

## Pattern of germline variants detected in Sri Lankan patients referred for genetic evaluation of hereditary breast cancer using a multi-gene cancer panel test

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DOI: <http://doi.org/10.4038/jdp.v11i2.7708>

### Introduction

Genes in which germline mutations confer highly or moderately increased risks of cancer are called cancer predisposition genes (CPGs). Hereditary breast cancers occur in individuals with germline variants in various CPGs such as *BRCA1*, *BRCA2*, *CHEK2*, *ATM*, *PALB2*, *TP53*, *PTEN*, *STK11*, *BRIP1*, *CDKN2A*, *BARD1*, *FANCI*. Multi-gene panel testing for detection of clinically actionable genetic variants in CPGs that are critical for cancer care is useful in routine clinical practice. This study aimed to describe the pattern of germline variants in a cohort of Sri Lankan patients referred for genetic evaluation of hereditary breast cancer to our centre.

### Methodology

After providing pre-test counselling and obtaining written informed consent, blood samples from eleven individuals referred for genetic evaluation of hereditary breast cancer were tested using a 94-gene cancer panel test on the Illumina MiSeq NGS platform, followed by bioinformatics analysis.

### Results

There were 9 (81.8%) patients with invasive carcinoma and 2 (18.2%) asymptomatic individuals. Their mean age was 47.4 years. Germline variants in seven CPGs were identified in 10 (90.9%) patients. The two most common variants were *BRCA2* (27.3%) [c.9117G>A;p.Pro3039 =;c.784G>A;p.Ala262Thr;c.2488A>G;p.Asn830Asp] and *BRCA1* (18.2%) [c.823G>A;p.Gly275Ser;c.5289delG;p.Leu1764Terf]. The remaining variants were in moderate-penetrance genes: *CHEK2* (9.1%) [c.1630G>A;p.Glu544Lys], *ATM*

(9.1%) [c.2932T>C;p.Ser978Pro], *PALB2* (9.1%) [c.2768T>G;p.Val923Gly], *CDKN2A* (9.1%) [c.377A>C;p.Gln126Pro] and *FANCI* (9.1%) [c.3179T>C;p.Ile1060Thr]. Twenty percent were pathogenic variants, another 20% were likely pathogenic and 60% were variants of uncertain significance.

### Discussion

Variants in both high-penetrance and moderate-penetrance genes associated with hereditary breast cancer were present in the patients tested. These risks would have been missed if testing were guided strictly by established single-gene and/or syndrome testing guidelines.

### Conclusion

Identifying the underlying germline variants using multi-gene cancer panel testing is valuable in guiding treatment decisions and genetic counselling/screening of at-risk family members.