

Variant: *NM_000527.5(LDLR):c.2252G>A (p.Arg751Gln)*

Version: 1.0

CA023654 [↗](#)

161286 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 4c3500b5-196e-41cb-9c85-e39a63577757

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HGVS expressions

NM_000527.5:c.2252G>A

NM_000527.5(LDLR):c.2252G>A (p.Arg751Gln)

NC_000019.10:g.11123285G>A

CM000681.2:g.11123285G>A

NC_000019.9:g.11233961G>A

CM000681.1:g.11233961G>A

NC_000019.8:g.11094961G>A

NG_009060.1:g.38905G>A

ENST00000252444.10:c.2510G>A

ENST00000559340.2:c.*321G>A

ENST00000560467.2:c.2132G>A

ENST00000558518.6:c.2252G>A

ENST00000252444.9:c.2506G>A

ENST00000455727.6:c.1748G>A

ENST00000535915.5:c.2129G>A

ENST00000545707.5:c.1718G>A

ENST00000557933.5:c.2252G>A

ENST00000558013.5:c.2252G>A

ENST00000558518.5:c.2252G>A

NM_000527.4:c.2252G>A

NM_001195798.1:c.2252G>A

NM_001195799.1:c.2129G>A

NM_001195800.1:c.1748G>A

NM_001195803.1:c.1718G>A

NM_001195798.2:c.2252G>A

NM_001195799.2:c.2129G>A

NM_001195800.2:c.1748G>A

NM_001195803.2:c.1718G>A

Uncertain Significance

Met criteria codes **3**

PP4

PM2

PS4_Supporting

Not Met criteria codes **23**

PS1

PS2

PS3

BA1

PP1

PP2

PP3

PM1

PM3

PM5

PM4

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.2252G>A (p.Arg751Gln) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PS4_supporting and PP4) 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 = 0.0001602 (0.01602%) in African/African American exomes+genomes (gnomAD v2.1.1). PS4_supporting - Variant meets PM2 and is identified in 2 unrelated index cases (1 case published in PMID: 16250003 (Fouchier et al., 2005), Netherlands; 1 case published in PMID: 16159606 (Graham et al., 2005), United Kingdom). PP4 - Variant meets PM2. PMID: 16159606 - 1 case who fulfills Simon-Broome criteria for FH.

Met criteria codes

PP4			Variant meet PM2. PMID: 16159606 - 1 case who fulfills Simon-Broome criteria for FH.
PM2			PopMax MAF = 0.0001602 (0.01602%) in African/African American exomes+genomes (gnomAD v2.1.1).
PS4_Supporting			Variant meets PM2 and is identified in 2 unrelated index cases (1 case published in PMID: 16250003 (Fouchier et al., 2005), Netherlands; 1 case published in PMID: 16159606 (Graham et al., 2005), United Kingdom).

Not Met criteria codes

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
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 = 0.506, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. Variant is exonic and at least 50bp downstream from canonical donor site and creates AG. MES scores: de novo variant = 5.2; canonical acceptor = 8.76. Ratio de novo variant/canonical acceptor = 5.2/8.76 = 0.59 --- it is below 0.8 Variant is not predicted to be damaging or alter splicing.
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.2251C>T (p.Arg751Trp) (ClinVar ID 926358) - 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			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
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
BP4			REVEL = 0.506, it is not below 0.5.
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
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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