

Variant: *NM_000527.5(LDLR):c.251C>T (p.Pro84Leu)*

Version: 1.0

CA10576272 [↗](#)

226310 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 07c7b461-166a-4594-a32f-e4d763eef195

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HGVS expressions

NM_000527.5:c.251C>T

NM_000527.5(LDLR):c.251C>T (p.Pro84Leu)

NC_000019.10:g.11102724C>T

CM000681.2:g.11102724C>T

NC_000019.9:g.11213400C>T

CM000681.1:g.11213400C>T

NC_000019.8:g.11074400C>T

NG_009060.1:g.18344C>T

ENST00000252444.10:c.509C>T

ENST00000559340.2:c.251C>T

ENST00000560467.2:c.251C>T

ENST00000558518.6:c.251C>T

ENST00000252444.9:c.505C>T

ENST00000455727.6:c.251C>T

ENST00000535915.5:c.190+2379C>T

ENST00000545707.5:c.251C>T

ENST00000557933.5:c.251C>T

ENST00000557958.1:n.337C>T

ENST00000558013.5:c.251C>T

ENST00000558518.5:c.251C>T

NM_000527.4:c.251C>T

NM_001195798.1:c.251C>T

NM_001195799.1:c.190+2379C>T

NM_001195800.1:c.251C>T

NM_001195803.1:c.251C>T

NM_001195798.2:c.251C>T

NM_001195799.2:c.190+2379C>T

NM_001195800.2:c.251C>T

NM_001195803.2:c.251C>T

Uncertain Significance

Met criteria codes **3**

PP4

PM2

PP1_Moderate

Not Met criteria codes **3**

BP4

PP3

PM5

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.251C>T (p.Pro84Leu) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence code PM2, PP1_Moderate 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) PP1_Moderate - Variant segregates with FH phenotype in at least 4 informative meioses from 2 families from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA). In one family 2 family members positive for variant with LDL > 75th percentile, in the other 2 family members negative for variantwith LDL < 50th percentile. PP4 - Variant meets PM2 and is identified in one index case who fulfill FH/DLCN>=6 criteria for FH from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) after alternative causes of high cholesterol were excluded.

Met criteria codes

PP4			Variant meets PM2 and is identified in one index case who fulfill FH/DLCN>=6 criteria for FH from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1)
PP1_Moderate			Variant segregates with FH phenotype in at least 4 informative meioses from 2 families from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA). In one family 2 family members positive for variant with LDL > 75th percentile, in the other 2 family members negative for variantwith LDL < 50th percentile.

Not Met criteria codes

BP4			REVEL = 0.666, it is not below 0.50
PP3			REVEL = 0.666, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. - Variant is exonic and at least 50bp downstream from canonical acceptor site but it does not create GT. - There is a GT nearby. MES scores: variant cryptic = -7.00, wt cryptic = -6.77, canonical donor = 9.90. Ratio variant cryptic/wt cryptic: -7,00/-6.77 = 1,03 --- it is not above 1.1 Ratio variant cryptic/canonical donor: -7.00/9,90 = -0,71 --- it is not above 0.9 - Variant is exonic and at least 50bp upstream from canonical donor site but it does not create AG. - There is no AG nearby
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.250C>T (p.Pro84Ser) Uncertain significance - insufficient evidence by these guidelines. - NM_000527.5(LDLR):c.251C>G (p.Pro84Arg) Uncertain significance - insufficient evidence by these guidelines. There are 2 variants in the same codon classified as Uncertain significance

- insufficient evidence by these guidelines. PS4 is not met Variant meets PM2 but is identified in one index case who fulfill FH/DLCN $\geq$ 6 criteria for FH from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA).

Curation History [↗](#)

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