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Molecular genetics of familial hypercholesterolemia in Israel revisited

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Objective: Familial hypercholesterolemia (FH) is an autosomal dominant disease caused by mutations in the genes for LDL receptor (LDLR), apolipoprotein B (APOB) and Proprotein convertase subtilisin/kexin type9 (PCSK9). The purpose of the current investigation was to define the current spectrum of mutations causing FH in Israel.

Methods: New families were collected through the MEDPED (Make Early Diagnosis Prevent Early Death) FH program. Molecular analysis of the LDLR, PCSK9 and APOB genes were done using High Resolution Melt and direct sequencing in 67 index cases. A 6-SNP LDL-C gene score calculation for polygenic hypercholesterolaemia was done using TaqMan genotyping.

Results: Mean serum cholesterol was 7.48±1.89mmol/L and the mean serum LDL-C was 5.99±1.89mmol/L. Mutations in the LDLR and APOB gene were found in 24 cases (35.8%), with 16 in LDLR, none in PCSK9 and one, p.(R3527Q) in the APOB gene, which is the first APOB mutation carrier identified in the Israeli population. Of the LDLR mutations, two were novel; p.(E140A) and a promoter variant, c.-191C>A. The c.2479G>A p.(V827I) in exon 17 of the LDLR gene was found in 8 patients (33.3% of the mutations) with modestly elevated LDL-C but also in a compound heterozygous patient with a clinical homozygous FH phenotype, consistent with this being a "mild" FH-causing variant. A significantly higher 6-SNP LDL-C score was found in mutation-negative cases compared with a normal Caucasian cohort (p=0.03), confirming that polygenic inheritance of common LDL-C raising SNPs can produce an FH phenocopy.

Conclusions: The results indicate a different spectrum of genetic causes of FH from that found previously, in concordance with the heterogeneous and changing origins of the Israeli population, and confirm that a polygenic cause is also contributing to the FH phenotype in Israel.