

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

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HGVS expressions

NM_000527.5(LDLR):c.510C>A (p.Asp170Glu)

NM_000527.5:c.510C>A

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 PM1 PM2 PS4_Supporting

Not Met criteria codes 2

BP4 PP3

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).
PM1			Variant meets PM2 and is missense in exon 4.
PM2			PopMax MAF = 0.00002664 (0.002664%) in African/African American exomes (gnomAD v4.1.0).
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

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.
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.

Curation History 

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