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.1090T>C (p.Cys364Arg)

Version: 1.0

CA10585298

251657 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 83db5c0d-e02c-4534-a6b3-3d2b3f49ec5b
Approved on: 2025/3/24
Published on: 2025/3/24

HGVS expressions

NM_000527.5(LDLR):c.1090T>C (p.Cys364Arg)
NM_000527.5:c.1090T>C
NC_000019.10:g.11111543T>C
CM000681.2:g.11111543T>C
NC_000019.9:g.11222219T>C
CM000681.1:g.11222219T>C
NC_000019.8:g.11083219T>C
NG_009060.1:g.27163T>C
ENST00000252444.10:c.1348T>C
ENST00000559340.2:c.1090T>C
ENST00000560467.2:c.970T>C
ENST00000558518.6:c.1090T>C
ENST00000252444.9:c.1344T>C
ENST00000455727.6:c.586T>C
ENST00000535915.5:c.967T>C
ENST00000545707.5:c.709T>C
ENST00000557933.5:c.1090T>C
ENST00000558013.5:c.1090T>C
ENST00000558518.5:c.1090T>C
ENST00000560173.1:n.89T>C
ENST00000560467.1:c.570T>C
NM_000527.4:c.1090T>C
NM_001195798.1:c.1090T>C
NM_001195799.1:c.967T>C
NM_001195800.1:c.586T>C
NM_001195803.1:c.709T>C
NM_001195798.2:c.1090T>C
NM_001195799.2:c.967T>C
NM_001195800.2:c.586T>C
NM_001195803.2:c.709T>C

Likely Pathogenic

Met criteria codes 7

PP3 PP4 PM2 PM1 PM3 PS4_Supporting PP1_Moderate

Not Met criteria codes 9

PS1 PS3 PM5 BA1 BS1 BS4 BS3 BP4 BP2

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*
  - **PDF**
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1090T>C (p.Cys364Arg) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PM3, PP1_Moderate, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 24 March 2025. The supporting evidence is as follows: PM1: Variant meets PM2 and alters Cys364, one of the highly conserved cysteine residues listed. PM2: PopMax MAF=0.00001666 (0.001666%) in Admixed American exomes + genomes (gnomAD v4.1.0). PP3: REVEL=0.984. PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism, Italy; 1 case with modified Simon-Broome criteria from PMID 23064986 (Ahmad et al., 2012), USA). PP1_Moderate: Variant segregates with FH phenotype in 5 informative meiosis from 2 families from different labs (Laboratory of Genetics and Molecular Cardiology, Brazil and Research Lab of Molecular Genetics of Lipid Metabolism, Italy): 3 affected family members have the variant and 2 unaffected family members do not have the variant. PM3: Variant meets PM2 and is identified in at least 1 clinically diagnosed HoFH, homozygous for the variant (PMID 37119068; PMID 27940769).

Met criteria codes

PP3	✔	REVEL = 0.984, it is above 0.75
PP4	✔	Variant meets PM2 and is identified in 2 index cases (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2	✔	PopMax MAF = 0.00001666 (0.001666%) in Admixed American exomes+genomes (gnomAD v4.1.0).
PM1	✔	Variant meets PM2, is missense in exon 4, and alters Cys364, one of the cysteine residues listed.
PM3	✔	Variant meets PM2 and is identified in at least 1 clinically diagnosed HoFH homozygous for the variant: 1 from the CASCADE FH Registry (PMID: 37119068) and in a 7y old boy with cLDL=946 mg/dL, xanthomas+aortic valve stenosis (PMID: 27940769), both in USA.
PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism, Italy; 1 case with modified Simon-Broome criteria from PMID 23064986 (Ahmad et al., 2012), USA).

PP1_Moderate	✔	Variant segregates with FH phenotype in 5 informative meiosis in 2 families from different labs (Laboratory of Genetics and Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca Department of Translational and Precision Medicine): 3 affected family members have the variant and 2 unaffected family members do not have the variant.

Not Met criteria codes

PS1	✖	Variant meets PM1, and there is one more missense variant that is classified as Likely Pathogenic.
PS3	✖	Compound heterozygous, should we use this evidence?
PM5	✖	Variant meets PM1, and there is one more missense variant that is classified as Likely Pathogenic.
BA1	✖	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	✖	REVEL = 0.984, it is above 0.75
BP2	✖	Cis/trans status is unknown

Curation History

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