

Variant: *NM_000527.5(LDLR):c.498C>T (p.Ala166=)*

Version: 1.0

CA043710 [↗](#)

328050 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c11017c3-bd59-4caa-8e79-2ba6693d1fc0

Approved on: 2024/8/30

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HGVS expressions

NM_000527.5(LDLR):c.498C>T (p.Ala166=)

NM_000527.5:c.498C>T

NC_000019.10:g.11105404C>T

CM000681.2:g.11105404C>T

NC_000019.9:g.11216080C>T

CM000681.1:g.11216080C>T

NC_000019.8:g.11077080C>T

NG_009060.1:g.21024C>T

ENST00000252444.10:c.756C>T

ENST00000559340.2:c.498C>T

ENST00000560467.2:c.498C>T

ENST00000558518.6:c.498C>T

ENST00000252444.9:c.752C>T

ENST00000455727.6:c.314-1988C>T

ENST00000535915.5:c.375C>T

ENST00000545707.5:c.314-1161C>T

ENST00000557933.5:c.498C>T

ENST00000558013.5:c.498C>T

ENST00000558518.5:c.498C>T

ENST00000560467.1:c.98C>T

NM_000527.4:c.498C>T

NM_001195798.1:c.498C>T

NM_001195799.1:c.375C>T

NM_001195800.1:c.314-1988C>T

NM_001195803.1:c.314-1161C>T

NM_001195798.2:c.498C>T

NM_001195799.2:c.375C>T

NM_001195800.2:c.314-1988C>T

NM_001195803.2:c.314-1161C>T

Likely Benign

Met criteria codes **3**

BS1 BP4 BP7

Not Met criteria codes **23**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

PVS1

BS4

BS3

BP3

BP1

BP2

BP5

PS1

PS2

PS3

PS4

BA1

PP1

PP2

PP3

PP4

PM1

PM3

PM5

PM4

PM6

PM2

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.498C>T (p.Ala166=) variant is classified as Likely Benign for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes BS1, BP4 and BP7 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (spcification version 1.2) on 30 August 2024. The supporting evidence is as follows: BS1: FAF=0.004221 (0.42%) in African/African American exomes + genomes (gnomAD v4.1.0). BP4: No REVEL, splicing evaluation required. Functional data on splicing not available. A) not on limits. B) does not create a GT. C) there is a GT nearby. MES scores: variant cryptic = -2.92, wt cryptic = -2.92, canonical donor = 7.67. Cryptic scores are negative, so cryptic site is not used - variant is not predicted to alter splicing. BP7: Variant is synonymous and meets BP4.

Met criteria codes

BS1			FAF = 0.004221 (0.42%) in African/African American exomes + genomes (gnomAD v4.1.0). It is above 0.2%, so BS1 is met
BP4			No REVEL, splicing evaluation required. Functional data on splicing not available. A) not on limits. B) does not create a GT. C) there is a GT nearby. MES scores: variant cryptic = -2.92, wt cryptic = -2.92, canonical donor = 7.67. Cryptic scores are negative, so cryptic site is not used - Variant is not predicted to alter splicing.
BP7			Variant is synonymous and meets BP4.

Not Met criteria codes

BS2			not identified in normolipidemic individuals
PVS1			variant is synonymous, so not applicable
BS4			No family members tested
BS3			no published functional studies
BP3			not applicable
BP1			not applicable

BP2			Identified in 1 index case also heterozygous for LDLR variant c.1636G>A with LDL-c 250 mg/dl (not reported if LDL values are treated or untreated). Unknown if the 2 variants are in cis or trans, so BP2 is not met
BP5			not applicable
PS1			variant is synonymous, so not applicable
PS2			no de novo occurrence
PS3			no published functional studies
PS4			Variant was identified in 3 unrelated index cases from one lab, after alternative causes of high cholesterol were excluded (1 case with Simon Broome criteria of possible FH and 2 cases with DLCN criteria ≥ 6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France). Variant does not meet PM2, so PS4 is not met.
BA1			FAF = 0.004221 (0.42%) in African/African American exomes + genomes (gnomAD v4.1.0). It is not above 0.5%, so BA1 is not met
PP1			No family members tested
PP2			not applicable
PP3			No REVEL, splicing evaluation required. Functional data on splicing not available. A) not on limits. B) does not create a GT. C) there is a GT nearby. MES scores: variant cryptic = -2.92, wt cryptic = -2.92, canonical donor = 7.67. Cryptic scores are negative, so cryptic site is not used - Variant is not predicted to alter splicing.
PP4			Variant was identified in 3 unrelated index cases from one lab, after alternative causes of high cholesterol were excluded (1 case with Simon Broome criteria of possible FH and 2 cases with DLCN criteria ≥ 6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France). Variant does not meet PM2, so PP4 is not met.
PM1			variant is synonymous, so not applicable
PM3			Identified in 1 index case also heterozygous for LDLR variant c.1636G>A with LDL-c 250 mg/dl (not reported if LDL values are treated or untreated). Unknown if the 2 variants are in cis or trans, so PM3 is not met
PM5			variant is synonymous, so not applicable
PM4			variant is synonymous, so not applicable
PM6			no de novo occurrence

PM2

PopMax MAF = 0.004622 (0.4622%) in African/African American exomes + genomes (gnomAD v4.1.0). It is not below 0.02%, so not met

Curation History [↗](#)

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