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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.

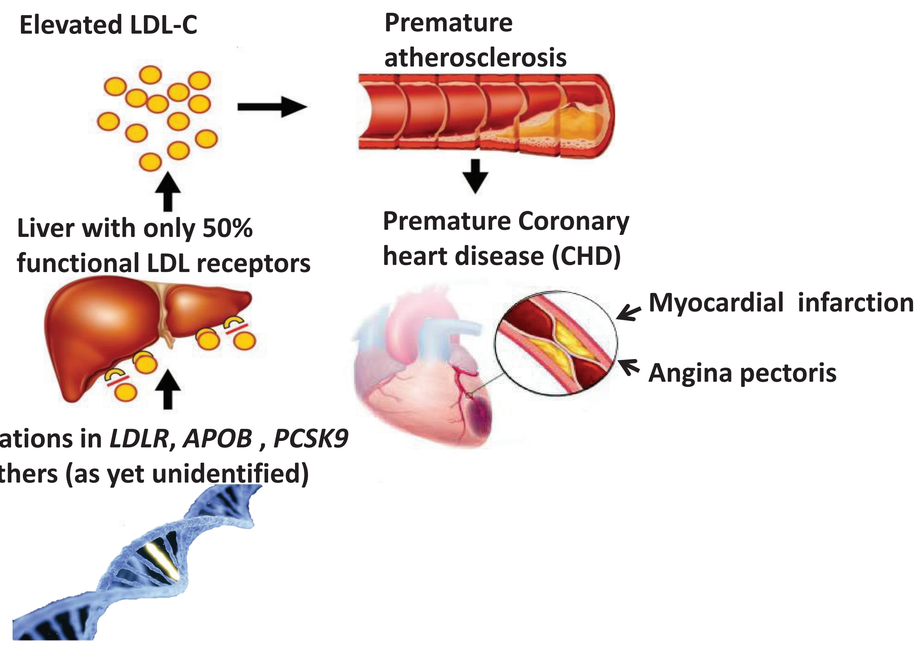

Figure 1: Pathophysiology of heterozygous familial hypercholesterolaemia. PCSK9, proprotein convertase subtilisin/kexin type 9; APOB, apolipoprotein B. Adapted from (1).

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.

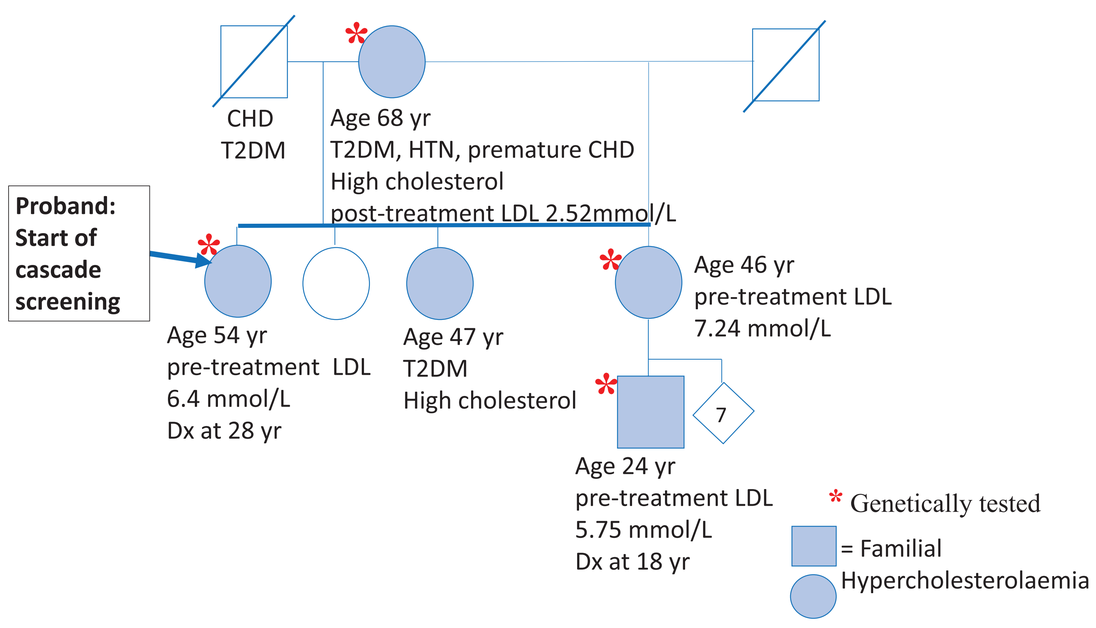

Figure 2: Pedigree of a family with FH. Squares and circles indicate males and females respectively; T2DM, type 2 diabetes mellitus; HTN, hypertension; yr, years; Dx, diagnosed.

