

Variant: NM_000527.5(LDLR):c.1495T>C (p.Ser499Pro)

Version: 1.0

CA10585480 [↗](#)

251870 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

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HGVS expressions

NM_000527.5(LDLR):c.1495T>C (p.Ser499Pro)

NM_000527.5:c.1495T>C

NC_000019.10:g.11113671T>C

CM000681.2:g.11113671T>C

NC_000019.9:g.11224347T>C

CM000681.1:g.11224347T>C

NC_000019.8:g.11085347T>C

NG_009060.1:g.29291T>C

ENST00000252444.10:c.1753T>C

ENST00000559340.2:c.1495T>C

ENST00000560467.2:c.1375T>C

ENST00000558518.6:c.1495T>C

ENST00000252444.9:c.1749T>C

ENST00000455727.6:c.991T>C

ENST00000535915.5:c.1372T>C

ENST00000545707.5:c.1114T>C

ENST00000557933.5:c.1495T>C

ENST00000558013.5:c.1495T>C

ENST00000558518.5:c.1495T>C

ENST00000559340.1:c.216T>C

NM_000527.4:c.1495T>C

NM_001195798.1:c.1495T>C

NM_001195799.1:c.1372T>C

NM_001195800.1:c.991T>C

NM_001195803.1:c.1114T>C

NM_001195798.2:c.1495T>C

NM_001195799.2:c.1372T>C

NM_001195800.2:c.991T>C

NM_001195803.2:c.1114T>C

Likely Pathogenic

Met criteria codes 5

PM2

PP1_Moderate

PS4_Moderate

PP3

PP4

Not Met criteria codes 17

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM1

PM3

PM5

PM6

BS1

BS4

BS3

BS2

PS1

PS2

PS3

BP5

BP4

BP1

BP2

BA1

PP2

Evidence Links 0

- [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.1495T>C (p.Ser499Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PS4_Moderate, PP1_Moderate, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.0.0). PP3: REVEL = 0.758. PS4_Moderate, PP4: Variant meets PM2 and is identified in at least 6 unrelated index cases who fulfill criteria for FH (4 cases with DLCN score >=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; 2 cases with possible FH by Simon Broome criteria from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France). PP1_Moderate - Variant segregates with FH phenotype in 4 informative meioses in 4 families from different labs (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France): 4 affected family members have the variant.

Met criteria codes

PM2			PM2_Met: This variant is absent from gnomAD (v4.0.0).
PP1_Moderate			PP1_Moderate: Variant segregates with phenotype in 4 informative meioses in 4 families (2 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) and 2 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France).
PS4_Moderate			PS4_Moderate: Variant meets PM2 and is identified in 6 unrelated cases (4 with DLCN score>=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) and 2 with Simon Broome possible from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France).
PP3			PP3_Met: REVEL = 0.758.
PP4			PP4_Met: Variant meets PM2 and is identified in 6 probands (4 with DLCN score >=6 and 2 with Simon Broome possible).

Not Met criteria codes

PM1			PM1_Not Met: Variant meets PM2 but is in exon 10.
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PM3			Variant meets PM2 but is not identified in an index case with heterozygous or homozygous FH phenotype as well as LDLR variant, in trans, or APOB/PCSK9 variant classified as Pathogenic by these or general ACMG guidelines.
PM5			PM5_Not Met: There is 1 variant in the same codon (c.1496C>G (p.Ser499Cys)) but is not classified as pathogenic by these guidelines.
PM6			No de novo cases were identified.
BS1			This variant is absent from gnomAD (v4.0.0).
BS4			No instance of variant non-segregation with FH phenotype in at least 2 informative meioses from at least 2 families with at least one unaffected relative (LDL-C <50th centile) who is positive for the variant.
BS3			BS3_Not Met: Functional studies are not available.
BS2			Variant not identified in normolipidemic individuals
PS1			Not applicable
PS2			No de novo cases were identified.
PS3			PS3_Not Met: Functional studies are not available.
BP5			not applicable
BP4			REVEL = 0.758. Score is not below 0.50.
BP1			Not applicable
BP2			Variant meets PM2 but is not identified in an index case with heterozygous or homozygous FH phenotype as well as LDLR variant, in trans, or APOB/PCSK9 variant classified as Pathogenic by these or general ACMG guidelines.
BA1			This variant is absent from gnomAD (v4.0.0).
PP2			Not applicable

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