

Variant: NM\_000527.5(LDLR):c.283T>G (p.Cys95Gly)

Version: 1.0

CA10584825 [↗](#)

251112 (ClinVar) [↗](#)

**Gene:** LDLR ([HGNC:3949](#))

**Condition:** hypercholesterolemia, familial ([MONDO:0007750](#))

**Inheritance Mode:** Semidominant inheritance

**UUID:** 0cd36ed2-b053-4bf7-9626-482b541fde93

**Approved on:** 2024/2/23

**Published on:** 2025/8/29

### HGVS expressions

**NM\_000527.5(LDLR):c.283T>G (p.Cys95Gly)**

**NM\_000527.5:c.283T>G**

NC\_000019.10:g.11102756T>G

CM000681.2:g.11102756T>G

NC\_000019.9:g.11213432T>G

CM000681.1:g.11213432T>G

NC\_000019.8:g.11074432T>G

NG\_009060.1:g.18376T>G

ENST00000252444.10:c.541T>G

ENST00000559340.2:c.283T>G

ENST00000560467.2:c.283T>G

ENST00000558518.6:c.283T>G

ENST00000252444.9:c.537T>G

ENST00000455727.6:c.283T>G

ENST00000535915.5:c.190+2411T>G

ENST00000545707.5:c.283T>G

ENST00000557933.5:c.283T>G

ENST00000557958.1:n.369T>G

ENST00000558013.5:c.283T>G

ENST00000558518.5:c.283T>G

NM\_000527.4:c.283T>G

NM\_001195798.1:c.283T>G

NM\_001195799.1:c.190+2411T>G

NM\_001195800.1:c.283T>G

NM\_001195803.1:c.283T>G

NM\_001195798.2:c.283T>G

NM\_001195799.2:c.190+2411T>G

NM\_001195800.2:c.283T>G

NM\_001195803.2:c.283T>G

Likely Pathogenic

Met criteria codes **5**

PP3 PP4 PM2 PM1

PS4\_Supporting

Not Met criteria codes **17**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

BS1

BS4

BS3

BP4

BP3

BP1

PVS1

BP5

BP7

BA1

PS3

PP1

PP2

PM3

PM5

PM4

Evidence Links 0

- [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.283T>G (p.Cys95Gly) 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 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.949. PM1: Variant meets PM2 and alters one highly conserved Cys residue (Cys95). PS4\_Supporting, PP4: Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill clinical diagnostic criteria for FH (1 case from Spain with MedPed criteria in PMID 16627557 (Blesa et al., 2006), and 2 cases from Japan meeting Japan Atherosclerosis Society criteria in PMID 18718593 (Miyake et al., 2009)).

**Met criteria codes**

|                |  |  |                                                                                                                                                                                                                                                                                            |
|----------------|--|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3            |  |  | PP3: REVEL = 0.949. It is above 0.75, so PP3 is met.                                                                                                                                                                                                                                       |
| PP4            |  |  | - PP4: Variant meets PM2 and is identified in at least 1 index case fulfilling clinical diagnostic criteria for FH, after alternative causes of high cholesterol were excluded.                                                                                                            |
| PM2            |  |  | PM2: This variant is absent from gnomAD (gnomAD v2.1.1).                                                                                                                                                                                                                                   |
| PM1            |  |  | Variant meets PM2 and alters one higly conserved Cys residue (Cys95).                                                                                                                                                                                                                      |
| PS4_Supporting |  |  | Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill clinical diagnostic criteria for FH. One case (Spain) with MedPed criteria in PMID: 16627557, and two cases (Japan) with national Japanese (Japan Atherosclerosis Society) criteria in PMID: 18718593. |

**Not Met criteria codes**

|     |  |  |                                                                                                                                                                                                                              |
|-----|--|--|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BS2 |  |  | not met, (no information of several index cases or segregation data/cases in different families)                                                                                                                             |
| BS1 |  |  | This variant is absent from gnomAD (gnomAD v2.1.1), therefore BS1 is not met.                                                                                                                                                |
| BS4 |  |  | not met, (no information of several index cases or segregation data/cases in different families)                                                                                                                             |
| BS3 |  |  | not met. Functional studies (PMID: 18718593) Level 2 assay using compound heterozygous (with p.(Leu568Val)) patients' fibroblasts, 125I-LDL assays - results - 20% LDL-LDLR binding. Due to compHtz, PS3 was not considered. |



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