

Variant: *NM_000527.5(LDLR):c.301G>A (p.Glu101Lys)*

Version: 1.1

CA023687 [↗](#)

161266 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 07409e96-2c49-47c8-8e87-1e15283ee370

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HGVS expressions

NM_000527.5:c.301G>A

NM_000527.5(LDLR):c.301G>A (p.Glu101Lys)

NC_000019.10:g.11102774G>A

CM000681.2:g.11102774G>A

NC_000019.9:g.11213450G>A

CM000681.1:g.11213450G>A

NC_000019.8:g.11074450G>A

NG_009060.1:g.18394G>A

ENST00000252444.10:c.559G>A

ENST00000559340.2:c.301G>A

ENST00000560467.2:c.301G>A

ENST00000558518.6:c.301G>A

ENST00000252444.9:c.555G>A

ENST00000455727.6:c.301G>A

ENST00000535915.5:c.190+2429G>A

ENST00000545707.5:c.301G>A

ENST00000557933.5:c.301G>A

ENST00000557958.1:n.387G>A

ENST00000558013.5:c.301G>A

ENST00000558518.5:c.301G>A

NM_000527.4:c.301G>A

NM_001195798.1:c.301G>A

NM_001195799.1:c.190+2429G>A

NM_001195800.1:c.301G>A

NM_001195803.1:c.301G>A

NM_001195798.2:c.301G>A

NM_001195799.2:c.190+2429G>A

NM_001195800.2:c.301G>A

NM_001195803.2:c.301G>A

Pathogenic

Met criteria codes **7**

PS3_Moderate PP1_Strong PP3
PP4 PM3 PM2 PS4

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BA1BP5BP7BP4BP3BP1BP2BS2BS1BS4BS3PP2PM1PM5PM4PM6PVS1PS1PS2

Evidence Links 0

- [Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.301G>A (p.Glu101Lys) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PP1_Strong, PS4, PM2, PM3, PS3_Moderate, PP3 and PP4) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PP1_strong - variant segregates with the FH phenotype in at least 19 relatives with the variant and LDL-C above the 75th percentile from several labs (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, Ambry, Robarts Research Institute), so PP1_Strong is met. PS4 - variant meets PM2 and is identified in at least 16 index cases who fulfill validated clinical criteria for FH from several labs (SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge and DLCN >=6 from Color, Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) and Robarts Research Institute), so PS4 is met. PM2 - PopMax MAF = 0.00003266 (0.003%) in south asian exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PM3 - variant meets PM2 and was identified in 1 index case with LDL 16.2 mmol/L and also LDLR exon 15 deletion from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) - Likely pathogenic by these guidelines, so PM3 is met PS3_moderate - Level 2 FS: Hobbs et al., 1992 (PMID 1301956): Hmz patient fibroblast, 125I-LDL assays - results: 15-30% LDLR activity. Activity is below 70% of wild-type, so PS3_Moderate is met. PP3 - REVEL = 0.896. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and is identified in at least 1 index case who fulfills SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. so, PP4 is met

Met criteria codes

PS3_Moderate			Level 2(pathogenic) FS: Hobbs et al., 1992 (PMID 1301956): Hmz patient fibroblast, 125I-LDL assays - results: 15-30% LDLR activity. Activity is below 70% of wild-type, so PS3_Moderate is met
PP1_Strong			variant segregates with the FH phenotype in at least 19 relatives from several families: - 16 relatives from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (16 with variant and LDL-C >75th percentile) - at least 2 relatives from 2 families from Ambry (with variant and LDL-C >75th percentile) - 1 relative from Robarts Research Institute (with variant and LDL-C >75th percentile) so PP1_Strong is met
PP3			REVEL = 0.896. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and is identified in at least 1 index case who fulfills SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. (for more cases see PS4) so, PP4 is met
PM3			variant meets PM2 and was identified in: - 1 index case with LDL 16.2 mmol/L and also exon 15 deletion from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) - Likely pathogenic by these guidelines - 1 index case with LDL 412mg/dl on treatment, who is also het for NM_000384.3(APOB):c.3208G>A (p.Asp1070Asn) (ClinVar ID 630412) from Ambry - VUS by the general guidelines by FH VCEP meeting on Oct 7th 2021, Likely pathogenic variants are accepted for PM3, so PM3 is met

PM2			PopMax MAF = 0.00003266 (0.003%) in south asian exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met
PS4			variant meets PM2 and is identified in at least 16 index cases: - 1 index case who fulfills SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; - 1 index case with DLCN >=6 from Color; - 10 unrelated index cases with DLCN >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); - 4 unrelated index cases with DLCN >=6 from Robarts Research Institute; so, PS4 is met
Not Met criteria codes			
BA1			FAF = 0.000007010 (0.000701%) in european non-finnish exomes (gnomAD v2.1.1). It is not above 0.5%, so BA1 is not met
BP5			Not applicable
BP7			variant is missense, so not applicable
BP4			REVEL = 0.896. It is not below 0.5, so BP4 is not met
BP3			not applicable
BP1			Not applicable
BP2			variant was identified in - 1 index case from University of British Columbia with also the NM_000527.5(LDLR):c.970G>A (p.Gly324Ser) variant - 1 star, Conflicting interpretations of pathogenicity: Benign(5);Likely benign(4);Likely pathogenic(1);Pathogenic(1);Uncertain significance(2) - Benign by these guidelines and a phenotype of Heterozygous FH. variant is not Pathogenic, so BP2 is not met
BS2			not identified in normolipidemic individuals: 0/208 non-FH alleles from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge and 0/1000 controls from Robarts Research Institute, so BS2 is not met
BS1			FAF = 0.000007010 (0.000701%) in european non-finnish exomes (gnomAD v2.1.1). It is not above 0.2%, so BS1 is not met
BS4			Data in VCI: 11 family members positive for the variant, 6 family members negative for the variant. No segregation. From Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) but no specification of phenotypes, so not met
BS3			Level 3(benign) FS: Hobbs et al., 1992 (PMID 1301956): Hmz patient fibroblast, 125I-LDL assays - results: 15-30% LDLR activity. Activity is not above 90% of wild-type, so BS3_Supporting is not met
PP2			Not applicable
PM1			variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so PM1 is not met

PM5			1 other missense variant in the same codon: - NM_000527.5(LDLR):c.302A>G (p.Glu101Gly) - LP - 1 star in ClinVar - VUS by these guidelines so, PM5 is not met
PM4			variant is missense, so not applicable
PM6			no de novo occurrence was identified
PVS1			variant is missense and not in initiation codon, so PVS1 is not met
PS1			no other missense variant leads to the same amino acid change, so PS1 is not met
PS2			no de novo occurrence was identified

Curation History 		
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