

Variant: *NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro)*

Version: 1.0

CA10576302 [↗](#)

226352 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: a4cb57c2-99f7-4f49-9061-443b0d7a8f88

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HGVS expressions

NM_000527.5:c.1217G>C

NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro)

NC_000019.10:g.11113308G>C

CM000681.2:g.11113308G>C

NC_000019.9:g.11223984G>C

CM000681.1:g.11223984G>C

NC_000019.8:g.11084984G>C

NG_009060.1:g.28928G>C

ENST00000252444.10:c.1475G>C

ENST00000559340.2:c.1217G>C

ENST00000560467.2:c.1097G>C

ENST00000558518.6:c.1217G>C

ENST00000252444.9:c.1471G>C

ENST00000455727.6:c.713G>C

ENST00000535915.5:c.1094G>C

ENST00000545707.5:c.836G>C

ENST00000557933.5:c.1217G>C

ENST00000558013.5:c.1217G>C

ENST00000558518.5:c.1217G>C

ENST00000560173.1:n.216G>C

ENST00000560467.1:c.697G>C

NM_000527.4:c.1217G>C

NM_001195798.1:c.1217G>C

NM_001195799.1:c.1094G>C

NM_001195800.1:c.713G>C

NM_001195803.1:c.836G>C

NM_001195798.2:c.1217G>C

NM_001195799.2:c.1094G>C

NM_001195800.2:c.713G>C

NM_001195803.2:c.836G>C

Likely Pathogenic

Met criteria codes **6**

PS4_Supporting

PP1

PP3

PP4

PM5

PM2

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 16

BS2 PVS1 BS1 BS4 BS3
BP4 BP2 BP7 PS1 PS2 PS3
BA1 PM1 PM3 PM4 PM6

Evidence Links 0

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PM5, PS4_Supporting, PP1, 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 - This variant is absent from gnomAD (gnomAD v2.1.1). PP3 - REVEL = 0.89, which is above the threshold of 0.75. 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.Arg406Trp) - Pathogenic by these guidelines. There is 1 variant in the same codon classified as Pathogenic by these guidelines. - therefore PM5 is met. PS4_Supporting - Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (1 case with SB criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation- FH VCEP member lab; 1 case with DLCN criteria from PMID: 16250003) PP1 - Variant segregates with phenotype in 2 informative meioses from 2 families in data provided by FH VCEP member labs (Laboratory of Genetics and Molecular Cardiology - 1 family: 1 affected family member with the variant; Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation - 1 family: 1 affected family member with the variant). PP4 - Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.

Met criteria codes

PS4_Supporting			Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (1 case with SB criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation- FH VCEP member lab; 1 case with DLCN criteria from PMID: 16250003).
PP1			Variant segregates with phenotype in 2 informative meioses from 2 families in data provided by FH VCEP member labs (Laboratory of Genetics and Molecular Cardiology - 1 family: 1 affected family member with the variant; Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation - 1 family: 1 affected family member with the variant).
PP3			REVEL = 0.89
PP4			Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
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.Arg406Trp) - Pathogenic by these guidelines - therefore PM5 is met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			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			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
BP7			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
BA1			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

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

Curation History 		
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