

Variant: NM_000527.5(LDLR):c.1069G>A (p.Glu357Lys)

Version: 1.0

CA10585290 [↗](#)

251649 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: ccc16f7d-5c58-4e8c-ae15-1a7624c918e6

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HGVS expressions

NM_000527.5:c.1069G>A

NM_000527.5(LDLR):c.1069G>A (p.Glu357Lys)

NC_000019.10:g.11111522G>A

CM000681.2:g.11111522G>A

NC_000019.9:g.11222198G>A

CM000681.1:g.11222198G>A

NC_000019.8:g.11083198G>A

NG_009060.1:g.27142G>A

ENST00000252444.10:c.1327G>A

ENST00000559340.2:c.1069G>A

ENST00000560467.2:c.949G>A

ENST00000558518.6:c.1069G>A

ENST00000252444.9:c.1323G>A

ENST00000455727.6:c.565G>A

ENST00000535915.5:c.946G>A

ENST00000545707.5:c.688G>A

ENST00000557933.5:c.1069G>A

ENST00000558013.5:c.1069G>A

ENST00000558518.5:c.1069G>A

ENST00000560173.1:n.68G>A

ENST00000560467.1:c.549G>A

NM_000527.4:c.1069G>A

NM_001195798.1:c.1069G>A

NM_001195799.1:c.946G>A

NM_001195800.1:c.565G>A

NM_001195803.1:c.688G>A

NM_001195798.2:c.1069G>A

NM_001195799.2:c.946G>A

NM_001195800.2:c.565G>A

NM_001195803.2:c.688G>A

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM2 PM3

PS4_Moderate

Not Met criteria codes 21

BP5 BP7 BP4 BP3 BP1 BP2
PS1 PS2 PS3 PP1 PP2 PM6
PM1 PM5 PM4 PVS1 BA1
BS2 BS1 BS4 BS3

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

The NM_000527.5(LDLR):c.1069G>A (p.Glu357Lys) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PM3, PS4_moderate, PP3 and PP4) 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). PM3 - Variant meets PM2 and is identified in 2 compound heterozygous cases (1 case in PMID: 30179711 (Lock et al., 2018) with LDL = 23.89 mmol/L and also LDLR c.2043C>A - Pathogenic by these guidelines; 1 case in PMID: 19026292 (Kolansky et al., 2008) with LDL = 16.29 mmol/L and also LDLR c.1775G>A - Pathogenic by these guidelines). PS4_moderate - Variant meets PM2 and is identified in 8 unrelated index cases (3 cases with DLCN criteria>=6 and 1 case with Simon-Broome criteria of possible FH from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 unrelated case fulfilling internationally accepted criteria (Defesche 2000; Goldstein et al. 1995) for definite heterozygous FH published in PMID: 11810272 (Fouchier et al., 2001), The Netherlands; 1 unrelated case fulfilling WHO criteria published in PMID: 21382890 (van der Graaf et al., 2011), The Netherlands; 1 unrelated case fulfilling WHO criteria published in PMID: 10735632 (Lombardi et al., 2000), The Netherlands; 1 unrelated case with DLCN criteria>=6 published in PMID: 28502510 (Bañares et al., 2017), Argentina). PP3 - REVEL = 0.976. PP4 - Variant meets PM2 and is identified in at least one index case who fufills clinical criteria for FH (see PS4 for details), after alternative causes for high cholesterol were excluded.

Met criteria codes

PP3		✓	REVEL = 0.976
PP4		✓	Variant meets PM2 and is identified in at least one index case who fufills clinical criteria for FH (see PS4 for details), after alternative causes for high cholesterol were excluded.
PM2		✓	This variant is absent from gnomAD (gnomAD v2.1.1).
PM3		✓	Variant meets PM2 and is identified in 2 compound heterozygous cases (1 case in PMID: 30179711 (Lock et al., 2018) with LDL = 23.89 mmol/L and also LDLR c.2043C>A - Pathogenic by these guidelines; 1 case in PMID: 19026292 (Kolansky et al., 2008) with LDL = 16.29 mmol/L and also LDLR c.1775G>A - Pathogenic by these guidelines).
PS4_Moderate		✓	Variant meets PM2 and is identified in 8 unrelated index cases (3 cases with DLCN criteria>=6 and 1 case with Simon-Broome criteria of possible FH from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 unrelated case fulfilling internationally accepted criteria (Defesche 2000; Goldstein et al. 1995) for

definite heterozygous FH published in PMID: 11810272 (Fouchier et al., 2001), The Netherlands; 1 unrelated case fulfilling WHO criteria published in PMID: 21382890 (van der Graaf et al., 2011), The Netherlands; 1 unrelated case fulfilling WHO criteria published in PMID: 10735632 (Lombardi et al., 2000), The Netherlands; 1 unrelated case with DLCN criteria $\geq$ 6 published in PMID: 28502510 (Bañares et al., 2017), Argentina).

Not Met criteria codes

BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1069G>C (p.Glu357Gln) (ClinVar ID 431519) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1070A>G (p.Glu357Gly) (ClinVar ID 251651) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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

Curation History 		
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