Results

Sequence analysis

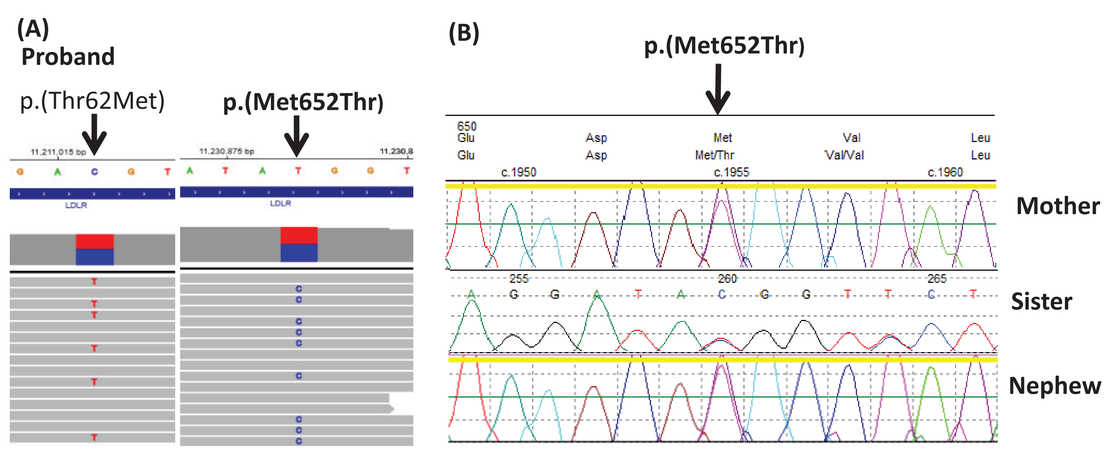

Figure 3: (A) Next generation sequencing detected compound heterozygous mutations in the proband: a non-deleterious p.(Thr62Met) variant (as previously shown in the literature) and a likely pathogenic p.(Met652Thr) missense variant. **(B)** Targeted mutational analysis by Sanger sequencing in affected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

Structure of LDLR

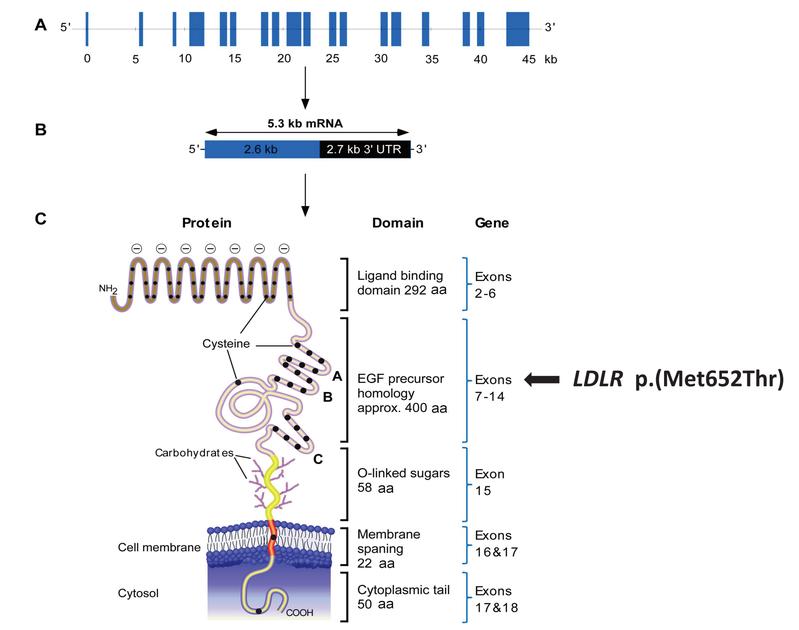

Figure 4: Schematic representation of the **(A)** human LDLR gene, exons are marked blue, size in kb is listed below the figure; **(B)** mRNA and **(C)** LDLR domains. UTR: untranslated region of the mRNA transcript. Adapted from (2).

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 SNPs3D 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

1. B. G. Nordestgaard *et al.,* FH is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. https://doi.org/10.1093/eurheartj/eht273
2. J. L. Goldstein *et al.* In: The Metabolic and Molecular Basis of Inherited Diseases. DOI: 10.1036/ommbid.149

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Conflict of interest: None declared.

ESPE European Society for Paediatric Endocrinology