

Variant: *NM_000527.5(LDLR):c.1567G>T (p.Val523Leu)*

Version: 1.0

CA10585504 [↗](#)

251900 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 26373548-6259-48c4-9a6c-0d1ed62bb223

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HGVS expressions

NM_000527.5(LDLR):c.1567G>T (p.Val523Leu)

NM_000527.5:c.1567G>T

NC_000019.10:g.11113743G>T

CM000681.2:g.11113743G>T

NC_000019.9:g.11224419G>T

CM000681.1:g.11224419G>T

NC_000019.8:g.11085419G>T

NG_009060.1:g.29363G>T

ENST00000252444.10:c.1825G>T

ENST00000559340.2:c.1567G>T

ENST00000560467.2:c.1447G>T

ENST00000558518.6:c.1567G>T

ENST00000252444.9:c.1821G>T

ENST00000455727.6:c.1063G>T

ENST00000535915.5:c.1444G>T

ENST00000545707.5:c.1186G>T

ENST00000557933.5:c.1567G>T

ENST00000558013.5:c.1567G>T

ENST00000558518.5:c.1567G>T

ENST00000559340.1:c.288G>T

NM_000527.4:c.1567G>T

NM_001195798.1:c.1567G>T

NM_001195799.1:c.1444G>T

NM_001195800.1:c.1063G>T

NM_001195803.1:c.1186G>T

NM_001195798.2:c.1567G>T

NM_001195799.2:c.1444G>T

NM_001195800.2:c.1063G>T

NM_001195803.2:c.1186G>T

Likely Pathogenic

Met criteria codes **4**

PP1_Strong

PP3

PM2

PM5

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

BS1

BS4

BS3

BP4

BP1

BP2

BP5

BA1

PS1

PS2

PS3

PS4

PP2

PP4

PM6

PM1

PM3

Evidence Links

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- 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.1567G>T (p.Val523Leu) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PP1_Strong, PM2, PM5 and PP3 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 27 January 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (v2.1.1). PP3: REVEL = 0.904. PM5: There is 1 missense variant in the same codon, NM_000527.5(LDLR):c.1567G>A (p.Val523Met), classified as Pathogenic by these guidelines. PP1_Strong: Variant segregates with FH phenotype in 7 informative meioses from 1 family from Laboratory of Genetics and Molecular Cardiology, Brazil.

Met criteria codes

PP1_Strong			PP1_strong: Variant segregates with FH phenotype in 7 informative meiosis from 1 family from Laboratory of Genetics and Molecular Cardiology.
PP3			PP3_Met : REVEL = 0.904
PM2			PM2_Met : This variant is absent from gnomAD (v2.1.1).
PM5			PM5_Met : There is 1 missense variant in the same codon (NM_000527.5(LDLR):c.1567G>A (p.Val523Met)) classified as Pathogenic by these guidelines.

Not Met criteria codes

BS2			Variant not identified in normolipidemic individuals
BS1			This variant is absent from gnomAD (v2.1.1).
BS4			No instance of variant non-segregation with FH phenotype in at least 2 informative meiosis from at least 2 families with at least one unaffected relative (LDL-C <50th centile) who is positive for the variant.
BS3			No functional assays performed/found
BP4			REVEL = 0.904. 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.
BP5			not applicable
BA1			This variant is absent from gnomAD (v2.1.1).
PS1			PS1_Not Met : There is one missense variant that leads to the same aminoacid change (c.1567G>C (p.Val523Leu)) but it is not classified as pathogenic by these guidelines.
PS2			No de novo cases were identified
PS3			No functional assays performed/found
PS4			PS4_Not Met : Variant meets PM2 and is identified in 3 patients (1 from Laboratory of Genetics and Molecular Cardiology, 1 in PMID: 20809525 and 1 in PMID: 15199436) but clinical criteria are not available.
PP2			Not applicable
PP4			PP4_Not Met : Variant meets PM2 but clinical criteria of patients are not available.
PM6			No de novo cases were identified
PM1			Variant meets PM2 but it is in exon 10. Not applicable.
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.

Curation History 

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