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: Familial Hypercholesterolaemia (FH) is a common autosomal dominant disorder of low-density lipoprotein (LDL) metabolism characterised by elevated levels of plasma LDL-cholesterol (LDL-C), accelerated atherosclerosis and premature cardiovascular disease (CVD). In the Gulf Co-operation Council states, CVD is often diagnosed at a younger age and is the leading cause of mortality. As such, early genetic diagnosis and treatment of FH is important for risk stratification and aggressive targeted treatment to lower 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 CVD. Successful genetic diagnosis will allow subsequent cascade screening in relatives.

2.To treat genetically proven FH-positive individuals with lipid lowering therapy at an earlier age.

Methods: Detailed family history was recorded and clinical and biochemical data were collected. Genomic DNA from a 54 year old female with hypercholesterolaemia (pre-treatment LDL-C=6.4mmol/L) was tested for variants in the known FH genes by next generation sequencing, followed by targeted mutational analysis by Sanger sequencing in affected family members.

Results: DNA sequencing of *LDLR* in the proband detected compound heterozygous mutations: a non-deleterious p.(Thr62Met) variant and a likely pathogenic p.(Met652Thr) missense variant; the latter was demonstrated to be maternally inherited.

Familial segregation analysis was performed; results demonstrated that the p.(Met652Thr) mutation is inherited and segregates with the disease phenotype and lipid profiles in the mother, sister and a 24 year old nephew of the proband. Prediction of the damaging effect at the protein level of the mutation p.(Met652Thr) was assessed using 3 *in silico* tools and predicted to be deleterious, not tolerated and probably damaging and thus is most likely pathogenic. LDL-C levels dropped significantly to near normal levels in response to Statin/Ezetimibe combination therapy in both proband and her mother.

Conclusions: We describe an Emirati family with clinical and biochemical features characteristic of FH, carrying a novel heterozygous *LDLR* mutation. This study highlights the importance of genetic diagnosis especially in a pre-symptomatic early age as demonstrated here in the nephew who was asymptomatic and not treated prior to genetic testing. The knowledge of the underlying genetic mutation will aid in effective treatment, family member testing, genetic counseling, and a better understanding of the effect of *LDLR* mutations on the response to pharmacological treatment to reduce the risk of morbidity and mortality.