

Variant: *NM_000527.5(LDLR):c.811G>A (p.Val271Ile)*

Version: 1.0

CA023769 [↗](#)

189297 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 8b200ce4-e051-4069-bed7-419e0ce94047

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HGVS expressions

NM_000527.5:c.811G>A

NM_000527.5(LDLR):c.811G>A (p.Val271Ile)

NC_000019.10:g.11106681G>A

CM000681.2:g.11106681G>A

NC_000019.9:g.11217357G>A

CM000681.1:g.11217357G>A

NC_000019.8:g.11078357G>A

NG_009060.1:g.22301G>A

ENST00000252444.10:c.1069G>A

ENST00000559340.2:c.811G>A

ENST00000560467.2:c.811G>A

ENST00000558518.6:c.811G>A

ENST00000252444.9:c.1065G>A

ENST00000455727.6:c.314-711G>A

ENST00000535915.5:c.688G>A

ENST00000545707.5:c.430G>A

ENST00000557933.5:c.811G>A

ENST00000558013.5:c.811G>A

ENST00000558518.5:c.811G>A

ENST00000558528.1:n.326G>A

ENST00000560467.1:c.411G>A

NM_000527.4:c.811G>A

NM_001195798.1:c.811G>A

NM_001195799.1:c.688G>A

NM_001195800.1:c.314-711G>A

NM_001195803.1:c.430G>A

NM_001195798.2:c.811G>A

NM_001195799.2:c.688G>A

NM_001195800.2:c.314-711G>A

NM_001195803.2:c.430G>A

Uncertain Significance

Met criteria codes **4**

BP4 PP1 PP4 PM2

Not Met criteria codes **17**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BA1BS2BS1BS3BP3BP2

PVS1PS1PS2PS3PS4

PP3PM1PM3PM5PM4

PM6

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.811G>A (p.Val271Ile) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP1, PP4, and BP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.00011 (0.011%) in East Asian exomes+genomes (gnomAD v2.1.1). BP4: REVEL=0.33. It is below 0.5, splicing evaluation required. Functional data on splicing not available. A) not on limits. B) does not create GT. C) there is no GT nearby. Variant is not predicted to alter splicing. PP1: Variant segregates with FH phenotype in 3 informative meioses in 1 family from PMID 26036859 (Brønne I et al., 2016). 2 affected family members have the variant. PP4: Variant meets PM2 and is identified in 1 index case with DLCN score >=6 from PMID 26036859 (Brønne I et al., 2016: LDL-C 286 mg/dl and a history of premature CAD, DLCN=7).

Met criteria codes

BP4		✓	REVEL=0.33. It is below 0.5, splicing evaluation required. Functional data on splicing not available. A) not on limits. B) does not create GT C) there is no GT nearby Variant is not predicted to alter splicing. So, BP4 is met.
PP1		✓	Variant segregates with FH phenotype in 3 informative meioses in 1 families from PMID 26036859. 2 affected family members have the variant. So, PP1 is met.
PP4		✓	Variant meets PM2. PMID 26036859 (Brønne I et al) 2016, 1 patient who fulfill DLCN criteria of probable FH (LDL-C= 286 mg/dl and a history of premature CAD, DLCN=7). So, PP4 is met.
PM2		✓	PopMax MAF = 0.00011 (0.011%) in East Asian exomes+genomes (gnomAD v2.1.1). So PM2 is met.

Not Met criteria codes

BA1		✗	PopMax MAF = 0.00011 (0.011%) in East Asian exomes+genomes (gnomAD v2.1.1).
BS2		✗	No data available.
BS1		✗	PopMax MAF = 0.00011 (0.011%) in East Asian exomes+genomes (gnomAD v2.1.1).
BS3		✗	No functional study available.
BP3		✗	No in-frame deletions/insertions

BP2			No data available.
PVS1			Not a null variant
PS1			No other missense variant in the same codon.
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No functional study available.
PS4			Variant meets PM2 and is identified in 1 case from PMID 26036859.
PP3			REVEL=0.33. It is below 0.75, splicing evaluation required. Functional data on splicing not available. A) not on limits. B) does not create GT C) there is no GT nearby Variant is not predicted to alter splicing.
PM1			Not in exon 4. Not a cysteine residue.
PM3			No data available.
PM5			No other missense variant in the same codon.
PM4			No in-frame deletions/insertions
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
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