

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

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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

- PM1
- PM2
- PS4_Supporting
- PP3
- PP4

Not Met criteria codes 21

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

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

PM1			Variant meets PM2 and alters Cys289, one of the cysteine residues listed.
PM2			This variant is absent from gnomAD (gnomAD v4.1.0)
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)
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.

Not Met criteria codes

PM3			Not identified in individuals with other variants.
PM5			Cannot apply PM5 as variant already meets PM1.
PM4			Not applicable.
PM6			No de novo cases were identified.
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.
BS2			No unaffected individuals identified with the variant.

PVS1			Missense variant. Not applicable.
PS1			Variant meets PM1, so not applicable.
PS2			No de novo cases were identified.
PS3			No functional assays performed/found - not applicable.
BP5			Not applicable.
BP7			Missense variant. 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.
BA1			No population data was found for this allele in gnomAD (gnomAD v4.1.0).
PP1			No segregations were identified/found.
PP2			Not applicable.

Curation History 		
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