

Variant: *NM\_000527.5(LDLR):c.1898G>T (p.Arg633Leu)*

Version: 1.0

CA10585677 [↗](#)

252107 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** 3807abd5-9d1c-4dbb-b1fc-4b4f1cd6837b

**Approved on:** 2023/11/7

**Published on:** 2025/8/26

### *HGVS expressions*

**NM\_000527.5(LDLR):c.1898G>T (p.Arg633Leu)**

**NM\_000527.5:c.1898G>T**

NC\_000019.10:g.11120144G>T

CM000681.2:g.11120144G>T

NC\_000019.9:g.11230820G>T

CM000681.1:g.11230820G>T

NC\_000019.8:g.11091820G>T

NG\_009060.1:g.35764G>T

ENST00000252444.10:c.2156G>T

ENST00000559340.2:c.1758G>T

ENST00000560467.2:c.1778G>T

ENST00000558518.6:c.1898G>T

ENST00000252444.9:c.2152G>T

ENST00000455727.6:c.1394G>T

ENST00000535915.5:c.1775G>T

ENST00000545707.5:c.1517G>T

ENST00000557933.5:c.1898G>T

ENST00000558013.5:c.1898G>T

ENST00000558518.5:c.1898G>T

ENST00000559340.1:c.479G>T

NM\_000527.4:c.1898G>T

NM\_001195798.1:c.1898G>T

NM\_001195799.1:c.1775G>T

NM\_001195800.1:c.1394G>T

NM\_001195803.1:c.1517G>T

NM\_001195798.2:c.1898G>T

NM\_001195799.2:c.1775G>T

NM\_001195800.2:c.1394G>T

NM\_001195803.2:c.1517G>T

**Likely Pathogenic**

Met criteria codes **4**

PP3 PP4 PM2 PM5

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

PS4

PP1

BA1

PM6

BS1

BS4

BS3

PM1

PM3

PM4

BS2

BP7

BP4

BP2

PVS1

Evidence Links 

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- 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.1898G>T (p.Arg633Leu) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM5, PP4 and PP3 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 7 November 2023. The supporting evidence is as follows: PM2: Absent from gnomAD version v2.1.1. PP3: REVEL= 0.899. PM5: There is a variant in the same codon classified as Pathogenic by these guidelines, NM\_000527.5(LDLR):c.1898G>A (p.Arg633His) (ClinVar ID: 226380). PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills criteria for FH from PMID 16250003 (Fouchier et al., 2005), The Netherlands, after alternative causes of high cholesterol were excluded.

Met criteria codes

|     |             |             |                                                                                                                                                                                    |
|-----|-------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3 | <div></div> | <div></div> | REVEL= 0.899. This is greater than 0.75 so PP3 is met.                                                                                                                             |
| PP4 | <div></div> | <div></div> | Variant meets PM2 and is identified in at least 1 index case who fulfills definite criteria for FH from PMID 16250003, after alternative causes of high cholesterol were excluded. |
| PM2 | <div></div> | <div></div> | Absent from gnomAD version v 2.1.1                                                                                                                                                 |
| PM5 | <div></div> | <div></div> | There is a variant in the same codon classified as Pathogenic by these guidelines, NM_000527.5(LDLR):c.1898G>A (p.Arg633His) (ClinVar ID: 226380).                                 |

Not Met criteria codes

|     |             |             |                                                                         |
|-----|-------------|-------------|-------------------------------------------------------------------------|
| PS1 | <div></div> | <div></div> | No pathogenic variants at same codon leading to same amino acid change. |
| PS2 | <div></div> | <div></div> | Not met.                                                                |
| PS3 | <div></div> | <div></div> | No data available.                                                      |
| PS4 | <div></div> | <div></div> | No data available.                                                      |
| PP1 | <div></div> | <div></div> | No data available.                                                      |

|      |                                                                                     |                                                                                     |                                                            |
|------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------|
| BA1  |       |       | Absent from gnomAD version v 2.1.1                         |
| PM6  |    |    | Not met.                                                   |
| BS1  |    |    | Absent from gnomAD version v 2.1.1                         |
| BS4  |    |    | No data available.                                         |
| BS3  |    |    | No data available.                                         |
| PM1  |    |    | Not a missense variant in exon 4 or on a cysteine residue. |
| PM3  |    |    | No data available.                                         |
| PM4  |    |    | Not an in-frame deletion/insertion.                        |
| BS2  |    |    | No data available.                                         |
| BP7  |    |    | Not a synonymous variant.                                  |
| BP4  |  |  | REVEL= 0.899. This is greater than 0.5 so BP4 is not met.  |
| BP2  |  |  | No data available.                                         |
| PVS1 |  |  | Not a null variant.                                        |

| Curation History  |  |  |
|------------------------------------------------------------------------------------------------------|--|--|
| owing 1 to 1 of 1 rows                                                                               |  |  |
|                                                                                                      |  |  |

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