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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
Approved on: 2022/5/6
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HGVS expressions

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

PM3 PM2 PP1_Moderate PS4_Moderate PP3 PP4

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specifications for this VCEP

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 meiosis 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

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).
PP1_Moderate	✔	Variant segregates with FH phenotype in at least 4 informative meiosis 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
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.

Curation History

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