TARGETED SEQUENCING REVEAL TWO PATHOGENIC MUTATIONS IN LDLR AND APOE GENES IN PATIENT WITH FAMILY HYPERCHOLESTEROLEMIA: CASE REPORT

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Familial hypercholesterolemia (FH) is a serious inherited disorder that can lead to early development of cardiovascular disease (CVD) due to the high blood cholesterol levels. In our study, we identified in FH patient likely pathogenic variant of *LDLR* and *APOE* genes. Interest in the homozygous state of FH is understandable given its rarity and severe health consequences. The homozygous state, when both LDL receptor alleles mutated, demonstrates even higher cholesterol levels and an earlier and more severe clinical course compared with the heterozygous state. In our study, we report an interesting case of homozygous FH due to its rare prevalence.

Patient U., 16 years old, woman, admitted to the National Research Cardiac Surgery Center (NRCC), was diagnosed with FH, congenital heart disease (CHD), bicuspidal aortic valve (AV) type 1. Both parents (mother and father) were included for reliable analysis. DNA was isolated from the venous blood sample by using the column method of QIAamp DNA Mini Kit. Targeted NGS using TruSight Cardio panel for 174 genes was performed on MiSeq, Illumina. Identified genetic variants were classified according to the ACMG guidelines. Pathogenic variants were validated by Sanger sequencing. Additionally, databases of the VarSome and ClinVar were used for analysis.

Sequencing of 96 genes and bioinformatics analysis identified 2 likely pathogenic variants - C526T:p.R176C in *APOE* and G295A:p.E99K in *LDLR* gene, 4 uncertain significance variants in *APOB, TTN, COL3A1, NOTCH1* and 90 benign variants in *APOB*, *TTN*, *LAMA4*, *MYPN*, *DMD*. *LDLR* (G295A:p.E99K) and *APOE* (C526T:p.R176C) were validated and confirmed by Sanger sequencing in patients and her father and mother.

The main function of the *APOE* gene is to make the protein apolipoprotein E, which is involved in fat metabolism. In our study, the patient had a heterozygous variant of CT polymorphism rs7412 in the *APOE* gene, which indicates the presence of a possible disorder of fat metabolism. *LDLR* gene encodes a protein called low-density lipoprotein receptor, which is responsible for the uptake of cholesterol-carrying lipoprotein particles in cells. In our study, a patient with a homozygous AA variant of the *LDLR* gene was found to be pathogenic. Disruption of the uptake of cholesterol-carrying lipoprotein particles in cells can have serious consequences for the body. This can lead to cholesterol accumulation in the blood and tissues, which in turn can contribute to the development of atherosclerosis and other CVD. We found that both parents had a heterozygous genotype of G295A:p.E99K in *LDLR* gene; and mother had a heterozygous genotype and father had a homozygous genotype of C526T:p.R176C in *APOE* gene.

In our study, we found the genetic mutations - two likely pathogenic genetic variants *LDLR* (G295A:p.E99K) and *APOE* (C526T:p.R176C) associated with FH in patient with clinical phenotype of FH using TruSight Cardio targeted panel of 96 genes. Genetic testing using targeted NGS or whole exome sequencing would be useful for right diagnosis and might improve personalize treatment for these patients. To identify other genes associated with FH whole exome sequencing can be recommend.

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