

Variant: *NM_000527.5(LDLR):c.337G>A (p.Glu113Lys)*

Version: 1.0

CA043209 [↗](#)

237872 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: a09d8e79-7df9-4d5f-b357-ebd7eff7a82c

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HGVS expressions

NM_000527.5(LDLR):c.337G>A (p.Glu113Lys)

NM_000527.5:c.337G>A

NC_000019.10:g.11105243G>A

CM000681.2:g.11105243G>A

NC_000019.9:g.11215919G>A

CM000681.1:g.11215919G>A

NC_000019.8:g.11076919G>A

NG_009060.1:g.20863G>A

ENST00000252444.10:c.595G>A

ENST00000559340.2:c.337G>A

ENST00000560467.2:c.337G>A

ENST00000558518.6:c.337G>A

ENST00000252444.9:c.591G>A

ENST00000455727.6:c.314-2149G>A

ENST00000535915.5:c.214G>A

ENST00000545707.5:c.314-1322G>A

ENST00000557933.5:c.337G>A

ENST00000558013.5:c.337G>A

ENST00000558518.5:c.337G>A

NM_000527.4:c.337G>A

NM_001195798.1:c.337G>A

NM_001195799.1:c.214G>A

NM_001195800.1:c.314-2149G>A

NM_001195803.1:c.314-1322G>A

NM_001195798.2:c.337G>A

NM_001195799.2:c.214G>A

NM_001195800.2:c.314-2149G>A

NM_001195803.2:c.314-1322G>A

Pathogenic

Met criteria codes **6**

PS4_Moderate

PP1_Strong

PP4

PM2

PM1

PM3

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PVS1

BS2

BS1

BS4

BS3

BP5

BP7

BP4

BP3

BP1

BP2

PS1

PS2

PS3

PP2

PP3

BA1

PM6

PM5

PM4

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.337G>A (p.Glu113Lys) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PP1_Strong, PM1, PM2, PM3, PS4_Moderate and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: PopMax MAF = 0.0001 (0.01%) in South Asian (gnomAD v4.0.0). PM1: Variant meets PM2 and is missense in exon 4. PS4_Moderate, PP4: Variant meets PM2 and is identified in at least 8 unrelated index cases who fulfill criteria for FH (1 case with possible FH by Simon Broome criteria from the Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; 1 case with possible FH by Simon Broome criteria and 1 case with DLCN score >=6 from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France; 1 case with possible FH by Simon Broome criteria from PMID 17539906 (Taylor et al., 2007), UK; 1 case with DLCN score >=6 from PMID 16250003 (Fouchier et al., 2005), The Netherlands; 1 case with possible FH by Simon Broome criteria from PMID 10807540 (Wu et al., 2000), USA; 2 cases with definite FH by Simon Broome criteria from PMID 34456049 (Marco-Benedi et al., 2022). PP1_Strong: Variant segregates with FH phenotype in 8 informative meioses in 1 family in PMID: 10807540 (Wu et al., 2000), USA: 7 affected family members have the variant. PM3: Variant meets PM2 and is identified in an index case with a homozygous FH phenotype (10 yo with LDLc= 14.9 mmol/L); variant is in compound heterozygosity with c.2389G>T (p.Val797Leu), which is classified as Likely pathogenic by these guidelines and is in trans, from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France (VCI).

Met criteria codes

PS4_Moderate			PS4_Moderate - Variant meets PM2 and is identified in 8 unrelated index cases - 1 case with Simon Broome criteria of possible FH from the Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; 1 case with Simon-Broome criteria of possible FH and 1 case with DLCN criteria>=6 from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France; 1 case with Simon-Broome criteria of possible FH in PMID: 17539906 (Taylor et al., 2007), UK; 1 case with DLCN criteria>=6 in PMID: 16250003 (Fouchier et al., 2005), The Netherlands; 1 case with Simon-Broome criteria of possible FH in PMID: 10807540 (Wu et al., 2000), USA; 2 cases with Simon-Broome criteria of definite FH in PMID: 34456049 (Marco-Benedi et al., 2022);
PP1_Strong			PP1_strong - Variant segregates with FH phenotype in 8 informative meioses in 1 family in PMID: 10807540 (Wu et al., 2000), USA: 7 affected family members have the variant;
PP4			PP4 - Variant meets PM2 and is identified in at least 1 index case who fulfills clinical criteria for FH, after alternative causes of high cholesterol were excluded (see PS4 for details).
PM2			PM2 - PopMax MAF = 0.0001 (0.01%) in South Asian (gnomAD v4.0.0)
PM1			PM1 - Variant meets PM2 and is missense in exon 4.

PM3			PM3 - Variant meets PM2 and is identified in an index case with a homozygous FH phenotype (10 yo with LDLc= 14.9 mmol/L); variant is in compound heterozygosity with c.2389G>T (p.Val797Leu), which is classified as Likely pathogenic by these guidelines and is in trans (1 of 2 variants was found in mother - hypercholesterolemic father not tested); from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France (VCI).
Not Met criteria codes			
PVS1			Not applicable
BS2			Variant not identified in normolipidemic individuals
BS1			Not applicable
BS4			BS4 - Variant does not segregate with FH phenotype in 2 informative meioses from 2 families from different labs (Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France/PMID: 10807540 (Wu et al., 2000), USA: 2 affected family members do not have the variant, however no unaffected relatives were positive for the variant, so BS4 cannot be applied.
BS3			BS3 - Functional studies are not available.
BP5			Not applicable
BP7			Not applicable
BP4			BP4 - REVEL = 0.658; it is not below 0.5, so BP4 is not met.
BP3			Not applicable
BP1			Not applicable
BP2			Not applicable
PS1			Not applicable
PS2			No de novo cases were identified
PS3			PS3 - Functional studies are not available.
PP2			Not applicable
PP3			PP3 - REVEL=0.658, splicing evaluation required. A) Variant not on limits B) does not create AG C) there is an AG nearby MES scores: variant cryptic site = -7.58, wt cryptic site = -16.76, canonical acceptor site = 8.16. Ratio

variant cryptic/wt cryptic score: $-7.58/-16.76 = 0.45$ --- it is not above 1.1 Ratio variant cryptic/canonical acceptor score: $-7.58/8.16 = -0.92$ --- it is not above 0.9 ---PP3 is not met.

BA1			Not applicable
PM6			No de novo cases were identified
PM5			PM5 - There is 1 variant in the same codon [c.337G>T, p.(Glu113Ter)] but it is not missense
PM4			Not applicable

Curation History

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