CLONAL HEMATOPOIESIS OF INDETERMINATE POTENTIAL MUTATIONS AND CARDIOVASCULAR RISK IN KAZAKHSTANI COHORT

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Background: Clonal haematopoiesis of indeterminate potential (CHIP) is an age-related condition associated with an increased risk of cardiovascular disease (CVD). Mutations in CHIP-related genes such as *DNMT3A*, *JAK2*, and *TET2* are common and linked to accelerated atherosclerosis and adverse outcomes. There is a growing body of evidence at a global level. However, data on CHIP in Kazakhstani populations remains limited.

Materials and methods: The aim of this study was to evaluate the prevalence and characteristics of 74 genes associated with CHIP among Kazakhstani patients with atherosclerotic disease. A total of 401 patients with pre-existing CVD, divided by risk levels according to ESC/EAS (2019) recommendations was divided: low-risk (n = 74), high-risk (n = 135) and very-high-risk (n = 192). Variant annotation and interpretation were performed using international genomic databases (ClinVar, ExAC, 1000 Genomes) and the ACMG/AMP classification system through InterVar.

Results: According to ACMG criteria, we identified 2 pathogenic variants (*DNMT3A* and *PDS5B*) and 3 likely pathogenic variants (*JAK2 and CEBPRA*) variants, and for the uncertain significance counts 701 variants, the CLNSIG classification shows 2 pathogenic variants (*MPL*) and 1 likely_ pathogenic (*CREBBP*) and pathogenic/likely pathogenic 1 variant (*ASXL1*). There were 174 female participants (mean age 53.8 ± 9.1 years) and 227 male participants (mean age 52.2 ± 9.9 years). Most patients were ≥50 years across all risk categories. Among females, the very-high-risk group showed a balanced age distribution, while in males it was predominantly younger. Low and high-risk groups were dominated by older patients, especially men, indicating potential sex differences in risk onset.

Conclusion: This study provides the first evidence of CHIP-associated variants across 74 genes in Kazakhstani patients with atherosclerotic disease. The study identified pathogenic, likely pathogenic, and numerous variants of uncertain significance, highlighting their potential contribution to increased cardiovascular risk in this population. These findings emphasise the importance of CHIP in identifying cardiovascular risk and the value of genomic screening.

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