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.510C>A (p.Asp170Glu)

Version: 1.0

CA16609804

403662 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 64d0b8e1-535a-413f-b7d4-5d7c305a9aa6
Approved on: 2025/3/9
Published on: 2025/3/9

HGVS expressions

NM_000527.5:c.510C>A
NM_000527.5(LDLR):c.510C>A (p.Asp170Glu)
NC_000019.10:g.11105416C>A
CM000681.2:g.11105416C>A
NC_000019.9:g.11216092C>A
CM000681.1:g.11216092C>A
NC_000019.8:g.11077092C>A
NG_009060.1:g.21036C>A
ENST00000252444.10:c.768C>A
ENST00000559340.2:c.510C>A
ENST00000560467.2:c.510C>A
ENST00000558518.6:c.510C>A
ENST00000252444.9:c.764C>A
ENST00000455727.6:c.314-1976C>A
ENST00000535915.5:c.387C>A
ENST00000545707.5:c.314-1149C>A
ENST00000557933.5:c.510C>A
ENST00000558013.5:c.510C>A
ENST00000558518.5:c.510C>A
ENST00000560467.1:c.110C>A
NM_000527.4:c.510C>A
NM_001195798.1:c.510C>A
NM_001195799.1:c.387C>A
NM_001195800.1:c.314-1976C>A
NM_001195803.1:c.314-1149C>A
NM_001195798.2:c.510C>A
NM_001195799.2:c.387C>A
NM_001195800.2:c.314-1976C>A
NM_001195803.2:c.314-1149C>A

Likely Pathogenic

Met criteria codes 4

PP4 PM2 PM1 PS4_Supporting

Not Met criteria codes 2

PP3 BP4

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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.510C>A (p.Asp170Glu) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 9 March 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.00002664 (0.002664%) in African/African American exomes (gnomAD v4.1.0). PM1: Variant meets PM2 and is missense in exon 4. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 2 unrelated index cases who fulfill Simon Broome criteria for possible FH (1 case from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; 1 case meeting Simon Broome criteria for possible FH in PMID 27824480 (Gabčová et al., 2017)).

Met criteria codes

PP4	✔	Variant meets PM2 and is identified in at least 1 index case who fulfills SB possible FH criteria after alternative causes of high cholesterol were excluded (Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation).
PM2	✔	PopMax MAF = 0.00002664 (0.002664%) in African/African American exomes (gnomAD v4.1.0).
PM1	✔	Variant meets PM2 and is missense in exon 4.
PS4_Supporting	✔	Variant meets PM2 and is identified in at least 2 unrelated index cases who fulfill SB possible criteria for FH. (1) 1 FH patient meeting SB possible criteria carries the variant (Molecular Genetics Laboratory ,Centre for Cardiovascular Surgery and Transplantation) (2) 1 FH patient meeting SB possible criteria carries the variant (PMID: 27824480)

Not Met criteria codes

PP3	✖	REVEL = 0.29. It is below 0.50, so splicing evaluation is required. Functional data on splicing not available. A) not on limits; B) does not create AG/GT; C) there is an AG nearby. MES scores: variant cryptic = -1.47, wt cryptic = -0.20, canonical donor = 8.16. Ratio variant cryptic/wt cryptic: -1.47/-0.20 = 7.35 --- it is above 1.1. Ratio variant cryptic/canonical donor: -1.47/8.16 = -0.18 --- it is not above 0.9. Variant is not predicted to alter splicing. PP3 is not met; BP4 is not met.
BP4	✖	REVEL = 0.29. It is below 0.50, so splicing evaluation is required. Functional data on splicing not available. A) not on limits; B) does not create AG/GT; C) there is an AG nearby. MES scores: variant cryptic = -1.47, wt cryptic = -0.20, canonical donor = 8.16. Ratio variant cryptic/wt cryptic: -1.47/-0.20 = 7.35 --- it is above 1.1. Ratio variant cryptic/canonical donor: -1.47/8.16 = -0.18 --- it is not above 0.9. Variant is not predicted to alter splicing. PP3 is not met; BP4 is not met.

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.510C>A (p.Asp1...	Likely Pathogenic	Hypercholesterolemia, Familial	2025-03-09	1.0	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR

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