OP-20: Germline genetic variants, their frequency, and clinico-pathological features in Sri Lankan patients with hereditary breast cancer

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Introduction: The incidence of breast cancer in Sri Lankan women is rising at an alarming rate of 4% per year. Next-generation sequencing (NGS)-based whole exome sequencing (WES) is increasingly being utilised to detect germline variants in cancer predisposing genes and to predict inherited cancer risk. This study aims to assess the frequency of germline genetic variants and clinico-pathological features in a cohort of Sri Lankan hereditary breast cancer patients.

Methods: Genomic data of 72 hereditary breast cancer patients who underwent WES between January 2015 and December 2021 were maintained prospectively in a database and analysed retrospectively. Data were subjected to bioinformatics analysis and variants were classified according to international standard guidelines. Information including demographic data, family history of cancer, tumour histopathology and receptor status were also analysed.

Results: Germline variants were identified in 33/72 (45.8%) patients. Among them, 32 (96.9%) were females and 17 (51.5%) had cancer onset before the age of 50 years. 16/33 (48.5%) had pathogenic/likely pathogenic variants and 17/33 (51.5%) had variants of uncertain significance. Highest frequency of pathogenic/likely pathogenic variants were in *BRCA1* (n=7; 43.8%) and *BRCA2* (n=7; 43.8%) genes. *BRCA2*:c.1294_1295GA;p.Asn433fs was the most frequently occurring pathogenic variant (n=3; 18.8%). Non-*BRCA* likely pathogenic variants were detected in *PALB2* (n=1; 6.3%) and *PTCH1* (n=1; 6.3%) genes. *PALB2*:c.2768T>G;p.V923G and *BRCA1*:c.5225A>C;p.Q1742P were novel likely pathogenic variants. Predominant histopathology was ductal carcinoma (n=20; 79.1%). Oestrogen and progesterone receptor negativity was observed in (n=4; 50%) harbouring *BRCA* variants and triple negativity was seen in only two patients both of whom were harbouring *BRCA2* variants. Family history of breast cancer was present in 24 (77.4%).

Conclusions: Highest frequency of pathogenic/likely pathogenic germline variants were detected in the *BRCA1* and *BRCA2* genes, respectively. Predominant tumour histopathology was ductal carcinoma. WES allows identification of germline genetic variants in families with hereditary breast cancer predisposition which would be beneficial for guiding implementation of therapeutic and preventive risk-reduction measures.

Keywords: hereditary breast cancer, germline variants, NGS