

## PREVALENCE OF DAMAGING GENETIC VARIANTS IN GENES OF LIPID METABOLISM PATHWAY IN KAZAKHSTANI ATHEROSCLEROSIS COHORT

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**Background:** Atherosclerosis is a leading factor in cardiovascular diseases, and polymorphisms in the *LDLR*, *APOB*, *PCSK9*, *GCKR*, *LPL*, and *APOE* genes play a key role in lipid metabolism disorders. The aim of the study was to study the prevalence of genetic variations associated with lipid metabolism and their relationship to the risk of atherosclerosis in the population of Kazakhstan.

**Materials and methods:** The purpose of the study conducted in Kazakhstan was to identify a genetic predisposition to hyperlipidemia and its relationship to the risk of cardiovascular diseases. The study included 402 patients (23-65 years old) with pre-existing CVD, divided by risk levels according to ESC/EAS (2019) recommendations: very high (n=192), high (n=136) and low (n=74). All participants underwent complete exome sequencing with analysis of the *GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, and *APOE* genes; the data were processed using ANNOVAR, VarScan, and InterVar, and the classification of variants was performed according to ACMG/AMP criteria.

**Results:** Analysis of lipid metabolism genes in Kazakhstani patients with atherosclerosis has shown that the number of pathogenic (P) and likely pathogenic (LP) variants increases with increasing risk. The low-risk group has P and LP in *APOE* and *GCKR*, the high-risk group has P variants in *APOE* and *MYO15A* and some LP in *APOE*, *GCKR*, *SLC22A5*, and the very high-risk group has P in *APOE* and *MYO15A*, as well as all other LP

in *GCKR*, *SLC22A5*, *LPL*, *FLCN*, *LDLR*, *APOE*. The total number of variants with uncertain significance also increased: 278 in 120 genes in the low-risk group, 460 in 136 genes in the high-risk group, and 615 in 145 genes in the very high-risk group. The correlation between the increase in P/LP mutations in *APOE*, *SLC22A5*, *LDLR*, and *LPL* and the high-risk group confirms their contribution to predisposition and progression of atherosclerosis in the Kazakhstani population.

**Conclusion:** An analysis of a Kazakh cohort of patients with atherosclerosis revealed a correlation between the level of cardiovascular risk and the accumulation of P and LP variants in genes regulating lipid metabolism, in particular *APOE*, *SLC22A5*, *LDLR* and *LPL*. The increase in the number of such variants, as well as the high frequency of VUS, emphasize the genetic determinacy of hyperlipidemia and the progression of atherosclerosis. The results of the study substantiate the need to integrate genetic screening into the risk stratification system and develop personalized strategies for the prevention of cardiovascular diseases in Kazakhstan.

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