

Variant: *NM_000527.5(LDLR):c.1661C>G (p.Ser554Trp)*

Version: 1.0

CA404089220 [↗](#)

3231953 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: cfb31f6a-db7a-45f6-bf10-9edafdad2508

Approved on: 2025/5/9

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HGVS expressions

NM_000527.5:c.1661C>G

NM_000527.5(LDLR):c.1661C>G (p.Ser554Trp)

NC_000019.10:g.11116168C>G

CM000681.2:g.11116168C>G

NC_000019.9:g.11226844C>G

CM000681.1:g.11226844C>G

NC_000019.8:g.11087844C>G

NG_009060.1:g.31788C>G

ENST00000252444.10:c.1919C>G

ENST00000559340.2:c.1661C>G

ENST00000560467.2:c.1541C>G

ENST00000558518.6:c.1661C>G

ENST00000252444.9:c.1915C>G

ENST00000455727.6:c.1157C>G

ENST00000535915.5:c.1538C>G

ENST00000545707.5:c.1280C>G

ENST00000557933.5:c.1661C>G

ENST00000558013.5:c.1661C>G

ENST00000558518.5:c.1661C>G

ENST00000559340.1:c.382C>G

NM_000527.4:c.1661C>G

NM_001195798.1:c.1661C>G

NM_001195799.1:c.1538C>G

NM_001195800.1:c.1157C>G

NM_001195803.1:c.1280C>G

NM_001195798.2:c.1661C>G

NM_001195799.2:c.1538C>G

NM_001195800.2:c.1157C>G

NM_001195803.2:c.1280C>G

Uncertain Significance

Met criteria codes **1**

PM2

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

BS2

PVS1

PS1

PS2

PS3

PS4

BP7

BP4

BP2

BA1

PP1

PP3

PP4

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>G (p.Ser554Trp) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence code PM2 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: This variant is absent from gnomAD (gnomAD v4.1.0).

Met criteria codes

PM2

✓

This variant is absent from gnomAD (gnomAD v4.1.0), so PM2 is Met.

Not Met criteria codes

- 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>T (p.Ser554Leu) (ClinVar ID: 251960) - 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.
- BS1

✗

This variant is absent from gnomAD (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.
- BS2

✗

Case-control data not reported, so BS2 is Not Met.
- PVS1

✗

Variant is missense, so PVS1 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 PS3 is Not Met.
PS4			Variant meets PM2 but phenotype data is not reported, so PS4 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.554, it is not below 0.50, so BP4 is Not Met.
BP2			Not observed in trans with other LP/P variants, so BP2 is Not Met.
BA1			This variant is absent from gnomAD (gnomAD v4.1.0), so BA1 is Not Met.
PP1			Segregation data not reported, so PP1 is Not Met.
PP3			REVEL = 0.554, it is not above 0.75, 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.
PP4			Variant meets PM2 but phenotype data is not reported, so PP4 is Not Met.

Curation History 

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