

*Variant: NM\_000527.5(LDLR):c.1049G>C (p.Arg350Pro)*

Version: 1.0

CA10576296 [↗](#)

226343 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** baa65fd0-7621-400f-b358-8c8d1aaafcc5

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### *HGVS expressions*

**NM\_000527.5(LDLR):c.1049G>C (p.Arg350Pro)**

**NM\_000527.5:c.1049G>C**

NC\_000019.10:g.11110760G>C

CM000681.2:g.11110760G>C

NC\_000019.9:g.11221436G>C

CM000681.1:g.11221436G>C

NC\_000019.8:g.11082436G>C

NG\_009060.1:g.26380G>C

ENST00000252444.10:c.1307G>C

ENST00000559340.2:c.1049G>C

ENST00000560467.2:c.941-754G>C

ENST00000558518.6:c.1049G>C

ENST00000252444.9:c.1303G>C

ENST00000455727.6:c.545G>C

ENST00000535915.5:c.926G>C

ENST00000545707.5:c.668G>C

ENST00000557933.5:c.1049G>C

ENST00000558013.5:c.1049G>C

ENST00000558518.5:c.1049G>C

ENST00000560173.1:n.48G>C

ENST00000560467.1:c.541-754G>C

NM\_000527.4:c.1049G>C

NM\_001195798.1:c.1049G>C

NM\_001195799.1:c.926G>C

NM\_001195800.1:c.545G>C

NM\_001195803.1:c.668G>C

NM\_001195798.2:c.1049G>C

NM\_001195799.2:c.926G>C

NM\_001195800.2:c.545G>C

NM\_001195803.2:c.668G>C

Likely Pathogenic

Met criteria codes 5

PS4\_SupportingPS3\_ModeratePP4PM2PP1\_Moderate

Not Met criteria codes 8

PVS1BS1BS4BS3BP4BA1PP3PM1

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

NM\_000527.4(LDLR): c.1049G>C (p.Arg350Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PS4\_Supporting, PP1\_Moderate, PP4, and PS3 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1016/j.gim.2021.09.012). The supporting evidence is as follows: . PM2: This variant is absent from gnomAD (gnomAD v2.1.1). . PS4\_Supporting: Variant meets PM2 and is identified in 5 index cases: 4 cases with DLCN criteria>=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), 1 case with DLCN criteria>=6 in Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France . PP1\_Moderate: Variant segregates with FH phenotype in 5 informative meioses in 3 families from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA). 3 relatives without the phenotype and the variant, 2 relatives with the phenotype and the variant . PP4: Variant meets PM2 and is identified in at least 1 index case with DLCN>=6 after alternative causes of high cholesterol were excluded. Data is from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) and Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France. . PS3\_moderate: Level 2 assays: PMID 15100232 Heterologous cells (CHO) ACS, WB and NMR Spectroscopy <10% cell surface LDLR, 65% binding, (WB), ~10% expression

Met criteria codes

|                |  |   |                                                                                                                                                                                                                                                                                                                     |
|----------------|--|---|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PS4_Supporting |  | ✓ | Variant meets PM2 and is identified in 5 index cases: 4 cases with DLCN criteria>=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), 1 case with DLCN criteria>=6 in Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France                               |
| PS3_Moderate   |  | ✓ | Level 2 assays: PMID 15100232 Heterologous cells (CHO) ACS, WB and NMR Spectroscopy <10% cell surface LDLR, 65% binding, (WB), ~10% expression                                                                                                                                                                      |
| PP4            |  | ✓ | Variant meets PM2 and is identified in at least 1 index case with DLCN>=6 after alternative causes of high cholesterol were excluded. Data is from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) and Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France. |
| PM2            |  | ✓ | This variant is absent from gnomAD (gnomAD v2.1.1).                                                                                                                                                                                                                                                                 |
| PP1_Moderate   |  | ✓ | Variant segregates with FH phenotype in 5 informative meioses in 3 families from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA). 3 relatives without the phenotype and the variant, 2 relatives with the phenotype and the variant                                                            |

Not Met criteria codes

|      |                                                                                     |                                                                                     |                                                                                                                                                                                                                                        |
|------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PVS1 |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                             |
| BS1  |    |    | This variant is absent from gnomAD (gnomAD v2.1.1).                                                                                                                                                                                    |
| BS4  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                             |
| BS3  |    |    | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                             |
| BP4  |    |    | REVEL = 0.648. It is not above 0.75, splicing evaluation needed. Functional data on splicing not available. A) variant not on limits. B) Variant does not create GT. C) there is no GT nearby. Variant is predicted to alter splicing. |
| BA1  |    |    | This variant is absent from gnomAD (gnomAD v2.1.1).                                                                                                                                                                                    |
| PP3  |    |    | REVEL = 0.648. It is not above 0.75, splicing evaluation needed. Functional data on splicing not available. A) variant not on limits. B) Variant does not create GT. C) there is no GT nearby. Variant is predicted to alter splicing. |
| PM1  |  |  | Variant no on Exon 4                                                                                                                                                                                                                   |

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.