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Entitled

CEULLULAR BASIS OF MISSENSE VARIANTS CAUSING FAMILIAL HYPERCHOLESTEROLEMIA IN UAE

by

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Abstract

Familial hypercholesterolemia is an autosomal dominant disorder characterized by elevated levels of low density lipoprotein (LDL) carrying cholesterol in the blood. FH is mainly caused by mutations in the gene encoding the low density lipoprotein receptor (LDLR) which causes altered lipid metabolism. LDLR is synthesized and initially modified by glycosylation in the endoplasmic reticulum (ER) and transferred to the plasma membrane by Golgi to carry out LDL clearance from the blood stream. Defective LDLR can therefore lead to increased levels of LDL in the blood which may lead to atherosclerosis and premature coronary artery diseases.

For the past few years, cardiovascular diseases have been found to be the leading cause of morbidity and mortality in UAE. In this study, I evaluated the pathogenesis of a group of seven missense LDLR variants (p. Cys167Phe), (p. Asp178Asn), (p. Glu277Lys), (p. Gly314Arg), (p. His327Tyr), (p. Met652Thr) and (p. Arg814Gln) identified in Emirati patients with suspected familial hypercholesterolemia (FH). The aim of this project was to generate the identified missense LDLR variants in mammalian expression vector, establish their subcellular localization using confocal microscopy and evaluate their glycosylation status. I found that several of these variants resulted in an apparent partial retention of the LDLR mutants in the ER and hence their possible failure to pass the ER quality control system. Several of the studied missense mutants will be further studied in the future to investigate their exact pathogenicity mechanism and cellular impact on the ER and endoplasmic reticulum associated protein degradation (ERAD).

Keywords: Familial hypercholesterolemia (FH), low density lipoprotein receptor (LDLR), premature coronary artery disease (CAD), endoplasmic reticulum associated protein degradation (ERAD). Endoplasmic reticulum (ER).