The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2021/6/9
Published on: 2021/6/24

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

PM2 PP1_Strong PS4 PP3 PP4

Not Met criteria codes 21

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PVS1 PM1 PM3 PM5 PM4
PM6 BA1 BS1 BS4 BS3
BS2 BP5 BP7 BP4 BP3 BP1
BP2 PS1 PS2 PS3 PP2

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

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

PM2	✔	PopMax MAF = 0.00001548 (0.0015%) in European non-Finnish (gnomAD v2.1.1). MAF is below 0.02%.
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).

Not Met criteria codes

PVS1	✖	Missense variant. 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). Unsuficient 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.
BA1		✖	no FAF, just total MAF = 0.000003976 (0.0004%) in European non-Finnish (gnomAD v2.1.1). MAF is not above 0.5%
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.
BS2		✖	No unaffected individuals identified with the variant.
BP5		✖	Not applicable.
BP7		✖	Missense variant. 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.
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.
PP2		✖	Not applicable.

Curation History

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