EDITORIAL

Genetic Variants in a Population – Implications for Molecular Pathology

Syed Zulfiqar Ali Naqvi[1*]
[1]*Liaquat National Hospital, Karachi, Pakistan*

In the era of precision medicine, the recognition of genetic variability within populations has emerged as a cornerstone in advancing our understanding of cancer biology. Genetic variants, both germline and somatic, are increasingly informing risk stratification, diagnostic classification, prognostication, and treatment selection in oncology. However, the landscape of these variants is highly influenced by population-specific genetic backgrounds, underscoring the need for a more inclusive approach to molecular pathology.

Historically, genomic databases and cancer studies have been dominated by data from populations of European descent. This lack of diversity has led to significant knowledge gaps, particularly in interpreting variants of unknown significance (VUS), identifying population-specific driver mutations, and understanding the differential responses to targeted therapies. For molecular pathologists, this translates into challenges in the accuracy and equity of genomic diagnostics and treatment recommendations. Furthermore, understanding genetic variants within populations is crucial not only for common diseases but also for rare Mendelian disorders, where early and timely diagnosis can significantly impact patient management and outcomes [1, 2].

Recent large-scale initiatives, such as the All of Us Research Program (NIH) and international efforts to sequence underrepresented populations, are beginning to address these disparities. As we incorporate more diverse genomic data into clinical workflows, molecular pathology stands at a pivotal intersection—tasked with translating complex population-level genetic insights into actionable clinical knowledge.

This editorial examines the impact of population-specific genetic variants on molecular diagnostics, with contributions that highlight advances in variant classification, the discovery of novel biomarkers, and the ethical implications of genomic equity. We also examine the integration of bioinformatics tools tailored to ancestry-specific genomic interpretation and their role in reducing misclassification and overtreatment. Moving forward, the oncology community must foster cross-disciplinary collaborations, embrace genomic inclusivity, and invest in training the next generation of pathologists to navigate the nuances of population genomics.

Recent meta-analyses of genome-wide association studies (GWAS) have confirmed that loci such as 5p15.33 (TERT/CLPTM1L) and 6p21–6p22 (BAG6/MSH5) significantly impact lung cancer susceptibility, varying notably across ethnicities and histologic subtypes, highlighting the critical role of genetic background in interpreting pathogenicity [3].

Low-frequency and rare variants—particularly those detected by whole-exome/genome sequencing contribute disproportionately to disease predisposition and often display population specificity. Notably, rare variant aggregation tests have identified functional alleles affecting complex diseases in diverse ethnic cohorts.

Importantly, discrepancies in molecular diagnostic rates across populations have been documented. For instance, African-American colorectal cancer patients carry KRAS mutations at a significantly higher frequency than Caucasians, underscoring how ancestry should inform molecular testing and therapeutic decisions [4]. Similarly, large-scale tumor profiling has revealed ancestry-linked differences in mutation burdens in various cancers.

Emerging guidelines emphasize integrating population-based reference data (*e.g.*, gnomAD) into variant interpretation pipelines to reduce both false-positive and false-negative classifications in somatic and germline testing [5, 6].

In summary, population-specific genetic variation directly influences variant classification, biomarker discovery, and therapeutic outcomes. Recognizing and integrating these differences into molecular pathology practice is critical to realizing the promise of inclusive precision oncology.

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**Corresponding author: Syed Zulfiqar Ali Naqvi, Liaquat National Hospital, Karachi, Pakistan, Email: zulfiqar.naqvi@lnh.edu.pk*
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