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Germline Landscape of Cancer Predisposition in Nepal: Founder Variants and Population-Specific Implications in Precision Oncology

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Background

Population-specific germline genomic data from underrepresented ethnicities are crucial for equity in precision oncology. It improves variant interpretation, identification of founder mutations, and designing population-specific hereditary cancer testing strategies. We present the largest pan-cancer analysis of germline cancer predisposition in a Nepalese cohort, providing a comprehensive overview of hereditary risk and its implications for precision medicine.

Methods

A retrospective analysis was done on 558 Nepalese patients diagnosed with solid tumors or referred for hereditary cancer risk assessment; these individuals underwent germline NGS-based sequencing with multi-gene panels.

Results

Pathogenic germline variants were identified in 32.6% (n=182) of the patients. BRCA1 was the predominant susceptibility gene accounting for 70.9% of the mutation positive patients and 67.9% of all pathogenic variants, followed by BRCA1 (9.3% patients; 9.5% mutations), BUB1B (2.2%; 2.1%), TP53 (2.2%; 2.1%), and MUTYH (1.6%; 2.1%). Breast (49.5%) and ovarian (16.7%) cancers constituted the majority of the cohort, with BRCA1 (62.5% and 86.4%) and BRCA2 (18.0% and 4.5%) being the most frequently altered genes, respectively. Two recurrent BRCA1 variants, p.K739* (40.5%) and p.K1711* (18.9%), together accounted for nearly 60% of BRCA1 pathogenic variants and were observed across multiple malignancies, including breast, ovarian, fallopian tube, colorectal, dual primary,

and cancers of unknown primary. While p.K739* is a known founder mutation, our result support a possible founder effect of p.K1711* in the Nepalese population. Further, HRR genes including BRCA1, BRCA2, ATM, PALB2 and RAD54L were seen in 82.3% of the mutation positive patients (79.5% mutations).

Conclusions

This study represents the largest systematically characterized germline pan-cancer cohort from Nepal, that outlines the hereditary predisposition genomic landscape. The recurrent BRCA1 mutations accounting for ~60% of all BRCA1-positive cases, support the possibility of a strong founder effect with direct implications for cost-effective hereditary cancer testing.

Clinical trial identification

Editorial acknowledgement

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