

Variant: NM_000527.5(LDLR):c.1196C>A (p.Ala399Asp)

Version: 1.0

CA10576301 [↗](#)

226350 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: b81fb118-4d2b-4441-8fe1-db5668f18578

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HGVS expressions

NM_000527.5(LDLR):c.1196C>A (p.Ala399Asp)

NM_000527.5:c.1196C>A

NC_000019.10:g.11113287C>A

CM000681.2:g.11113287C>A

NC_000019.9:g.11223963C>A

CM000681.1:g.11223963C>A

NC_000019.8:g.11084963C>A

NG_009060.1:g.28907C>A

ENST00000252444.10:c.1454C>A

ENST00000559340.2:c.1196C>A

ENST00000560467.2:c.1076C>A

ENST00000558518.6:c.1196C>A

ENST00000252444.9:c.1450C>A

ENST00000455727.6:c.692C>A

ENST00000535915.5:c.1073C>A

ENST00000545707.5:c.815C>A

ENST00000557933.5:c.1196C>A

ENST00000558013.5:c.1196C>A

ENST00000558518.5:c.1196C>A

ENST00000560173.1:n.195C>A

ENST00000560467.1:c.676C>A

NM_000527.4:c.1196C>A

NM_001195798.1:c.1196C>A

NM_001195799.1:c.1073C>A

NM_001195800.1:c.692C>A

NM_001195803.1:c.815C>A

NM_001195798.2:c.1196C>A

NM_001195799.2:c.1073C>A

NM_001195800.2:c.692C>A

NM_001195803.2:c.815C>A

Likely Pathogenic

Met criteria codes 5

- PP1_Strong
- PP3
- PP4
- PM2
- PS4_Supporting

Not Met criteria codes 17

- PS1
- PS2
- PS3
- BA1
- PM6
- BS1
- BS4
- BS3
- PM1
- PM3
- PM5
- PM4
- BS2
- BP7
- BP4
- BP2
- PVS1

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.1196C>A (p.Ala399Asp) variant is classified as **Likely Pathogenic for Familial Hypercholesterolemia** by applying ACMG/AMP evidence codes **PP1_Strong**, **PM2**, **PS4_Supporting**, **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 = 0.000003390 (0.0003390%) in European non-Finnish exomes+genomes (gnomAD v4.1).** **PP3: REVEL = 0.82.** **PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill criteria for FH from different labs (2 cases with DLCN score >=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; at least 1 case with DLCN score >=6 from PMID 11810272 (Fouchier et al., 2001), The Netherlands).** **PP1_Strong - Variant segregates with FH phenotype in at least 6 informative meioses (minimum 6) from 2 families from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia: 5 affected family members have the variant and 1 non-affected family member does not have the variant.**

Met criteria codes

PP1_Strong			Variant segregates with FH phenotype in at least 6 informative meioses (minimum 6) from 2 families from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA): 5 affected family members have the variant and 1 non-affected family member does not have the variant, so PP1_Strong is met.
PP3			REVEL = 0.82. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill criteria for FH from different labs (2 unrelated index cases, both with Dutch lipid clinic network >=6; at least 1 index case who fulfills DLCN>9 criteria for FH (definite FH) from The Netherlands (PMID: 11810272)), after alternative causes of high cholesterol were excluded so PP4 is met.
PM2			PopMax MAF = 0.000003390 (0.0003390%) in European non Finnish exomes+genomes (gnomAD v4.1), so PM2 is Met.
PS4_Supporting			Variant meets PM2 and is identified in at least 3 unrelated index cases who fulfill criteria for FH from different labs (2 unrelated index cases, both with Dutch lipid clinic network >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); at least 1 index case who fulfills DLCN>9 criteria for FH (definite FH) from The Netherlands (PMID: 11810272)), so PS4_Supporting is Met.

Not Met criteria codes

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			There are no functional studies reported for this variant, so PS3 is Not Met.
BA1			PopMax MAF = 0.000003390 (0.0003390%) in European non Finnish exomes+genomes (gnomAD v4.1), so BA1 is not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.

BS1		✖	PopMax MAF = 0.000003390 (0.0003390%) in European non Finnish exomes+genomes (gnomAD v4.1), so BS1 is not Met.
BS4		✖	Lack of segregation data not reported, so BS4 is Not Met.
BS3		✖	There are no functional studies reported for this variant, so BS3 is Not Met.
PM1		✖	Variant meets PM2 but is not located in exon 4 or alters a cysteine residue, so PM1 is Not Met.
PM3		✖	Not observed in trans with other LP/P variants, so PM3 is Not Met.
PM5		✖	3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1195G>A (p.Ala399Thr) (ClinVar ID 183109) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.1195G>T (p.Ala399Ser) (ClinVar ID 440632) - Uncertain significance 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.
BS2		✖	Case-control data not reported, so BS2 is Not Met.
BP7		✖	Variant is not synonymous, so BP7 is Not Met.
BP4		✖	REVEL = 0.82. It is not below 0.50, so BP4 is Not Met.
BP2		✖	Not observed in trans with other LP/P variants, so BP2 is Not Met.
PVS1		✖	Variant is missense, so PVS1 is Not Met.

Curation History 		
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