

Variant: *NM_000527.5(LDLR):c.1133A>C (p.Gln378Pro)*

Version: 1.0

CA023422 [↗](#)

183108 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: fca19a2f-0ac0-4e25-92fc-299cd965e460

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HGVS expressions

NM_000527.5:c.1133A>C

NM_000527.5(LDLR):c.1133A>C (p.Gln378Pro)

NC_000019.10:g.11111586A>C

CM000681.2:g.11111586A>C

NC_000019.9:g.11222262A>C

CM000681.1:g.11222262A>C

NC_000019.8:g.11083262A>C

NG_009060.1:g.27206A>C

ENST00000252444.10:c.1391A>C

ENST00000559340.2:c.1133A>C

ENST00000560467.2:c.1013A>C

ENST00000558518.6:c.1133A>C

ENST00000252444.9:c.1387A>C

ENST00000455727.6:c.629A>C

ENST00000535915.5:c.1010A>C

ENST00000545707.5:c.752A>C

ENST00000557933.5:c.1133A>C

ENST00000558013.5:c.1133A>C

ENST00000558518.5:c.1133A>C

ENST00000560173.1:n.132A>C

ENST00000560467.1:c.613A>C

NM_000527.4:c.1133A>C

NM_001195798.1:c.1133A>C

NM_001195799.1:c.1010A>C

NM_001195800.1:c.629A>C

NM_001195803.1:c.752A>C

NM_001195798.2:c.1133A>C

NM_001195799.2:c.1010A>C

NM_001195800.2:c.629A>C

NM_001195803.2:c.752A>C

Likely Pathogenic

Met criteria codes **6**

PP3

PP4

PM3

PM2

PS4_Moderate

PP1_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1133A>C (p.Gln378Pro) variant is classified as likely pathogenic for Familial Hypercholesterolemia by applying evidence code PM2, PS4_Moderate, PM3, PP1_Moderate, PP3, and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows: PM2: PopMax MAF = 0.00001760 (0.001760%) in European (non-Finnish) exomes (gnomAD v2.1.1). PP3: REVEL = 0.754. PP1_moderate: Variant segregates with FH phenotype in at least 4 informative meioses from 1 family from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation). PS4_moderate: Variant meets PM2 and is identified in at least 6 unrelated index cases: 1 case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with Simon Broome definite criteria; 1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with Dutch lipid clinic network >=6; 1 case from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory with Dutch lipid clinic network >=6; 1 case from South Africa in PMID: 9664576; 1 case from Spain in PMID: 15241806; 1 case from Italy in PMID: 23375686. PM3: PMID: 27784735 - variant identified in two children with homozygous FH: in one patient confirmed in trans with LDLR p.Ile792Thr and in the second patient confirmed in trans with a LP/P LDLR exonic deletion; given this exonic deletion is LP/P, PM3 applies. PP4: Variant meets PM2 and is identified in >1 index case who fulfill clinical criteria for FH, after alternative causes of high cholesterol were excluded. Note: BS3 not met: PMID: 32015373 - Level 1 assay: Heterologous cells, FACS assays - results - cell surface LDLR (96%), binding (101%) were normal; LDL uptake (80%) activity is not above 90%, so BS3 not met. This result suggests this variant may only have a minor effect (i.e. 20% reduction in LDL uptake), although this is not insignificant.

Met criteria codes

PP3			REVEL = 0.754. It is above 0.75
PP4			Variant meets PM2 and is identified in >1 index case who fulfill clinical criteria for FH, after alternative causes of high cholesterol were excluded.
PM3			PMID: 27784735 - variant identified in two children with homozygous FH: in one patient confirmed in trans with LDLR p.Ile792Thr and in the second patient confirmed in trans with a LP/P LDLR exonic deletion; given this exonic deletion is LP/P, PM3 applies.
PM2			PopMax MAF = 0.00003 (0.003%) in European non-Finnish exomes (gnomAD v2.1.1).
PS4_Moderate			Variant meets PM2 and is identified in at least 6 unrelated index cases: - 1 case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with Simon Broome definite criteria - 1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with Dutch lipid clinic network >=6 - 1 case from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory with Dutch lipid clinic network >=6 -1 case from South Africa in PMID: 9664576 -1 case from Spain in PMID: 15241806 -1 case from Italy in PMID: 23375686
PP1_Moderate			Variant segregates with FH phenotype in at least 4 informative meioses from 1 family from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation)

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