benefit from multigene panel testing as it allows them to identify P/LP variants in other BC susceptibility genes, including actionable genes, which directly impact the clinical management of these patients and family members.

Keywords: Hereditary breast cancer.