

Variant: *NM_000527.5(LDLR):c.47T>C (p.Leu16Pro)*

Version: 1.0

CA10584733 [↗](#)

250982 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: ff62d848-368c-461c-8302-bd5947b0f8e7

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HGVS expressions

NM_000527.5:c.47T>C

NM_000527.5(LDLR):c.47T>C (p.Leu16Pro)

NC_000019.10:g.11089595T>C

CM000681.2:g.11089595T>C

NC_000019.9:g.11200271T>C

CM000681.1:g.11200271T>C

NC_000019.8:g.11061271T>C

NG_009060.1:g.5215T>C

ENST00000559340.2:c.47T>C

ENST00000560467.2:c.47T>C

ENST00000558518.6:c.47T>C

ENST00000455727.6:c.47T>C

ENST00000535915.5:c.47T>C

ENST00000545707.5:c.47T>C

ENST00000557933.5:c.47T>C

ENST00000557958.1:n.133T>C

ENST00000558013.5:c.47T>C

ENST00000558518.5:c.47T>C

ENST00000560502.5:n.133T>C

NM_000527.4:c.47T>C

NM_001195798.1:c.47T>C

NM_001195799.1:c.47T>C

NM_001195800.1:c.47T>C

NM_001195803.1:c.47T>C

NM_001195798.2:c.47T>C

NM_001195799.2:c.47T>C

NM_001195800.2:c.47T>C

NM_001195803.2:c.47T>C

NR_163945.1:n.65A>G

Uncertain Significance

Met criteria codes **3**

PP4

PM2

PS4_Supporting

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BA1BP4BP3BP2BS1BS4

BS3PP1PP3PM6PM1

PM3PM5PM4PS1PS2

PS3PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.47T>C (p.Leu16Pro) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes PS4_Supporting, PM2, 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: This variant is absent from gnomAD (gnomAD v2.1.1.). So PM2 is met. PS4_Supporting: Variant meets PM2 and is identified in 2 unrelated index cases, as follows: 1 case with Simon-Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with DLCN criteria =9 (>6) from PMID 33668494 (Sabatel-Pérez et al, 2021). So PS4_Supporting is met. PP4: Variant meets PM2. Identified in 2 unrelated index cases who fulfill clinical criteria for FH (see PS4_Supporting for details). So PP4 is met.

Met criteria codes

PP4			Variant meets PM2. Identified in 2 unrelated index cases who fulfill clinical criteria for FH (see PS4_Supporting for details). So PP4 is met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1.). So PM2 is met.
PS4_Supporting			Variant meets PM2 and is identified in 2 unrelated index cases, as follows: 1 case with Simon-Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with DLCN criteria =9 (>6) from PMID 33668494 (Sabatel-Pérez et al, 2021). So PS4_Supporting is met.

Not Met criteria codes

BA1			This variant is absent from gnomAD (gnomAD v2.1.1.).
BP4			REVEL is 0.674. It is >0.5, so BP4 is not met
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant is absent from gnomAD (gnomAD v2.1.1.).

BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL is 0.674. It is <0.75. Splicing prediction is required: cenario A, Acceptor site: The variant is not located at -20 to +3 bases of canonical acceptor splicing site of any exons. Scenario A, Donor site: The variant is not located at -3 to +6 bases of canonical donor splicing site of any exons. Scenario B, Acceptor site: The variant is out of range. No need to studying denovo AG site. Scenario B, Donor site: The variant is located within the range but does not create denovo GT site. Scenario C, Acceptor site: The variant is out of range. No need to studying nearby AG site. Scenario C, Donor site: The variant is within the range and does not create a denovo GT. There is no GT in downstream (3 Nt) or upstream (6 Nt). Interpretation: The variant does not affect splicing process. So PP3 is not met
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			One other missense variant in the same codon: NM_000527.5(LDLR):c.46C>G (p.Leu16Val) (ClinVar ID 919564) Uncertain significance by these guidelines
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			Not a null variant

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