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.1784G>T (p.Arg595Leu)

Version: 1.1

CA10585609

252029 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 2237748f-a124-413b-97a0-3a3e93660c25
Approved on: 2022/2/1
Published on: 2022/7/11

HGVS expressions

NM_000527.5(LDLR):c.1784G>T (p.Arg595Leu)
NM_000527.5:c.1784G>T
NC_000019.10:g.11116937G>T
CM000681.2:g.11116937G>T
NC_000019.9:g.11227613G>T
CM000681.1:g.11227613G>T
NC_000019.8:g.11088613G>T
NG_009060.1:g.32557G>T
ENST00000252444.10:c.2042G>T
ENST00000559340.2:c.1705+725G>T
ENST00000560467.2:c.1664G>T
ENST00000558518.6:c.1784G>T
ENST00000252444.9:c.2038G>T
ENST00000455727.6:c.1280G>T
ENST00000535915.5:c.1661G>T
ENST00000545707.5:c.1403G>T
ENST00000557933.5:c.1784G>T
ENST00000558013.5:c.1784G>T
ENST00000558518.5:c.1784G>T
ENST00000559340.1:c.426+725G>T
NM_000527.4:c.1784G>T
NM_001195798.1:c.1784G>T
NM_001195799.1:c.1661G>T
NM_001195800.1:c.1280G>T
NM_001195803.1:c.1403G>T
NM_001195798.2:c.1784G>T
NM_001195799.2:c.1661G>T
NM_001195800.2:c.1280G>T
NM_001195803.2:c.1403G>T

Likely Pathogenic

Met criteria codes 3

PP3 PM2 PM5_Strong

Not Met criteria codes 19

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP1 PP4 BA1 PM6 PM1 PM3 PM4 BS2 BS1 BS4 BS3 PS1 PS2 PS3 PS4 BP4 BP2 PVS1 BP7

Evidence Links 0

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1*

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1784G>T (p.Arg595Leu) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PM5_strong) 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 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. PP3 - REVEL = 0.959. It is above 0.75, so PP3 is Met. PM5_strong - 2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp) (ClinVar ID: 161290) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1784G>A (p.Arg595Gln) (ClinVar ID: 183126) - Pathogenic by these guidelines There are 2 variants in the same codon classified as Pathogenic by these guidelines, so PM5_Strong is Met.

Met criteria codes

PP3	✔	REVEL = 0.959. It is above 0.75, so PP3 is Met.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
PM5_Strong	✔	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp) (ClinVar ID: 161290) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1784G>A (p.Arg595Gln) (ClinVar ID: 183126) - Pathogenic by these guidelines There are 2 variants in the same codon classified as Pathogenic by these guidelines, so PM5_Strong is Met.

Not Met criteria codes

PP1	✖	Segregation data not reported, so PP1 is Not Met.
PP4	✖	Variant meets PM2, but data reported does not meet any validated criteria, so PP4 is Not Met.
BA1	✖	No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 is Not Met.
PM6	✖	de novo occurrence data not reported, so PM6 is Not Met.
PM1	✖	Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3	✖	Not observed in trans with other LP/P variants, so PM3 is Not Met.

PM4	ℹ	✖	Variant meets PM2 and is missense, so PM4 is Not Met.
BS2	ℹ	✖	Case-control data not reported, so BS2 is Not Met.
BS1	ℹ	✖	No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BS1 is Not Met.
BS4	ℹ	✖	Lack of segregation data not reported, so BS4 is Not Met.
BS3	ℹ	✖	There are no functional studies reported for this variant, so BS3 is not met.
PS1	ℹ	✖	No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2	ℹ	✖	de novo occurrence data not reported, so PS2 is Not Met.
PS3	ℹ	✖	There are no functional studies reported for this variant, so PS3 is not met.
PS4	ℹ	✖	Variant meets PM2, but data reported does not meet any validated criteria, so PS4 is Not Met.
BP4	ℹ	✖	REVEL = 0.959. It is not below 0.50, so BP4 is Not Met.
BP2	ℹ	✖	Not observed in trans with other LP/P variants, so BP2 is Not Met.
PVS1	ℹ	✖	Variant is missense, so PVS1 is Not Met.
BP7	ℹ	✖	Variant is not synonymous, so BP7 is Not Met.

Curation History

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