Poster Abstract Submission

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Research Title	Elucidation of Familial Hypercholesterolemia pathogenesis in the UAE

Abstract:

Title: Elucidation of Familial Hypercholesterolemia pathogenesis in the UAE. Author(s): *Aseel A., Jawabri1, **Divya S., Varghese1, ***Hinda Daggag2, ***Bindu Shobi2, ***Antoine Rimbert3, ***Bassam R., Ali1 Affiliation: 1Department of Genetics and Genomics, College of Medicine and Health Sciences, UAE University, UAE. 2Imperial College Diabetes Center, Abu Dhabi, UAE. 3University of Groningen, Netherlands Introduction: Familial Hypercholesterolemia (FH) is an autosomal dominant disorder characterized by elevated levels of LDL-C in the blood due to mutations in Low-Density Lipoprotein receptors (LDLR). Together, with our collaborators at Imperial College Diabetes Center in Abu Dhabi Groningen University in the Netherlands, we identified a list of ten LDLR missense variants in Emiratis. We propose that misfolding of these variants cause ER retention which induces Endoplasmic Reticulum Associated Degradation (ERAD). Aims and Objectives: To assess the subcellular localization, trafficking, and degradation of ten LDLR missense variants (p.Cys167Phe, p.Asp178Asn, p.Cys243Tyr, p.Glu277Lys, p.Gly314Arg, p.His327Tyr, p.Asp477Asn, p.Asp622Gly, p.Arg744Gln, and p.Arg814Gln) present in Emiratis with suspected FH. Materials and Methods: The above-mentioned LDLR missense variants were generated by site-directed mutagenesis and were transiently transfected into HeLa, HEK293T, and HRD1-KO cells. For subcellular localization, transiently transfected HeLa cells were fluorescently labeled with ER and plasma membrane markers. Transiently transfected HEK293T and HRD1-KO cells were used to analyze the overexpression and glycosylation profiles of the generated LDLR variants by Endoglycosidase H assay and western blot analysis. Results: Confocal laser microscopy revealed that p.Asp622Gly and p.Arg744Gln are ER retained while LDLR WT and the other variants are localized with the plasma membrane. Western blot analysis and Endoglycosidase H assay confirmed full retention, misfolding, and proteasomal degradation of p.Asp622Gly and p.Arg744Gln. Conclusion: We can conclude that ER retention and misfolding of p.Asp622Gly and p.Arg744Gln induce ERAD and are subjected to proteasomal-mediated degradation.