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# *Variant: NM_000527.5(LDLR):c.1897C>T (p.Arg633Cys)*

Version: 1.0

*CA10576325*

*226379 (ClinVar)*

**Gene**: LDLR (HGNC:3949)
**Condition**: hypercholesterolemia, familial (MONDO:0007750)
**Inheritance Mode**: Semidominant inheritance
**UUID:** ca9c3746-51fc-4695-995a-81bed008f106
**Approved on**: 2023/11/7
**Published on**: 2025/8/26

## *HGVS expressions*

**NM_000527.5(LDLR):c.1897C>T (p.Arg633Cys)**
**NM_000527.5:c.1897C>T**
NC_000019.10:g.11120143C>T
CM000681.2:g.11120143C>T
NC_000019.9:g.11230819C>T
CM000681.1:g.11230819C>T
NC_000019.8:g.11091819C>T
NG_009060.1:g.35763C>T
ENST00000252444.10:c.2155C>T
ENST00000559340.2:c.1757C>T
ENST00000560467.2:c.1777C>T
ENST00000558518.6:c.1897C>T
ENST00000252444.9:c.2151C>T
ENST00000455727.6:c.1393C>T
ENST00000535915.5:c.1774C>T
ENST00000545707.5:c.1516C>T
ENST00000557933.5:c.1897C>T
ENST00000558013.5:c.1897C>T
ENST00000558518.5:c.1897C>T
ENST00000559340.1:c.478C>T
NM_000527.4:c.1897C>T
NM_001195798.1:c.1897C>T
NM_001195799.1:c.1774C>T
NM_001195800.1:c.1393C>T
NM_001195803.1:c.1516C>T
NM_001195798.2:c.1897C>T
NM_001195799.2:c.1774C>T
NM_001195800.2:c.1393C>T
NM_001195803.2:c.1516C>T

**Pathogenic**

**Met criteria codes** 6

PP1 PP3 PP4 PM2 PM5 PS4

**Not Met criteria codes** 16

## Expert Panel

Familial Hypercholesterolemia VCEP

## Criteria Specification Information

BA1 PM6 PM1 PM3 PM4
BS2 BS1 BS4 BS3 PS1 PS2
PS3 BP4 BP2 PVS1 BP7

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.1897C>T (p.Arg633Cys) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PM2, PM5, PP1, PP3 and PP4 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: PopMax MAF = 0.00003 (0.003%) in South Asian exomes (gnomAD version 2.1.1). PP3: REVEL= 0.845. PM5: There is 1 variant in the same codon classified as Pathogenic by these guidelines, NM_000527.5(LDLR):c.1898G>A (p.Arg633His) (ClinVar ID: 226380). PS4, PP4: Variant meets PM2 and is identified in at least 10 unrelated index cases who fulfill criteria for FH (Simon-Broome criteria or with DLCN score >=6) from different labs (Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory, US; Robarts Research Institute, Canada; Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; Cardiovascular Research Group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; PMID 17094996 (Tosi et al., 2007), UK; PMID 31491741 (Hori et al., 2019), Japan) after alternative causes of high cholesterol were excluded. PP1: Variant segregates with phenotype in at least 2 informative meiosis in 2 families from different labs (Cardiovascular Research Group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal; Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France): 2 affected family members have the variant.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1** | ✔ | Variant segregates with FH phenotype in at least 2 informative meiosis from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge and Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies. |
| **PP3** | ✔ | REVEL= 0.845. This is greater than 0.75 so PP3 is met. |
| **PP4** | ✔ | Variant meets PM2 and is identified in at least 1 index case who fulfills SB possible or DLCN>=6 criteria for FH from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory, Robarts Research Institute and Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, after alternative causes of high cholesterol were excluded. |
| **PM2** | ✔ | PopMax MAF = 0.00003 (0.003%) in South Asian exomes (gnomAD version 2.1.1). |
| **PM5** | ✔ | Variant NM_000527.5(LDLR):c.1898G>A (p.Arg633His) (ClinVar 226380) is classified as pathogenic by these guidelines. |
| **PS4** | ✔ | Variant meets PM2 and is identified in at least 10 unrelated index cases who fulfill SB possible or DLCN>=6 criteria for FH from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory, Robarts Research Institute and Centre de |

Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, PMID 17094996, PMID 31491741, PMID after alternative causes of high cholesterol were excluded.

**Not Met criteria codes**

| | | |
|---|---|---|
| **BA1** | ✖ | FAF = 0.000002920 (0.0002920%) in European (non-Finnish) exomes (gnomAD version 2.1.1). |
| **PM6** | ✖ | Not met. |
| **PM1** | ✖ | Not located in exon 4 or at a cysteine residue. |
| **PM3** | ✖ | Not met. |
| **PM4** | ✖ | Not an in-frame deletion or insertion. |
| **BS2** | ✖ | No data available. |
| **BS1** | ✖ | FAF = 0.000002920 (0.0002920%) in European (non-Finnish) exomes (gnomAD version 2.1.1). |
| **BS4** | ✖ | Not met. |
| **BS3** | ✖ | Not met. |
| **PS1** | ✖ | No other pathogenic variants at the same codon that lead to the same amino acid change. |
| **PS2** | ✖ | Not met. |
| **PS3** | ✖ | Level 3 assay: PMID 32015373. LDLR expression, binding or internalization not <70% of wild-type. Heterozygous patient cells (CHO), FACS/ Microscopy assays - result - 70% cell surface LDLR, 72% LDL-LDLR binding and 75% uptake. |
| **BP4** | ✖ | REVEL= 0.845. This is greater than 0.5 so BP4 is not met. |
| **BP2** | ✖ | No data available. |
| **PVS1** | ✖ | Not a null variant. |
| **BP7** | ✖ | Not a synonymous variant. |

## Curation History

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.