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A Pedigree-Based Genetic Study of Familial Hypercholesterolemia

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ABSTRACT

Introduction: Familial hypercholesterolemia (FH) is a leading risk factor for premature atherosclerotic cardiovascular disease. Our study was designed to assess genetic variants in families clinically diagnosed with hyper-cholesterolemia.

Methods and Materials: DNA from three unrelated families with probable or possible FH based on Simon Broom criteria, referred for genetic counseling, were analyzed using whole exome sequencing followed by bioinformatics analysis. All variants were confirmed by PCR and Sanger sequencing using specific primers for each family.

Results: Data analysis showed three different mutations within the LDLR gene in the two unrelated patients. Proband I.1 from the F1 family was heterozygous for splice mutation (c.2547+5GA) in intron 17 of the LDLR gene. In contrast, proband II.2 from the F11 family demonstrated compound heterozygote variants within the *LDLR* gene: c.443GA in exon 4 and c.1592TG in exon 11, both of which were present in all family members. We found a novel heterozygous variant c.46GC within the *TXNIP* gene. Moreover, additional analysis of genomic data revealed rs3846662 in the *HMGCR* gene in F1 and SLCO1B1 rs4149056 in F7 related to statin efficacy.

Conclusion and Discussion: Cascade familial screening based on genetic findings can be considered in clinical practice to identify and treat those individuals with unrecognized FH. According to the site of mutations, study patients had different phenotype severity in clinical presentations. Besides identifying disease-causing genes, analyzing whole exome sequencing data with pharmacogenetics insights may enhance therapeutic decision-making. This approach will create opportunities for the development of targeted therapies in the near future.

Keywords: Familial hypercholesterolemia, LDLR, Xanthomatosis

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