

Genetic Landscape of Pakistani Familial Breast Cancer Patients Using Multigene Panel Testing

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Abstract

Pathogenic/likely pathogenic (P/LP) variants in high-, moderate-, and low-penetrance genes account for approximately half of all familial breast cancer (BC) cases. In Pakistan, data on P/LP variants beyond *BRCA1/2* remain limited. This study investigated the frequency and distribution of P/LP variants in Pakistani familial BC patients using a 14-gene hereditary breast and ovarian cancer (HBOC) core panel. A total of 160 familial BC patients previously tested negative for protein-truncating variants in *BRCA1*, *BRCA2*, *CHEK2*, *PALB2*, *RAD51C*, *RAD51D*, and *TP53* using conventional methods were included. Next-generation sequencing (NGS) was performed using the Illumina MiSeq platform, and all identified P/LP variants were validated by Sanger sequencing. Twenty-four unique P/LP variants were identified across seven genes: *BRCA1* (n=10), *BRCA2* (n=6), *TP53* (n=3), *CHEK2* (n=2), *PALB2*, *ATM*, and *RAD51C* (n=1 each). Two recurrent *BRCA1* variants, p.Gln169Ter and p.Val757Phefs*8, were identified in three patients each. NGS-detected P/LP variants were identified in 18.1% (29/160) of patients. When combined with previous germline testing in the same cohort, the overall detection rate increased to 50.2% (132/263): *BRCA1* (101/263; 38.4%), *BRCA2* (22/263; 8.4%), *TP53* (3/263; 1.1%), *CHEK2* (2/263; 0.8%), *PALB2* (2/263; 0.8%), *ATM* (1/263; 0.4%) and *RAD51C* (1/263; 0.4%). Among these, *BRCA1/2* variants accounted for 93.2% (123/132) of all P/LP variants. Our findings demonstrate that P/LP variants are concentrated in a limited number of genes, with *BRCA1/2* as the predominant contributors. We propose a cost-effective, first-tier genetic testing panel comprising seven genes (*ATM*, *BRCA1*, *BRCA2*, *CHEK2*, *RAD51C*, *PALB2*, and *TP53*) for familial BC risk assessment in Pakistan.