

Variant: NM_000527.5(LDLR):c.1195G>A (p.Ala399Thr)

Version: 1.0

CA023430 [↗](#)

183109 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: ce020df2-3589-49b1-989b-f1f494f3e1b3

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HGVS expressions

NM_000527.5(LDLR):c.1195G>A (p.Ala399Thr)

NM_000527.5:c.1195G>A

NC_000019.10:g.11113286G>A

CM000681.2:g.11113286G>A

NC_000019.9:g.11223962G>A

CM000681.1:g.11223962G>A

NC_000019.8:g.11084962G>A

NG_009060.1:g.28906G>A

ENST00000252444.10:c.1453G>A

ENST00000559340.2:c.1195G>A

ENST00000560467.2:c.1075G>A

ENST00000558518.6:c.1195G>A

ENST00000252444.9:c.1449G>A

ENST00000455727.6:c.691G>A

ENST00000535915.5:c.1072G>A

ENST00000545707.5:c.814G>A

ENST00000557933.5:c.1195G>A

ENST00000558013.5:c.1195G>A

ENST00000558518.5:c.1195G>A

ENST00000560173.1:n.194G>A

ENST00000560467.1:c.675G>A

NM_000527.4:c.1195G>A

NM_001195798.1:c.1195G>A

NM_001195799.1:c.1072G>A

NM_001195800.1:c.691G>A

NM_001195803.1:c.814G>A

NM_001195798.2:c.1195G>A

NM_001195799.2:c.1072G>A

NM_001195800.2:c.691G>A

NM_001195803.2:c.814G>A

Likely Pathogenic

Met criteria codes6

PS4_ModeratePP1PP3PP4PM2PM3

Not Met criteria codes16

PVS1BS2BS1BS4BS3BP7BP4BP2PS1PS2PS3BA1PM6PM1PM5PM4

Evidence Links1

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.1195G>A (p.Ala399Thr) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM3, PS4_Moderate, PP1, PP3, and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on January 23, 2026. The supporting evidence is as follows: PM2: PopMax MAF = 0.0000093 (0.00093%) in European non-Finnish exomes+genomes (gnomAD v4.1). PP3: REVEL = 0.755. PS4_Moderate, PP4: Variant meets PM2 and is identified in at least 7 index cases who fulfill criteria for FH from different labs (1 case with DLCN score >=6 from CMG UZA, Belgium; 1 case with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism - Department of Translational and Precision Medicine, Italy; 1 case with DLCN score >=6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case with DLCN score >=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; at least 1 case (0.6% in 169) who fulfills MEDPED criteria from PMID 21925044 (Diakou et al., 2011), Greece; at least 1 case with definite heterozygous FH from PMID 16250003 (Fouchier et al., 2005), The Netherlands; 1 case meeting Taiwan Lipids Guideline criteria from PMID 33994402 (Huang et al., 2022), Taiwan). PP1: Variant segregates with FH phenotype in at least 4 informative meiosis (minimum 2) from 1 family from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA): 1 affected family member has the variant and 3 non-affected family members do not have the variant. PM3: Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL >500mg/dL) and LDLR variant c.2475C>A/p.(Asn825Lys), classified as Pathogenic by these guidelines, in trans, from Spain (PMID 27784735 (Sánchez-Hernández et al., 2016)).

Met criteria codes

PS4_Moderate	i ✓	Variant meets PM2 and is identified in at least 7 index cases who fulfill criteria for FH from different labs (1 case with DLCN criteria>=6 from CMG UZA, Belgium; 1 index case with Dutch lipid clinic network >=6 from Research Lab of Molecular Genetics of Lipid Metabolism - Department of Translational and Precision Medicine, Italy; 1 index case with Dutch lipid clinic network >=6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 index case with Dutch lipid clinic network >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; at least 1 index case (0.6% in 169) who fulfills MEDPED criteria for FH from Greece (PMID: 21925044); at least 1 index case with diagnosed with definite heterozygous FH from The Netherlands (PMID: 16250003); 1 index case with Taiwan Lipids Guideline criteria for FH from Taiwan (33994402)), so PS4_Moderate is met.
PP1	i ✓	Variant segregates with FH phenotype in at least 4 informative meiosis (minimum 2) from 1 family from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA): 1 affected family member has the variant and 3 non-affected family members do not have the variant, so PP1 is met.
PP3	i ✓	REVEL = 0.755. It is above 0.75, so PP3 is met.

PP4			Variant meets PM2 and is identified in at least 7 index cases who fulfill criteria for FH from different labs (1 case with DLCN criteria ≥ 6 from CMG UZA, Belgium; 1 index case with Dutch lipid clinic network ≥ 6 from Research Lab of Molecular Genetics of Lipid Metabolism - Department of Translational and Precision Medicine, Italy; 1 index case with Dutch lipid clinic network ≥ 6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 index case with Dutch lipid clinic network ≥ 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; at least 1 index case (0.6% in 169) who fulfills MEDPED criteria for FH from Greece (PMID: 21925044); at least 1 index case with diagnosed with definite heterozygous FH from The Netherlands (PMID: 16250003); 1 index case with Taiwan Lipids Guideline criteria for FH from Taiwan (33994402)), after alternative causes of high cholesterol were excluded so PP4 is met.
PM2			PopMax MAF = 0.0000093 (0.00093%) in European non Finnish exomes+genomes (gnomAD v4.1), so PM2 is Met.
PM3			Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL >500 mg/dL) and LDLR variant c.2475C $>$ A/p.(Asn825Lys), classified as Pathogenic by these guidelines, in trans, from Spain (PMID: 27784735), so PM3 is met.

Not Met criteria codes

PVS1			Variant is missense, so PVS1 is Not Met.
BS2			Case-control data not reported, so BS2 is Not Met.
BS1			PopMax MAF = 0.0000093 (0.00093%) in European non Finnish exomes (gnomAD v4.1), so BS1 is not met.
BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			Level 1 assays: PMID 32015373: Heterologous cells, FACS - result - Normal cell surface LDLR (83%), 95% binding and 92% uptake. ---- results are not above 90% of wild-type activity for the whole cycle, so functional study is consistent with no damaging effect and BS3 is not met. 83% cell surface LDLR, 95% binding and 92% uptake in Heterologous cells (CHO), FACS assays PubMed:32015373 
BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.755. It is not below 0.50, so BP4 is Not Met.
BP2			index case also has APOB c.2789A $>$ G with LDL-C 224 mg/dL, but phase is unknown, so BP2 is not met.
PS1			No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.

PS3			Level 1 assays: PMID 32015373: Heterologous cells, FACS - result - Normal cell surface LDLR (83%), 95% binding and 92% uptake. ---- functional study is not consistent with damaging effect, so PS3 is Not Met. 83% cell surface LDLR, 95% binding and 92% uptake in Heterologous cells (CHO), FACS assays PubMed:32015373 
BA1			PopMax MAF = 0.0000093 (0.00093%) in European non Finnish exomes (gnomAD v4.1), so BA1 is not met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residue, so PM1 is Not Met.
PM5			3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1195G>T (p.Ala399Ser) (ClinVar ID 440632) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1196C>A (p.Ala399Asp) (ClinVar ID 226350) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.1196C>T (p.Ala399Val) (ClinVar ID 3074081) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines, so PM5 is not met.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.

Curation History 		
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