WHOLE EXOME SEQUENCING IDENTIFIES RARE NR1H3 VARIANTS LINKED TO FATTY LIVER AND ATHEROSCLEROSIS

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Background: *NR1H3* encodes Liver X Receptor- α (LXRα), which is a nuclear receptor regulating cholesterol efflux, lipid metabolism and inflammation. Impaired function of NR1H3 in the liver leads to hypertriglyceridemia and hepatic steatosis. Moreover, inactivation of the gene in macrophages increases inflammatory signaling that causes atherogenesis. This dual action of LXRα becomes a reason of fatty liver and cardiovascular disease. Human studies confirm that rare damaging *NR1H3* mutations cause hepatic cholesterol accumulation, inflammation and fibrosis, whereas common variants have been associated with carotid atherosclerosis.

Materials and Methods: The aim of this study is to investigate the role of *NR1H3* variants in the development of hepatic steatosis and atherosclerosis in a Kazakhstani cohort. 401 subjects were included with documented CVD. Whole exome sequencing was performed to analyze LXRα variants prevalence. Furthermore, clinical, biochemical, and imaging data (lipid profile, FibroScan, echocardiography, angiography) were analyzed to characterize phenotype– genotype correlations.

Results: Whole exome sequencing identified two patients aged 57 and 58, with likely pathogenic *NR1H3* variants (rs74842890, rs1591127791). Patients have type 2 diabetes and serious hepatic abnormalities. FibroScan revealed severe steatosis in both patients, with moderate fibrosis in one and mild in the other. The lipid profiles showed elevated LDL-C and high triglycerides level. Moreover, one patient exhibited an extremely high Lp(a) level at 178 mg/dL. Both patients demonstrated normal ejection fraction, though one case showed reduced strain. Clinically, two of them had documented atherosclerosis disease with very high risk.

Conclusion: These findings show correlation of *NR1H3* variants with phenotype of fatty liver, dyslipidemia, diabetes and atherosclerosis. Even with a small number of subjects, the results suggest impaired LXRα function may cause combined hepatic and cardiovascular pathology. **Acknowledgements:** Supported by the Committee of Science of the Ministry of Science and Higher Education of Republic of Kazakhstan (*AP23490249*), (*AR19677442*), (*BR24993023*), (*BR24992841*), (*BR21881970*) and Nazarbayev University CRP (*211123CRP1608*).

Key words: Atherosclerosis, Liver X Receptor-α, hepatotoxicity, inflammation