Identification of a novel heterozygous missense mutation in low-density lipoprotein receptor gene (LDLR) p.(Met652Thr) in an Emirati family with familial hypercholesterolaemia (FH), observed genotype-phenotype correlations and pharmacotherapeutic approaches

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Background

• FH is an autosomal dominant disorder of low-density lipoprotein (LDL) metabolism, often associated with functional variants in LDLR, APOB, PCSK9 and LDLRAP1 genes.
• In the states of The Gulf Co-operation Council, cardiovascular disease (CVD) is often diagnosed at a younger age and is the leading cause of mortality.
• Early genetic diagnosis and treatment of FH is important for risk stratification and aggressive targeted treatment to lower LDL-cholesterol (LDL-C) in affected individuals, to reduce the risk of arterial disease and premature CVD outcomes.

Aims

1. To identify FH-causing genetic variant(s) in this family including an individual diagnosed in adolescence and an individual with premature CHD.
2. To treat genetically diagnosed FH-positive individuals with lipid lowering therapy at an earlier age.

Methods

• Detailed family history including cardiovascular events in first-degree relatives were recorded and clinical and biochemical data were collected.

Results

Figure 1: Pathophysiology of heterozygous familial hypercholesterolaemia. PCSK9, proprotein convertase subtilisin/kexin type 9; APOB, apolipoprotein B. Adapted from (3).

Figure 2: Pedigree of a family with FH. Squares and circles indicate males and females respectively; T2DM, type 2 diabetes mellitus; HTN, hypertension; yr, years; Dx, diagnosed.

Structure of LDLR

Figure 3: (A) Next generation sequencing detected compound heterozygous mutations in the proband-a non-deleterious p.[Thr62Met] variant (as previously shown in the literature) and a likely pathogenic p.(Met652Thr) missense variant. (B) Targeted mutational analysis by Sanger sequencing in affected family members.

Bioinformatic analysis:

• In silico predictions of the damaging effect at the protein level of the maternally inherited mutation LDLR p.(Met652Thr) was assessed using PolyPhen, SIFT and SNAP3D and predicted to be deleterious, not tolerated and probably damaging respectively, thus is most likely pathogenic.

Discussion

• We describe a family with clinical and biochemical features characteristic of FH, carrying a novel likely pathogenic heterozygous LDLR mutation.
• Treatment with a combination of high dose statin (Rosuvastatin 40mg) and Ezetimibe 10 mg resulted in excellent control with a reduction of LDL levels to near normal in the proband and her affected mother and sister.

Conclusion

• This study highlights the importance of cascade screening especially in a pre-symptomatic early age as demonstrated here in the nephew who was asymptomatic and not treated prior to genetic diagnosis.

References


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