The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
UUID: 03bd189a-bd23-41fd-808e-20e389a75be8
Approved on: 2024/2/23
Published on: 2024/10/7

HGVS expressions

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

PP1_Moderate PM2 PP3 PP4 PS4_Moderate

Not Met criteria codes 17

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM1 PM3 PM5 PM6 BA1
BS1 BS4 BS3 BS2 BP5 BP4
BP1 BP2 PS1 PS2 PS3 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 meiosis 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

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).
PM2	✔	PM2_Met: This variant is absent from gnomAD (v4.0.0).
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).
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).

Not Met criteria codes

PM1	✖	PM1_Not Met: Variant meets PM2 but is in exon 10.

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.
BA1		✖	This variant is absent from gnomAD (v4.0.0).
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
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.
PS1		✖	Not applicable
PS2		✖	No de novo cases were identified.
PS3		✖	PS3_Not Met: Functional studies are not available.
PP2		✖	Not applicable

Curation History

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.