

Variant: *NM_000527.5(LDLR):c.2251C>T (p.Arg751Trp)*

Version: 1.0

CA039237 [↗](#)

926358 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 5a8e52f7-674e-40db-b967-033cf18032a1

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HGVS expressions

NM_000527.5(LDLR):c.2251C>T (p.Arg751Trp)

NM_000527.5:c.2251C>T

NC_000019.10:g.11123284C>T

CM000681.2:g.11123284C>T

NC_000019.9:g.11233960C>T

CM000681.1:g.11233960C>T

NC_000019.8:g.11094960C>T

NG_009060.1:g.38904C>T

ENST00000252444.10:c.2509C>T

ENST00000559340.2:c.*320C>T

ENST00000560467.2:c.2131C>T

ENST00000558518.6:c.2251C>T

ENST00000252444.9:c.2505C>T

ENST00000455727.6:c.1747C>T

ENST00000535915.5:c.2128C>T

ENST00000545707.5:c.1717C>T

ENST00000557933.5:c.2251C>T

ENST00000558013.5:c.2251C>T

ENST00000558518.5:c.2251C>T

NM_000527.4:c.2251C>T

NM_001195798.1:c.2251C>T

NM_001195799.1:c.2128C>T

NM_001195800.1:c.1747C>T

NM_001195803.1:c.1717C>T

NM_001195798.2:c.2251C>T

NM_001195799.2:c.2128C>T

NM_001195800.2:c.1747C>T

NM_001195803.2:c.1717C>T

Likely Benign

Met criteria codes **3**

PM2

BS2

BP4

Not Met criteria codes **23**

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

PVS1

PS1

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

[↗](#) Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR): c.2251C>T (p.Arg751Trp) variant is classified as Likely benign for Familial Hypercholesterolemia by applying evidence codes PM2, BS2 and BP4 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 - PopMax MAF = 0.0001202 (0.01202%) in African/African American exomes+genomes (gnomAD v2.1.1). BP4 - REVEL = 0.428, it is below 0.50, splicing evaluation required. Variant is exonic and at least 50bp downstream from canonical donor site, but it does not create AG/GT. BS2 - Variant identified in 717 heterozygotes and 72 homozygotes (PMID: 25414273). These subjects had the same level of LDLc as non-carriers (N=2408).

Met criteria codes

PM2			PopMax MAF = 0.0001202 (0.01202%) in African/African American exomes+genomes (gnomAD v2.1.1).
BS2			Variant identified in 717 heterozygotes and 72 homozygotes (PMID: 25414273). These subjects had the same level of LDLc as non-carriers (N=2408).
BP4			REVEL = 0.428, it is below 0.50, splicing evaluation required. Variant is exonic and at least 50bp downstream from canonical acceptor site, but it does not create AG/GT.

Not Met criteria codes

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			1 other missense variant in the same codon: - NM_000527.5(LDLR):c.2252G>A (p.Arg751Gln) (ClinVar ID 161286) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			PMID: 25414273 - Level 2 assay - Heterologous cells (COS7), WB assay: mature LDLR expression ~ 63% Heterologous cells (HepG2) LDLR binding activity: 12% reduction in binding ability - activity is not above 90%.
PVS1			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
PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			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
BA1			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

PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL = 0.428
PP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
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