

Variant: NM_000527.5(LDLR):c.1277T>C (p.Leu426Pro)

Version: 1.0

CA10585383 [↗](#)

251763 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 4dcc4075-4393-4110-9cc8-30a1485a0552

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HGVS expressions

NM_000527.5(LDLR):c.1277T>C (p.Leu426Pro)

NM_000527.5:c.1277T>C

NC_000019.10:g.11113368T>C

CM000681.2:g.11113368T>C

NC_000019.9:g.11224044T>C

CM000681.1:g.11224044T>C

NC_000019.8:g.11085044T>C

NG_009060.1:g.28988T>C

ENST00000252444.10:c.1535T>C

ENST00000559340.2:c.1277T>C

ENST00000560467.2:c.1157T>C

ENST00000558518.6:c.1277T>C

ENST00000252444.9:c.1531T>C

ENST00000455727.6:c.773T>C

ENST00000535915.5:c.1154T>C

ENST00000545707.5:c.896T>C

ENST00000557933.5:c.1277T>C

ENST00000558013.5:c.1277T>C

ENST00000558518.5:c.1277T>C

ENST00000560173.1:n.276T>C

ENST00000560467.1:c.757T>C

NM_000527.4:c.1277T>C

NM_001195798.1:c.1277T>C

NM_001195799.1:c.1154T>C

NM_001195800.1:c.773T>C

NM_001195803.1:c.896T>C

NM_001195798.2:c.1277T>C

NM_001195799.2:c.1154T>C

NM_001195800.2:c.773T>C

NM_001195803.2:c.896T>C

Likely Pathogenic

Met criteria codes 6

PP1_Moderate PS4_Moderate PP3
PP4 PM2 PM3

Not Met criteria codes 15

PS1 PS3 BA1 BS1 BS4 BS3
PM1 PM5 PM4 BS2 BP7
BP4 BP3 BP2 PVS1

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

- Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2
- PDF
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1277T>C (p.Leu426Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4_Moderate, PM2, PM3, PP1_Moderate, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on January 31, 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.00002229 (0.0022%) in East Asian exomes (gnomAD v4.1.0). So, PM2 is met. PP3: REVEL=0.883. It is above 0.75, so PP3 is met. PS4_Moderate, PP4: Variant meets PM2 and is identified in 9 unrelated index cases (2 cases with DLCN score >=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France; 5 cases with definite FH by DLCN criteria from U4M - Lille University & CHRU Lille, Université de Lille, France, published on ClinVar; 1 case with possible/definite FH by Simon-Broome criteria in PMID 33269076 (Miroshnikova et al., 2021); 1 case with DLCN score 9 in PMID 9763532 (Mak et al., 1998)). PP1_Moderate: Variant segregates with FH phenotype in 4 informative meioses in 1 family from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France: 4 affected family members have the variant. PM3: A homozygous proband is reported from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies with LDL of 860 mg/dL.

Met criteria codes

PP1_Moderate		✓	Variant segregates with FH phenotype in 4 informative meioses in 1 family from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies. So, PP1_Moderate is met.
PS4_Moderate		✓	Variant meets PM2 and is identified in 9 unrelated index cases (2 cases with DLCN criteria>=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies; 5 cases with DLCN criteria of definite FH fromU4M - Lille University & CHRU Lille, Université de Lille, published on ClinVar, 1 case with Simon-Broome criteria of possible/definite FH in PMID: 33269076 (Miroshnikova et al., 2021); 1 case with DLCN 9 in PMID: 9763532 (Mak et al., 1998)). So, PS4_Moderate is met.
PP3		✓	REVEL=0.883. It is above 0.75, so PP3 is met.
PP4		✓	Variant meets PM2 and is identified in 7 unrelated index cases who fulfill clinical criteria for FH from several labs (see PS4 for details), after alternative causes of high cholesterol were excluded. So, PP4 is met.
PM2		✓	PopMax MAF = 0.00002229 (0.0022%) in East Asian exomes (gnomAD v4.1.0). So, PM2 is met.

PM3			A homozygous proband is reported from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies with LDL of 860. So, PM3 is met.
Not Met criteria codes			
PS1			No other missense variant with the same amino acid change.
PS3			No data available.
BA1			PopMax MAF = 0.00002229 (0.0022%) in East Asian exomes (gnomAD v4.1.0).
BS1			PopMax MAF = 0.00002229 (0.0022%) in East Asian exomes (gnomAD v4.1.0).
BS4			No data available
BS3			No data available.
PM1			Not on exon 4. Not a cysteine residue.
PM5			1 other missense variants in the same codon: - NM_000527.5(LDLR):c.1277T>G (p.Leu426Arg) (ClinVar ID 1120245) - Likely pathogenic by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No in-frame deletions/insertions
BS2			No data available.
BP7			Not a synonymous (silent) variant
BP4			REVEL=0.883. It is above 0.5
BP3			No in-frame deletions/insertions
BP2			No evidence available
PVS1			Not a null variant

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