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.865T>C (p.Cys289Arg)

Version: 1.0

CA10585164

251492 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e80e5038-aebf-4b46-9d96-2f64261b49a0
Approved on: 2025/1/31
Published on: 2025/2/27

HGVS expressions

NM_000527.5:c.865T>C
NM_000527.5(LDLR):c.865T>C (p.Cys289Arg)
NC_000019.10:g.11107439T>C
CM000681.2:g.11107439T>C
NC_000019.9:g.11218115T>C
CM000681.1:g.11218115T>C
NC_000019.8:g.11079115T>C
NG_009060.1:g.23059T>C
ENST00000252444.10:c.1123T>C
ENST00000559340.2:c.865T>C
ENST00000560467.2:c.865T>C
ENST00000558518.6:c.865T>C
ENST00000252444.9:c.1119T>C
ENST00000455727.6:c.361T>C
ENST00000535915.5:c.742T>C
ENST00000545707.5:c.484T>C
ENST00000557933.5:c.865T>C
ENST00000558013.5:c.865T>C
ENST00000558518.5:c.865T>C
ENST00000558528.1:n.380T>C
ENST00000560467.1:c.465T>C
NM_000527.4:c.865T>C
NM_001195798.1:c.865T>C
NM_001195799.1:c.742T>C
NM_001195800.1:c.361T>C
NM_001195803.1:c.484T>C
NM_001195798.2:c.865T>C
NM_001195799.2:c.742T>C
NM_001195800.2:c.361T>C
NM_001195803.2:c.484T>C

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM2 PM1 PS4_Supporting

Not Met criteria codes 21

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

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.865T>C (p.Cys289Arg) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 31 January 2025. The supporting evidence is as follows: PM1 - Variant meets PM2 and alters Cys289, one of the cysteine residues listed; PM2 - This variant is absent from gnomAD (gnomAD v4.1.0); PP3 - REVEL = 0.933; PP4 - Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details), after alternative causes of high cholesterol were excluded; PS4_Supporting - Variant meets PM2 and is identified in 2 unrelated index cases (1 case fulfilling Japanese Atherosclerosis Society criteria from PMID: 35929461 (Funabashi et al., 2022), Japan; 1 case fulfilling internationally accepted criteria for FH from PMID: 16314194 (Robles-Osorio et al., 2006), Mexico).

Met criteria codes

PP3	✔	REVEL = 0.933
PP4	✔	Variant meets PM2 and is identified in 2 index cases who fulfill Japanese Atherosclerosis Society/other criteria for FH from PMID 35929461, 16314194, after alternative causes of high cholesterol were excluded.
PM2	✔	This variant is absent from gnomAD (gnomAD v4.1.0)
PM1	✔	Variant meets PM2 and alters Cys289, one of the cysteine residues listed.
PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases (1 case fulfilling Japanese Atherosclerosis Society criteria from PMID: 35929461 (Funabashi et al., 2022), Japan; 1 case fulfilling internationally accepted criteria for FH from PMID: 16314194 (Robles-Osorio et al., 2006), Mexico)

Not Met criteria codes

PS1	✖	Variant meets PM1, so not applicable.
PS2	✖	No de novo cases were identified.
PS3	✖	No functional assays performed/found - not applicable.
PP1	✖	No segregations were identified/found.
PP2	✖	Not applicable.
PM6	✖	No de novo cases were identified.
PM3	✖	Not identified in individuals with other variants.
PM5	✖	Cannot apply PM5 as variant already meets PM1.

PM4		✖	Not applicable.
BA1		✖	No population data was found for this allele in gnomAD (gnomAD v4.1.0).
BS2		✖	No unaffected individuals identified with the variant.
PVS1		✖	Missense variant. Not applicable.
BS1		✖	No population data was found for this allele in gnomAD (gnomAD v4.1.0).
BS4		✖	No non-segregations were identified/found.
BS3		✖	No functional assays performed/found - not applicable.
BP4		✖	REVEL = 0.933. Score is not below 0.50.
BP3		✖	Not applicable.
BP1		✖	Not applicable.
BP2		✖	Not identified in individuals with other variants.
BP5		✖	Not applicable.
BP7		✖	Missense variant. Not applicable.

Curation History

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