

Variant: *NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp)*

Version: 1.0

CA023581 [↗](#)

161290 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: ba5d5793-ffd3-48df-89c0-24c7600a8a6d

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HGVS expressions

NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp)

NM_000527.5:c.1783C>T

NC_000019.10:g.11116936C>T

CM000681.2:g.11116936C>T

NC_000019.9:g.11227612C>T

CM000681.1:g.11227612C>T

NC_000019.8:g.11088612C>T

NG_009060.1:g.32556C>T

ENST00000252444.10:c.2041C>T

ENST00000559340.2:c.1705+724C>T

ENST00000560467.2:c.1663C>T

ENST00000558518.6:c.1783C>T

ENST00000252444.9:c.2037C>T

ENST00000455727.6:c.1279C>T

ENST00000535915.5:c.1660C>T

ENST00000545707.5:c.1402C>T

ENST00000557933.5:c.1783C>T

ENST00000558013.5:c.1783C>T

ENST00000558518.5:c.1783C>T

ENST00000559340.1:c.426+724C>T

NM_000527.4:c.1783C>T

NM_001195798.1:c.1783C>T

NM_001195799.1:c.1660C>T

NM_001195800.1:c.1279C>T

NM_001195803.1:c.1402C>T

NM_001195798.2:c.1783C>T

NM_001195799.2:c.1660C>T

NM_001195800.2:c.1279C>T

NM_001195803.2:c.1402C>T

Pathogenic

Met criteria codes **5**

PP1_Strong PS4 PP3 PP4 PM2

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BS2

PVS1

BS1

BS4

BS3

BP4

BP3

BP1

BP2

BP5

BP7

PS1

PS2

PS3

BA1

PP2

PM1

PM3

PM5

PM4

PM6

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel			
<i>Familial Hypercholesterolemia VCEP</i>			
NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS4, PP1_Strong, 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: PS4 - Variant meets PM2. Variant identified in 12 index cases. PP1_strong - 10 informative meioses identified by Laboratory of Genetics and Molecular Cardiology. PM2 - PopMax MAF = 0.00001548 (0.0015%) in European non-Finnish (gnomAD v2.1.1). PP3 - REVEL: 0,89. PP4 - Variant meets PM2. Variant identified in 12 index cases fulfilling validated clinical criteria for FH (6 cases with Simon-Broome or DLCN criteria from Ambry Genetics; 2 cases with Simon-Broome from Color laboratory; 3 cases with Simon-Broome criteria from Laboratory of Genetics and Molecular Cardiology; 1 case with Simon-Broome criteria from GeneDx).			
Met criteria codes			
PP1_Strong			10 informative meioses identified by Laboratory of Genetics and Molecular Cardiology.
PS4			Variant meets PM2. Variant identified in 12 index cases (6 cases with Simon-Broome or DLCN criteria from Ambry Genetics; 2 cases with Simon-Broome from Color laboratory; 3 cases with Simon-Broome criteria from Laboratory of Genetics and Molecular Cardiology; 1 case with Simon-Broome criteria from GeneDx).
PP3			REVEL: 0,89. Score is above 0,75.
PP4			Variant meets PM2. Variant identified in 12 index cases fulfilling validated clinical criteria for FH (See PS4).
PM2			PopMax MAF = 0.00001548 (0.0015%) in European non-Finnish (gnomAD v2.1.1). MAF is below 0.02%.
Not Met criteria codes			
BS2			No unaffected individuals identified with the variant.
PVS1			Missense variant. Not applicable.
BS1			no FAF, just total MAF = 0.000003976 (0.0004%) in European non-Finnish (gnomAD v2.1.1). MAF is not above 0.5%
BS4			No non-segregations were identified/found.

BS3			No functional assays performed/found - not applicable.
BP4			REVEL: 0,89. Score is not below 0,15.
BP3			Not applicable.
BP1			Not applicable.
BP2			1 index case from Laboratory of Genetics and Molecular Cardiology is a compound heterozygote in trans with the NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) variant, phenotype similar to HoFH (LDLc 405 mg/dL treated). BP2 is not met.
BP5			Not applicable.
BP7			Missense variant. Not applicable.
PS1			No variant described that leads to the same amino acid change.
PS2			No de novo cases were identified.
PS3			No functional assays performed/found - not applicable.
BA1			no FAF, just total MAF = 0.000003976 (0.0004%) in European non-Finnish (gnomAD v2.1.1). MAF is not above 0.5%
PP2			Not applicable.
PM1			Missense at codon 595. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3			1 index case from Laboratory of Genetics and Molecular Cardiology is a compound heterozygote in trans with the NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) variant, phenotype similar to HoFH (LDLc 405 mg/dL treated). Unsufficient information about nontreated levels of LDLc. PM3 is not met.
PM5			No other missense variants classified as Pathogenic in the same codon. Two other missense variants described in the same codon (accessed 19 August 2020): (1)NM_000527.5(LDLR):c.1784G>T (p.Arg595Leu) (ClinVar ID 252029) - classified as VUS by these guidelines. (2)NM_000527.5(LDLR):c.1784G>A (p.Arg595Gln) (ClinVar ID 183126) - classified as VUS by these guidelines.
PM4			Missense variant. Not applicable.
PM6			No de novo cases were identified.

Curation History [↗](#)



Showing 1 to 1 of 1 rows

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