

Variant: *NM_000527.5(LDLR):c.1301C>A (p.Thr434Lys)*

Version: 1.0

CA10585392 [↗](#)

251773 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 968c6325-8093-4953-a591-6250a37c3174

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HGVS expressions

NM_000527.5(LDLR):c.1301C>A (p.Thr434Lys)

NM_000527.5:c.1301C>A

NC_000019.10:g.11113392C>A

CM000681.2:g.11113392C>A

NC_000019.9:g.11224068C>A

CM000681.1:g.11224068C>A

NC_000019.8:g.11085068C>A

NG_009060.1:g.29012C>A

ENST00000252444.10:c.1559C>A

ENST00000559340.2:c.1301C>A

ENST00000560467.2:c.1181C>A

ENST00000558518.6:c.1301C>A

ENST00000252444.9:c.1555C>A

ENST00000455727.6:c.797C>A

ENST00000535915.5:c.1178C>A

ENST00000545707.5:c.920C>A

ENST00000557933.5:c.1301C>A

ENST00000558013.5:c.1301C>A

ENST00000558518.5:c.1301C>A

ENST00000559340.1:c.22C>A

ENST00000560173.1:n.300C>A

ENST00000560467.1:c.781C>A

NM_000527.4:c.1301C>A

NM_001195798.1:c.1301C>A

NM_001195799.1:c.1178C>A

NM_001195800.1:c.797C>A

NM_001195803.1:c.920C>A

NM_001195798.2:c.1301C>A

NM_001195799.2:c.1178C>A

NM_001195800.2:c.797C>A

NM_001195803.2:c.920C>A

Likely Pathogenic

Met criteria codes **4**

PP4

PM2

PM5

PS4_Supporting

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Not Met criteria codes 18

BP4 BP3 BP2 PS1 PS2 PS3
PP1 PP3 PM6 PM1 PM3
PM4 PVS1 BA1 BS2 BS1
BS4 BS3

Evidence Links 0

Criteria Specification Information ⓘ

🔗 Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1301C>A (p.Thr434Lys) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4_Supporting, PM2, PM5, 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>). PS4_Supporting: Variant meets PM2 and is identified in 2 unrelated cases, as follows: 1 case with DLCN ≥ 6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case with clinical criteria based on Defesche J. 2000. Familial hypercholesterolemia. In: Betteridge J (ed): Lipids and Vascular Disease from PMID 11810272. So PS4_Supporting is met. PM2: PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). So, PM2 is met. PM5: 3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1301C>G (p.Thr434Arg) (ClinVar ID 251774) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1301C>T (p.Thr434Met)(ClinVar ID 251775) - Unknown significance by these guidelines - NM_000527.5(LDLR):c.1300A>C (p.Thr434Pro)(ClinVar ID 496018) - Unknown significance by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines. PP4: Variant meets PM2. Identified in 1 FH case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon with clinical DLCN Criteria score ≥ 6 , after alternative causes of high cholesterol were excluded.

Met criteria codes

PP4	ⓘ	✓	Variant meets PM2. Identified in 1 FH case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon with clinical DLCN Criteria score ≥ 6 , after alternative causes of high cholesterol were excluded.
PM2	ⓘ	✓	PopMax MAF = 0.00001 (0.001%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). So, PM2 is met.
PM5	ⓘ	✓	3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1301C>G (p.Thr434Arg) (ClinVar ID 251774) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1301C>T (p.Thr434Met)(ClinVar ID 251775) - Unknown significance by these guidelines - NM_000527.5(LDLR):c.1300A>C (p.Thr434Pro)(ClinVar ID 496018) - Unknown significance by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines.
PS4_Supporting	ⓘ	✓	Variant meets PM2 and is identified in 2 unrelated cases, as follows: 1 case with DLCN ≥ 6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case with clinical criteria based on Defesche J. 2000. Familial hypercholesterolemia. In: Betteridge J (ed): Lipids and Vascular Disease from PMID 11810272. So PS4_Supporting is met.

Not Met criteria codes

BP4	ⓘ	✗	REVEL = 0.652. It is not above 0.75, so splicing evaluation required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp upstream from the canonical donor site and creates AG.
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Wild type score= 6.59, Variant score= -0.05; Var/Wt ratio= -0.007. It is below 0.9. C) there is an AG nearby. Variant cryptic score= -16.29, Wild type cryptic score= -10.76; Var criptic/Wt criptic= 1.51, Var criptic/Wt score= -2.47. It is below 0.9. Variant is not predicted to alter splicing.

BP3			No in-frame deletions/insertions
BP2			No data available
PS1			No missense variant in the same codon resulting in the same amino acid change.
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			PMID 21868016, results: 40% the receptor activity (35% internalization and 40% degradation, 40% binding). Results are below 85% of wild-type activity. However, method and results of original functional data for this variant was not cited.
PP1			No data available
PP3			REVEL = 0.652. It is not above 0.75, so splicing evaluation required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp upstream from the canonical donor site and creates AG. Wild type score= 6.59, Variant score= -0.05; Var/Wt ratio= -0.007. It is below 0.9. C) there is an AG nearby. Variant cryptic score= -16.29, Wild type cryptic score= -10.76; Var criptic/Wt criptic= 1.51, Var criptic/Wt score= -2.47. It is below 0.9. Variant is not predicted to alter splicing.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Not in exon 4. Not a cysteine residue.
PM3			No data available
PM4			No in-frame deletions/insertions
PVS1			Not a null variant.
BA1			Allele frequency= 0.00000398.
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			Allele frequency= 0.00000398.

BS4			No data available
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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