Familial hypercholesterolaemia

Specimen type  EDTA
Referral reason  Diagnostic testing
Genes tested  LDLR, APOB, PCSK9, LDLRAP1
Heterozygous variant detected:
LRG_274t1(LDLR):c.654_656delTGG, p.(Gly219del)

Interpretation
A heterozygous pathogenic variant has been detected in the LDLR gene. This result would support a clinical diagnosis of LDLR-associated familial hypercholesterolaemia (FH).

See further comments below.

Comments
Genetic counselling is recommended to discuss the clinical and familial implications of this result. Genetic testing can be offered on the basis of this result to detect FH in first and second degree family members, and is available from this laboratory at no out-of-pocket cost. Test requests for family members must include a reference to the previously tested individual and/or the specific variant(s) detected.

Variant information:
Gly219del is an in-frame change. It is also known as Gly197del. This variant has been identified in multiple affected individuals in the literature. It is especially prevalent in Eastern European Ashkenazi Jewish populations (PMID 1867200, 9744476, 11309683). This variant may lead to impaired intracellular transport of the encoded LDL receptor (PMID 2088165).

Test information:
Massively parallel sequencing of coding exons and exon/intron boundaries of selected genes to a depth of >50X was performed using a Roche Hybridization Capture kit on the MiSeq Sequencing system. The following genes have been analysed for single nucleotide variants: LDLR (LRG_274t1), APOB (NM_000384.2), PCSK9 (LRG_275t1), and LDLRAP1 (LRG_276t1). Copy number variant analysis has been performed for LDLR only, using MLPA Probemix P062. Variants are classified using ACMG/AMP guidelines (PMID 25741868). Benign and likely benign variants are not reported. Unless otherwise specified, this test will not detect copy number variants, gene rearrangements, variants in regulatory and deep intronic regions, or variants in regions with sequence homology issues.

Genetic test results may have significant implications for both the patient and relatives. Corroboration of this result by reference to other clinical or laboratory information or by repeat testing may be warranted.

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