Familial hypercholesterolemia

Familial hypercholesterolemia is a genetic disorder. It is caused by a defect on chromosome 19. The defect makes the body unable to remove low density lipoprotein (LDL, or bad) cholesterol from the blood. This results in a high level of LDL in the blood.

It is caused by pathogenic variants in LDLR, APOB, PCSK9 and APOE genes. Ghaleb et al. sought to identify new candidate genes responsible for the ADH phenotype in patients without pathogenic variants in the known ADH-causing genes by focusing on a French family with affected and non-affected members who presented a high ADH polygenic risk score (wPRS). Linkage analysis, whole exome and whole genome sequencing resulted in the identification of variants p.(Pro398Ala) in CYP7A1, p.(Val1382Phe) in LRP6 and p.(Ser202His) in LDLRAP1. A total of 6 other variants were identified in 6 of 160 unrelated ADH probands: p.(Ala13Val) and p.(Aps347Asn) in CYP7A1; p.(Tyr972Cys), p.(Thr1479Ile) and p.(Ser1612Phe) in LRP6; and p.(Ser202LeufsTer19) in LDLRAP1. All six probands presented a moderate wPRS. Serum analyses of carriers of the p.(Pro398Ala) variant in CYP7A1 showed no differences in the synthesis of bile acids compared to the serums of non-carriers. Functional studies of the four LRP6 mutants in HEK293T cells resulted in contradictory results excluding a major effect of each variant alone. Within the family, none of the heterozygous for only the LDLRAP1 p.(Ser202His) variant presented ADH. Altogether, each variant individually does not result in elevated LDL-C; however, the oligogenic combination of two or three variants reveals the ADH phenotype [1)]

1)
Ghaleb Y, Elbitar S, Philippi A, El Khoury P, Azar Y, Andrianirina M, Loste A, Abou-Khalil Y, Nicolas G, Le Borgne M, Moulin P, Di-Filippo M, Charrière S, Farnier M, Yelnick C, Carreau V, Ferrières J, Lecerf JM, Derksen A, Bernard G, Gauthier MS, Coulombe B, Lütjohann D, Fin B, Boland A, Olaso R, Deleuze JF, Rabès JP, Boileau C, Abifadel M, Varret M. Whole Exome/Genome Sequencing Joint Analysis of a Family with Oligogenic Familial Hypercholesterolemia. Metabolites. 2022 Mar 18;12(3):262. doi: 10.3390/metabo12030262. PMID: 35323704; PMCID: PMC8955453.