

Variant: *NM_000527.5(LDLR):c.1216C>T (p.Arg406Trp)*

Version: 2.0

CA033073 [↗](#)

226351 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 20341145-6ce8-4ebf-bf2f-1b567994c9fb

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HGVS expressions

NM_000527.5:c.1216C>T

NM_000527.5(LDLR):c.1216C>T (p.Arg406Trp)

NC_000019.10:g.11113307C>T

CM000681.2:g.11113307C>T

NC_000019.9:g.11223983C>T

CM000681.1:g.11223983C>T

NC_000019.8:g.11084983C>T

NG_009060.1:g.28927C>T

ENST00000252444.10:c.1474C>T

ENST00000559340.2:c.1216C>T

ENST00000560467.2:c.1096C>T

ENST00000558518.6:c.1216C>T

ENST00000252444.9:c.1470C>T

ENST00000455727.6:c.712C>T

ENST00000535915.5:c.1093C>T

ENST00000545707.5:c.835C>T

ENST00000557933.5:c.1216C>T

ENST00000558013.5:c.1216C>T

ENST00000558518.5:c.1216C>T

ENST00000560173.1:n.215C>T

ENST00000560467.1:c.696C>T

NM_000527.4:c.1216C>T

NM_001195798.1:c.1216C>T

NM_001195799.1:c.1093C>T

NM_001195800.1:c.712C>T

NM_001195803.1:c.835C>T

NM_001195798.2:c.1216C>T

NM_001195799.2:c.1093C>T

NM_001195800.2:c.712C>T

NM_001195803.2:c.835C>T

Pathogenic

Met criteria codes **6**

PP1_Strong

PP3

PP4

PM2

PS3

PS4

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 16

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

Evidence Links 0

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c1216C>T (p.Arg406Trp) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PS3, PS4, PP1_Strong, and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PM2 - PopMax MAF = 0.000097 (0.0097%) in Ashkenazi Jewish exomes+genomes (gnomAD v2.1.1). PP3 - REVEL = 0.88, which is above the threshold of 0.75. PS3 - Level 1 functional studies: PMID: 2574186; Heterologous cells (CHO), FACS assays - variant results in 60-65% LDLR expression/biosynthesis, LDL binding and LDL internalization compared to wild-type; results meet <70% threshold. PS4 - Variant meets PM2 and is identified in at least 19 unrelated index cases who fulfill clinical criteria for FH (1 case with DLCN criteria from PathWest Laboratory Medicine WA - FH VCEP member lab; 18 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - FH VCEP member lab). PP1_Strong - Variant segregates with phenotype in 31 informative meioses from 15 families in data provided by FH VCEP member labs (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - 11 families: 23 affected with the variant and 1 unaffected without the variant; Laboratory of Genetics and Molecular Cardiology - 4 families: 4 affected with the variant and 3 unaffected without the variant). PP4 - Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded. Note: two other missense variants at this same codon have been reported: 1) NM_000527.5(LDLR):c.1217G>A (p.Arg406Gln) - Likely pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) - Likely pathogenic by these guidelines. -PM5 not applicable as such variants must be Pathogenic.

Met criteria codes

PP1_Strong			Variant segregates with phenotype in 31 informative meioses from 15 families in data provided by FH VCEP member labs (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - 11 families: 23 affected with the variant and 1 unaffected without the variant; Laboratory of Genetics and Molecular Cardiology - 4 families: 4 affected with the variant and 3 unaffected without the variant)
PP3			REVEL = 0.88
PP4			Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2			PopMax MAF = 0.000097 (0.0097%) in Ashkenazi Jewish exomes+genomes (gnomAD v2.1.1).
PS3			Level 1 studies performed: PMID: 2574186; Heterologous cells (CHO), FACS assays - variant results in 60-65% LDLR expression/biosynthesis, LDL binding AND LDL internalization compared to wild-type; results meet <70% threshold.
PS4			Variant meets PM2 and is identified in at least 19 unrelated index cases who fulfill clinical criteria for FH (1 case with DLCN criteria from PathWest Laboratory Medicine WA - FH VCEP member lab; 18 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - FH VCEP member lab).

Not Met criteria codes

BA1			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
BP4			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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No genotype-positive, phenotype-negative cases, which are required for BS4.
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			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
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			2 other missense variants in the same codon: 1) NM_000527.5(LDLR):c.1217G>A (p.Arg406Gln) – Likely pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) - Likely pathogenic 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

