

Variant: *NM_000527.5(LDLR):c.758G>C (p.Arg253Pro)*

Version: 1.0

CA10585115 [↗](#)

251435 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 5204a9d1-8c95-466b-b752-b6013d992ee4

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HGVS expressions

NM_000527.5(LDLR):c.758G>C (p.Arg253Pro)

NM_000527.5:c.758G>C

NC_000019.10:g.11106628G>C

CM000681.2:g.11106628G>C

NC_000019.9:g.11217304G>C

CM000681.1:g.11217304G>C

NC_000019.8:g.11078304G>C

NG_009060.1:g.22248G>C

ENST00000252444.10:c.1016G>C

ENST00000559340.2:c.758G>C

ENST00000560467.2:c.758G>C

ENST00000558518.6:c.758G>C

ENST00000252444.9:c.1012G>C

ENST00000455727.6:c.314-764G>C

ENST00000535915.5:c.635G>C

ENST00000545707.5:c.377G>C

ENST00000557933.5:c.758G>C

ENST00000558013.5:c.758G>C

ENST00000558518.5:c.758G>C

ENST00000558528.1:n.273G>C

ENST00000560467.1:c.358G>C

NM_000527.4:c.758G>C

NM_001195798.1:c.758G>C

NM_001195799.1:c.635G>C

NM_001195800.1:c.314-764G>C

NM_001195803.1:c.377G>C

NM_001195798.2:c.758G>C

NM_001195799.2:c.635G>C

NM_001195800.2:c.314-764G>C

NM_001195803.2:c.377G>C

Uncertain Significance

Met criteria codes **3**

PP3

PP4

PM2

Not Met criteria codes **13**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1

PS3

PS4

BP7

BP4

PM1

PM5

PM4

BA1

BS1

BS3

BS2

PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.758G>C (p.Arg253Pro) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence PM2, PP3, 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 (v2.1.1). PP3 - REVEL = 0.77, which is above the threshold of 0.75. PP4 - Variant meets PM2 and was identified in 1 index case with Simon Broome criteria for FH (PMID: 20236128) after alternative causes of cholesterol were excluded. Note: two other missense variants at this same codon have been reported: 1) NM_000527.5(LDLR):c.757C>T (p.Arg253Trp); 2) NM_000527.5(LDLR):c.758G>A (p.Arg253Gln); however, both are VUS by these LDLR guidelines (PM5 not applicable).

Met criteria codes

PP3			REVEL = 0.77; score is above 0.75 threshold.
PP4			Variant meets PM2 and is identified in one index case who fulfils SB criteria for FH from PMID: 20236128, after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PS1			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			Variant meets PM2. Reported in one index case who met Simon Broome criteria for FH (PMID: 20236128).
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
PM1			

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.757C>T (p.Arg253Trp)- VUS by these guidelines. 2) NM_000527.5(LDLR):c.758G>A (p.Arg253Gln) - VUS by these guidelines.
PM4			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
BS1			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
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

Curation History



 

 

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