

Variant: NM_000527.5(LDLR):c.1189T>A (p.Ser397Thr)

Version: 1.0

CA10585349 [↗](#)

251725 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 77844244-7a2f-49a5-927d-e7b9cfb90aad

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HGVS expressions

NM_000527.5(LDLR):c.1189T>A (p.Ser397Thr)

NM_000527.5:c.1189T>A

NC_000019.10:g.11113280T>A

CM000681.2:g.11113280T>A

NC_000019.9:g.11223956T>A

CM000681.1:g.11223956T>A

NC_000019.8:g.11084956T>A

NG_009060.1:g.28900T>A

ENST00000252444.10:c.1447T>A

ENST00000559340.2:c.1189T>A

ENST00000560467.2:c.1069T>A

ENST00000558518.6:c.1189T>A

ENST00000252444.9:c.1443T>A

ENST00000455727.6:c.685T>A

ENST00000535915.5:c.1066T>A

ENST00000545707.5:c.808T>A

ENST00000557933.5:c.1189T>A

ENST00000558013.5:c.1189T>A

ENST00000558518.5:c.1189T>A

ENST00000560173.1:n.188T>A

ENST00000560467.1:c.669T>A

NM_000527.4:c.1189T>A

NM_001195798.1:c.1189T>A

NM_001195799.1:c.1066T>A

NM_001195800.1:c.685T>A

NM_001195803.1:c.808T>A

NM_001195798.2:c.1189T>A

NM_001195799.2:c.1066T>A

NM_001195800.2:c.685T>A

NM_001195803.2:c.808T>A

Uncertain Significance

Met criteria codes 2

PM2PP4

Not Met criteria codes 6

PM5BS1PS1BP4BA1

PP3

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.1189T>A (p.Ser397Thr) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v20210610). PP4: Variant meets PM2 and is identified in at least 1 index case with clinical Dutch Lipid Clinic Network Criteria score ≥ 6 in PMID 11810272 (Fouchier et al., 2001), The Netherlands, after alternative causes of high cholesterol were excluded.

Met criteria codes

PM2			This variant is absent from gnomAD (gnomAD v20210610).
PP4			Variant meet PM2. PMID: 11810272 (Fouchier SW et al., 2001) in at least 1 patient that was clinically diagnosed with definite heterozygous FH by cardiologists and internists using a uniform protocol and internationally accepted criteria.

Not Met criteria codes

PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1189T>C (p.Ser397Pro) (ClinVar ID 923326) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1190C>T (p.Ser397Phe) (ClinVar ID 925475) - Uncertain significance by these guidelines by these guidelines There are no variant in the same codon classified as Pathogenic by these guidelines.
BS1			This variant is absent from gnomAD (gnomAD v20210610).
PS1			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1189T>C (p.Ser397Pro) (ClinVar ID 923326) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1190C>T (p.Ser397Phe) (ClinVar ID 925475) - Uncertain significance by these guidelines by these guidelines There are no variant in the same codon classified as Pathogenic by these guidelines.
BP4			

REVEL = 0.504. It is not below 0.5, splicing evaluation needed. Functional data on splicing not available. A) Variant within limits. MES scores: Canonical site variant = 7.03; canonical acceptor wt = 6.59. Ratio: 7.03/6.59 = 1.06---- It is > 1.0

BA1



This variant is absent from gnomAD (gnomAD v20210610).

PP3



REVEL = 0.504. It is not above 0.75, splicing evaluation needed. Functional data on splicing not available. A) Variant within limits. MES scores: Canonical site variant = 7.03; canonical acceptor wt = 6.59. Ratio: 7.03/6.59 = 1.06---- It is not <0.8. Variant is not predicted to alter splicing.

Curation History [↗](#)

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