The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2023/4/28
Published on: 2023/4/28

HGVS expressions

NM_000527.5:c.1049G>C
NM_000527.5(LDLR):c.1049G>C (p.Arg350Pro)
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

PM2 PS3_Moderate PP1_Moderate PS4_Supporting PP4

Not Met criteria codes 8

PM1 BA1 BS1 BS4 BS3 BP4 PVS1 PP3

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

PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).
PS3_Moderate	✔	Level 2 assays: PMID 15100232 Heterologous cells (CHO) ACS, WB and NMR Spectroscopy <10% cell surface LDLR, 65% binding, (WB), ~10% expression
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
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
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.

Not Met criteria codes

PM1	✖	Variant no on Exon 4
BA1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
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.
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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.

Curation History

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