

Variant: *NM_000527.5(LDLR):c.259T>C (p.Trp87Arg)*

Version: 1.1

CA404075655 [↗](#)

440552 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 9698a1b6-b4f5-4900-938d-4a063ce16f60

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HGVS expressions

NM_000527.5(LDLR):c.259T>C (p.Trp87Arg)

NM_000527.5:c.259T>C

NC_000019.10:g.11102732T>C

CM000681.2:g.11102732T>C

NC_000019.9:g.11213408T>C

CM000681.1:g.11213408T>C

NC_000019.8:g.11074408T>C

NG_009060.1:g.18352T>C

ENST00000252444.10:c.517T>C

ENST00000559340.2:c.259T>C

ENST00000560467.2:c.259T>C

ENST00000558518.6:c.259T>C

ENST00000252444.9:c.513T>C

ENST00000455727.6:c.259T>C

ENST00000535915.5:c.190+2387T>C

ENST00000545707.5:c.259T>C

ENST00000557933.5:c.259T>C

ENST00000557958.1:n.345T>C

ENST00000558013.5:c.259T>C

ENST00000558518.5:c.259T>C

NM_000527.4:c.259T>C

NM_001195798.1:c.259T>C

NM_001195799.1:c.190+2387T>C

NM_001195800.1:c.259T>C

NM_001195803.1:c.259T>C

NM_001195798.2:c.259T>C

NM_001195799.2:c.190+2387T>C

NM_001195800.2:c.259T>C

NM_001195803.2:c.259T>C

Uncertain Significance

Met criteria codes **3**

PP3 PM5 PM2

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

BA1

PP1

PP2

PP4

PM1

PM3

PM4

PM6

BS1

BS4

BS3

BS2

BP5

BP7

BP4

BP3

BP1

BP2

PVS1

Evidence Links

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- Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1*
- PDF
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.259T>C (p.Trp87Arg) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PM5 and PP3) 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. PM5 - 1 other missense variant in the same codon: - NM_000527.5(LDLR):c.259T>G (p.Trp87Gly) - Pathogenic by expert panel in ClinVar, so PM5 is met. PP3 - REVEL = 0.891. It is above 0.75, so PP3 is met.

Met criteria codes

PP3		✓	REVEL = 0.891. It is above 0.75, so PP3 is met
PM5		✓	1 other missense variant in the same codon: - NM_000527.5(LDLR):c.259T>G (p.Trp87Gly) - Pathogenic by expert panel in ClinVar so PM5 is met
PM2		✓	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met

Not Met criteria codes

PS1		✗	no other variant leads to the same amino acid change, so not met
PS2		✗	there is no report of this variant appearing de novo
PS3		✗	This variant was not studied in a functional study
BA1		✗	This variant is absent from gnomAD (gnomAD v2.1.1), so not met
PP1		✗	there is no segregation data for this variant
PP2		✗	not applicable
PP4		✗	variant meets PM2 and was identified in: - 1 index case from Mayo lab with clinical DLCN 1. so not met

PM1			variant is missense and meets PM2, but it is not in exon 4 and not does not alter Cys, so not met
PM3			there were no other variants identified in index cases
PM4			variant is missense, so not applicable
PM6			there is no report of this variant appearing de novo
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
BS4			there is no segregation data for this variant
BS3			This variant was not studied in a functional study
BS2			variant was not searched in normolipidemic individuals
BP5			not applicable
BP7			variant is missense, so not applicable
BP4			REVEL = 0.891. It is not below 0.50, so not met
BP3			not applicable
BP1			not applicable
BP2			there were no other variants identified in index cases
PVS1			variant is missense and not in initiation codon, so not applicable

Curation History [↗](#)

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