

Variant: NM_000527.5(LDLR):c.1661C>T (p.Ser554Leu)

Version: 1.0

CA10585551 [↗](#)

251960 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 9b184085-913b-494a-b2a9-9cb690ff1d93

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HGVS expressions

NM_000527.5:c.1661C>T

NM_000527.5(LDLR):c.1661C>T (p.Ser554Leu)

NC_000019.10:g.11116168C>T

CM000681.2:g.11116168C>T

NC_000019.9:g.11226844C>T

CM000681.1:g.11226844C>T

NC_000019.8:g.11087844C>T

NG_009060.1:g.31788C>T

ENST00000252444.10:c.1919C>T

ENST00000559340.2:c.1661C>T

ENST00000560467.2:c.1541C>T

ENST00000558518.6:c.1661C>T

ENST00000252444.9:c.1915C>T

ENST00000455727.6:c.1157C>T

ENST00000535915.5:c.1538C>T

ENST00000545707.5:c.1280C>T

ENST00000557933.5:c.1661C>T

ENST00000558013.5:c.1661C>T

ENST00000558518.5:c.1661C>T

ENST00000559340.1:c.382C>T

NM_000527.4:c.1661C>T

NM_001195798.1:c.1661C>T

NM_001195799.1:c.1538C>T

NM_001195800.1:c.1157C>T

NM_001195803.1:c.1280C>T

NM_001195798.2:c.1661C>T

NM_001195799.2:c.1538C>T

NM_001195800.2:c.1157C>T

NM_001195803.2:c.1280C>T

Uncertain Significance

Met criteria codes **3**

BP4

PP4

PM2

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BA1BS2BS1BS4BS3BP2

PVS1BP7PS1PS2PS3

PS4PP1PP3PM1PM3

PM5PM4PM6

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.1661C>T (p.Ser554Leu) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP4 and BP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 9 May 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.00001098 (0.001098%) in South Asian exomes (gnomAD v4.1.0). PP4: Variant meets PM2 and is identified in at least 1 index case with Possible FH by Simon-Broome criteria from Taiwan (PMID 22353362 (Chiou et al., 2012); PMID 33994402 (Huang et al., 2022)), after alternative causes of high cholesterol were excluded. BP4: REVEL = 0.456, it is below 0.50, splicing evaluation required. Functional data on splicing not available. A) variant not on limits B) variant is exonic and at least 50bp downstream from the canonical donor and acceptor site, but it does not create AG/GT. The variant is not predicted to alter splicing.

Met criteria codes

BP4			REVEL = 0.456, it is below 0.50, splicing evaluation required. Functional data on splicing not available. A) variant not on limits B) variant is exonic and at least 50bp downstream from the canonical donor and acceptor site, but it does not create AG/GT Variant is not predicted to alter splicing, so BP4 is Met.
PP4			Variant meets PM2 and is identified in at least 1 index cases who fulfill Simon-Broome criteria of possible FH from Taiwan (PMID: 22353362; PMID: 33994402), after alternative causes of high cholesterol were excluded, so PP4 is met.
PM2			PopMax MAF = 0.00001098 (0.001098%) in South Asian exomes (gnomAD v4.1.0), so PM2 is met.

Not Met criteria codes

BA1			PopMax MAF = 0.00001098 (0.001098%) in population exomes (gnomAD v4.1.0), so BA1 is Not Met.
BS2			Case-control data not reported, so BS2 is Not Met.
BS1			PopMax MAF = 0.00001098 (0.001098%) in population exomes (gnomAD v4.1.0), 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.

BP2			Not observed in trans with other LP/P variants, so BP2 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
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 BS3 is Not Met.
PS4			Variant meets PM2 and is identified in only 1 index cases who fulfill Simon-Broome criteria of possible FH from Taiwan (PMID: 22353362; PMID: 33994402), after alternative causes of high cholesterol were excluded, so PS4 is Not Met.
PP1			Segregation data not reported, so PP1 is Not Met.
PP3			REVEL = 0.456, it is below 0.50, splicing evaluation required. Functional data on splicing not available. A) not on limits B) variant is exonic and at least 50bp downstream from the canonical acceptor site, but it does not create GT C) variant is exonic, but there is no AG/GT nearby Variant is not predicted to alter splicing, so PP3 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			1 other missense variant in the same codon: - NM_000527.5(LDLR):c.1661C>G (p.Ser554Trp) (ClinVar ID: 3231953) - 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.
PM6			de novo occurrence data not reported, so PM6 is Not Met.

Curation History 

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