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Contribution of PALB2 and BLM Mutations to Familial Breast Cancer Risk in BRCA1/2 Negative South African Breast Cancer Patients Detected Using High-Resolution Melting Analysis

Authors : N. C. van der Merwe, J. Oosthuizen, M. F. Makhetha, J. Adams, B. K. Dajee, S-R. Schneider

Abstract : Women representing high-risk breast cancer families, who tested negative for pathogenic mutations in BRCA1 and BRCA2, are four times more likely to develop breast cancer compared to women in the general population. Sequencing of genes involved in genomic stability and DNA repair led to the identification of novel contributors to familial breast cancer risk. These include BLM and PALB2. Bloom's syndrome is a rare homozygous autosomal recessive chromosomal instability disorder with a high incidence of various types of neoplasia and is associated with breast cancer when in a heterozygous state. PALB2, on the other hand, binds to BRCA2 and together, they partake actively in DNA damage repair. Archived DNA samples of 66 BRCA1/2 negative high-risk breast cancer patients were retrospectively selected based on the presence of an extensive family history of the disease (> 3 affecteds per family). All coding regions and splice-site boundaries of both genes were screened using High-Resolution Melting Analysis. Samples exhibiting variation were bi-directionally automated Sanger sequenced. The clinical significance of each variant was assessed using various in silico and splice site prediction algorithms. Comprehensive screening identified a total of 11 BLM and 26 PALB2 variants. The variants detected ranged from global to rare and included three novel mutations. Three BLM and two PALB2 likely pathogenic mutations were identified that could account for the disease in these extensive breast cancer families in the absence of BRCA mutations (BLM c.11T > A, p.V4D; BLM c.2603C > T, p.P868L; BLM c.3961G > A, p.V1321I; PALB2 c.421C > T, p.Gln141Ter; PALB2 c.508A > T, p.Arg170Ter). Conclusion: The study confirmed the contribution of pathogenic mutations in BLM and PALB2 to the familial breast cancer burden in South Africa. It explained the presence of the disease in 7.5% of the BRCA1/2 negative families with an extensive family history of breast cancer. Segregation analysis will be performed to confirm the clinical impact of these mutations for each of these families. These results justify the inclusion of both these genes in a comprehensive breast and ovarian next generation sequencing cancer panel and should be screened simultaneously with BRCA1 and BRCA2 as it might explain a significant percentage of familial breast and ovarian cancer in South Africa.

Keywords : Bloom Syndrome, familial breast cancer, PALB2, South Africa
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