The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.1277T>G (p.Leu426Arg)

Version: 1.0

CA404084869

1120245 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 787b1bbb-1f79-47d7-8bbe-10a057c1522a
Approved on: 2025/1/31
Published on: 2025/3/9

HGVS expressions

NM_000527.5(LDLR):c.1277T>G (p.Leu426Arg)
NM_000527.5:c.1277T>G
NC_000019.10:g.11113368T>G
CM000681.2:g.11113368T>G
NC_000019.9:g.11224044T>G
CM000681.1:g.11224044T>G
NC_000019.8:g.11085044T>G
NG_009060.1:g.28988T>G
ENST00000252444.10:c.1535T>G
ENST00000559340.2:c.1277T>G
ENST00000560467.2:c.1157T>G
ENST00000558518.6:c.1277T>G
ENST00000252444.9:c.1531T>G
ENST00000455727.6:c.773T>G
ENST00000535915.5:c.1154T>G
ENST00000545707.5:c.896T>G
ENST00000557933.5:c.1277T>G
ENST00000558013.5:c.1277T>G
ENST00000558518.5:c.1277T>G
ENST00000560173.1:n.276T>G
ENST00000560467.1:c.757T>G
NM_000527.4:c.1277T>G
NM_001195798.1:c.1277T>G
NM_001195799.1:c.1154T>G
NM_001195800.1:c.773T>G
NM_001195803.1:c.896T>G
NM_001195798.2:c.1277T>G
NM_001195799.2:c.1154T>G
NM_001195800.2:c.773T>G
NM_001195803.2:c.896T>G

Likely Pathogenic

Met criteria codes 5

PS4_Supporting PP1 PP3 PP4 PM2

Not Met criteria codes 18

BA1 PM6 PM1 PM3 PM5 PM4 BS2 BS1 BS4 BS3 PS1 PS2 PS3 BP4 BP3 BP2 PVS1 BP7

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>G (p.Leu426Arg) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP1, PP3, PP4 and PS4_Supporting 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: This variant is absent from gnomAD (gnomAD v4.1.0). PP3: REVEL= 0.907. It is above 0.75, so PP3 is met. PS4_Supporting, PP4: Variant meets PM2. Identified in 3 unrelated cases (1 case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France with possible FH by Simon Broome criteria; 1 case with DLCN score of 6 from Lille University & CHRU Lille, France; 1 case with definite FH by Simon Broome criteria from Centre Hospitalo-Universitaire Xavier Bichat, Paris, France). PP1: Variant segregates with FH phenotype in 2 informative meioses identified by Centre Hospitalo-Universitaire Xavier Bichat, Paris.

Met criteria codes

PS4_Supporting	✔	Variant meets PM2. Identified in 3 unrelated cases (1 case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France with Simon Broome criteria of possible FH, 1 case from Lille University & CHRU Lille with DLCN of 6, and 1 case from Centre Hospitalo-Universitaire Xavier Bichat, Paris with Simon Broome criteria of definite FH.) So, PS4_Supporting is met.
PP1	✔	Variant segregates with FH phenotype in 2 informative meioses identified by Centre Hospitalo-Universitaire Xavier Bichat, Paris. So, PP1 is met.
PP3	✔	REVEL= 0.907. It is above 0.75, so PP3 is met.
PP4	✔	Variant meets PM2 and is identified in 3 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	✔	This variant is absent from gnomAD (gnomAD v4.1.0). So, PM2 is met.

Not Met criteria codes

BA1	✖	This variant is absent from gnomAD (gnomAD v4.1.0).

PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	Not on exon 4. Not a cysteine residue.
PM3		✖	No data available.
PM5		✖	1 other missense variants in the same codon: - NM_000527.5(LDLR):c.1277T>C (p.Leu426Pro) (ClinVar ID 251763) - 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.
BS1		✖	This variant is absent from gnomAD (gnomAD v4.1.0).
BS4		✖	No data available.
BS3		✖	No data available.
PS1		✖	No other missense variant with the same amino acid change.
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No data available.
BP4		✖	REVEL= 0.907. It is above 0.5.
BP3		✖	No in-frame deletions/insertions.
BP2		✖	No data available.
PVS1		✖	Not a null variant.
BP7		✖	Not a synonymous variant.

Curation History

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