Abstract: P156

Genetic causes of hypercholesterolaemia among participants of epidemiological study

Authors:
N Shcherbakova\(^1\), A Ershova\(^1\), A Zharikova\(^1\), A Kiseleva\(^1\), S Shalnova\(^1\), S Boytsev\(^2\), O Drapkina\(^1\), A Meshkov\(^1\), \(^1\)National Research Center for Preventive Medicine - Moscow - Russian Federation, \(^2\)Cardiology Research and Production Center - Moscow - Russian Federation,

Topic(s):
Basic Science - Vascular Biology and Physiology: Genetics, Epigenetics, ncRNA

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S41

Introduction. Familial hypercholesterolemia (FH) is a monogenic autosomal dominant disease accompanied by an increase in the level of low-density lipoprotein cholesterol in the blood and caused by mutations in one of three genes (LDLR, APOB and PCSK9). In the patients who are mutation negative, the clinical phenotype can be associated with an accumulation of common small-effect LDL cholesterol (LDL-C)-raising alleles, in the remaining cases mutation in a novel gene may be present.

The aim of the study was a molecular genetic analysis of the causes of increased levels of low-density lipoproteins in patients with a clinical diagnosis of familial hypercholesterolemia detected during the epidemiological study.

Materials and methods. The sample of our study consisted of participants from multicenter epidemiological prospective study of cardiovascular risk factors and diseases in three regions (4978 participants in total, aged 25-64). All participants who had LDL-C higher than 4.9 mmol/l and who had LDL-C less than or equal to 4.9 mmol/l but had statin therapy were examined and interviewed by experts in FH (according to Dutch Lipid Clinic Network Score). Whole-exome sequencing of 42 participants diagnosed definite or probable FH were performed. After the primary bioinformatics had been done in due standart pipelines, filtering and prioritisation of the variants in 23 genes previously associated with the lipid metabolism was performed. Among mutation negative patients the accumulation of common small-effect LDL-C-raising alleles was estimated and compared to the participants from other sub-study with the different levels of LDL-C and performed exome sequencing.

Results. Pathogenetic or probably pathogenetic variants in one of the three genes associated with familial hypercholesterolemia were identified in 11% of patients. In new recently identified genes causing FH pathogenetic or probably pathogenic variants were found in 7% of cases. In the remaining cases lipid genetic score was higher (p-value = 2.727e-05) than in sequenced participants who had LDL-C less than or equal to 4.9 mmol/l from other epidemiological sub-study.

Conclusions. In majority of patients with diagnosis of FH from epidemiological study no mutation was found in common FH-causing genes, it is most likely to be a polygenic cause for the clinical presentation.