Ethnic Disparities in Germline Variants of Myeloid Malignancies

Young-Uk Cho
Department of Laboratory Medicine, Asan Medical Center,
University of Ulsan College of Medicine, Seoul, Korea

Advances in genomic sequencing have revealed that a subset of myeloid malignancies arises in the context of inherited susceptibility. Germline variants in genes involved in hematopoiesis, DNA repair, and transcriptional regulation—including DDX41, RUNX1, CEBPA, GATA2, and ANKRD26—are now recognized as important contributors to the development of acute myeloid leukemia, myelodysplastic syndromes, and related myeloid neoplasms. As genomic testing becomes increasingly integrated into routine clinical practice, the identification and interpretation of tumor-predisposing germline variants have emerged as critical components of precision hematologic care.

However, accumulating evidence indicates that the prevalence and spectrum of these germline variants differ substantially across ethnic populations. Most currently recognized predisposition genes were initially characterized in cohorts of predominantly European ancestry, including large-scale biobanks such as the UK Biobank and Geisinger MyCode. Consequently, variant frequencies, penetrance estimates, and pathogenicity classifications derived from these datasets may not be directly generalizable to other populations. Studies in East Asian populations have revealed striking differences, particularly for DDX41, where distinct recurrent variants predominate: p.V152G is most frequent in Korean cohorts, while p.P258L, p.Y259C, and c.935+4A>T account for over half of pathogenic variants in Chinese populations. These cohorts also demonstrate population-specific clinical features, including differences in age of disease onset, penetrance patterns, and disease phenotype. Similar population-specific trends are emerging in Southeast Asian, African, and Hispanic/Latino populations, underscoring the critical importance of ethnic diversity in genomic research.

These disparities carry significant clinical implications. Ethnicity-specific variant frequencies complicate diagnostic interpretation and the classification of variants of uncertain significance, as standard ACMG/AMP criteria may perform inconsistently across ancestries. Accurate germline variant identification is essential for donor selection in hematopoietic stem cell transplantation, particularly when evaluating related donors who may carry the same predisposition allele. Furthermore, penetrance and risk estimates derived from European cohorts may inadequately inform surveillance strategies for at-risk family members from underrepresented populations. The persistent underrepresentation of non-European ancestries in genomic databases and clinical cohorts remains a fundamental barrier to accurate variant interpretation and equitable implementation of precision medicine in hematology.

This lecture will review the current understanding of germline predisposition to myeloid malignancies with a focus on ethnic variation in variant distribution, penetrance, and clinical presentation. I will discuss emerging data from diverse global populations, methodological challenges in distinguishing pathogenic variants from benign population polymorphisms, and the urgent need for ancestry-matched reference datasets. Finally, I will address the clinical and research priorities required to improve the recognition, risk stratification, and management of hereditary myeloid malignancies across all ethnic groups, with the goal of advancing health equity in genomic medicine.