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.1721G>T (p.Arg574Leu)

Version: 1.1

CA036228

237867 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 68efc539-d28f-4ac9-8921-fffe416b1827
Approved on: 2022/3/30
Published on: 2022/7/12

HGVS expressions

NM_000527.5:c.1721G>T
NM_000527.5(LDLR):c.1721G>T (p.Arg574Leu)
NC_000019.10:g.11116874G>T
CM000681.2:g.11116874G>T
NC_000019.9:g.11227550G>T
CM000681.1:g.11227550G>T
NC_000019.8:g.11088550G>T
NG_009060.1:g.32494G>T
ENST00000252444.10:c.1979G>T
ENST00000559340.2:c.1705+662G>T
ENST00000560467.2:c.1601G>T
ENST00000558518.6:c.1721G>T
ENST00000252444.9:c.1975G>T
ENST00000455727.6:c.1217G>T
ENST00000535915.5:c.1598G>T
ENST00000545707.5:c.1340G>T
ENST00000557933.5:c.1721G>T
ENST00000558013.5:c.1721G>T
ENST00000558518.5:c.1721G>T
ENST00000559340.1:c.426+662G>T
NM_000527.4:c.1721G>T
NM_001195798.1:c.1721G>T
NM_001195799.1:c.1598G>T
NM_001195800.1:c.1217G>T
NM_001195803.1:c.1340G>T
NM_001195798.2:c.1721G>T
NM_001195799.2:c.1598G>T
NM_001195800.2:c.1217G>T
NM_001195803.2:c.1340G>T

Uncertain Significance

Met criteria codes 4

PP3 PP4 PM2 PS4_Supporting

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BA1 PS1 PS2 PS3 PP1 PP2
PM1 PM3 PM5 PM4 PM6
BS2 BS1 BS4 BS3 BP4 BP3
BP1 BP2 BP5 BP7 PVS1

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

NM_000527.5(LDLR):c.1721G>T (p.Arg574Leu) variant is classified as variant of Uncertain significance for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, 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 = 0.0001848 (0.01848%) in European (Finnish) exomes+genomes (gnomAD v2.1.1). PP3 - REVEL = 0.937. PP4 - Variant meets PM2. Identified in 2 FH case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with clinical Simon Broome score possible/definite, after alternative causes of high cholesterol were excluded. PS4_supporting - Variant meets PM2. Variant identified in 2 index cases Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with Simon Broome criteria (possible/definite).

Met criteria codes

PP3	✔	REVEL = 0,937
PP4	✔	Variant meets PM2. Identified in 2 FH case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with clinical Simon Broome score possible/definite, after alternative causes of high cholesterol were excluded.
PM2	✔	PopMax MAF = 0.0001848 (0.01848%) in European (Finnish) exomes+genomes (gnomAD v2.1.1).
PS4_Supporting	✔	Variant meets PM2. Variant identified in 2 index cases Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with Simon Broome criteria (possible/definite).

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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

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
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	✖	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1720C>T (p.Arg574Cys) (ClinVar ID 183123) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1721G>A (p.Arg574His) (ClinVar ID 251996) - Likely pathogenic 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
BS2	✖	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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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
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
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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