

Variant: *NM_000527.5(LDLR):c.2324T>C (p.Val775Ala)*

Version: 1.0

CA039797 [↗](#)

440691 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 7c83984e-b866-4cfc-b84a-f95a0fe505d9

Approved on: 2025/3/28

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HGVS expressions

NM_000527.5(LDLR):c.2324T>C (p.Val775Ala)

NM_000527.5:c.2324T>C

NC_000019.10:g.11128020T>C

CM000681.2:g.11128020T>C

NC_000019.9:g.11238696T>C

CM000681.1:g.11238696T>C

NC_000019.8:g.11099696T>C

NG_009060.1:g.43640T>C

ENST00000252444.10:c.2582T>C

ENST00000559340.2:c.*393T>C

ENST00000560467.2:c.2204T>C

ENST00000558518.6:c.2324T>C

ENST00000252444.9:c.2578T>C

ENST00000455727.6:c.1820T>C

ENST00000535915.5:c.2201T>C

ENST00000545707.5:c.1790T>C

ENST00000557933.5:c.2324T>C

ENST00000558013.5:c.2324T>C

ENST00000558518.5:c.2324T>C

ENST00000560628.1:n.108+366T>C

NM_000527.4:c.2324T>C

NM_001195798.1:c.2324T>C

NM_001195799.1:c.2201T>C

NM_001195800.1:c.1820T>C

NM_001195803.1:c.1790T>C

NM_001195798.2:c.2324T>C

NM_001195799.2:c.2201T>C

NM_001195800.2:c.1820T>C

NM_001195803.2:c.1790T>C

Uncertain Significance

Met criteria codes **2**

BP4

PM2

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

PS4

BP7

BP3

BP2

PP1

PP3

PP4

PM1

PM3

PM5

PM4

BA1

PM6

BS1

BS4

BS3

BS2

PVS1

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.2324T>C (p.Val775Ala) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2 and BP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 March 2025. The supporting evidence is follows: PM2: PopMax MAF = 0.00002627 (0.0026%) in European (non-Finnish) exomes+genomes (gnomAD v4.1.0). BP4: REVEL=0.244. It is below 0.5, so splicing evaluation is required. A) not on limits B) does not create AG C) there is an AG nearby. MES scores: variant cryptic = 1.45, wt cryptic = 2.52, canonical acceptor = 11.36. Ratio variant cryptic/wt cryptic: 0.57 --- it is below 1.1. Ratio variant cryptic/canonical acceptor: 0.12--- it is below 0.9. Variant is not predicted to alter splicing.

Met criteria codes

BP4			REVEL=0.244. It is below 0.5, so splicing evaluation is required. A) not on limits B) does not create AG C) there is a AG nearby. MES scores: variant cryptic = 1.45, wt cryptic = 2.52, canonical acceptor = 11.36. Ratio variant cryptic/wt cryptic: 0.57 --- it is below 1.1 Ratio variant cryptic/canonical acceptor: 0.12--- it is below 0.9 Variant is not predicted to alter splicing. So, BP4 is met.
PM2			PopMax MAF = 0.00002627 (0.0026%) in European (non-Finnish) exomes+genomes (gnomAD v4.1.0). So, PM2 is met.

Not Met criteria codes

PS1			No other missense variant with the same amino acid change.
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No data available.
PS4			No data available.
BP7			Not a synonymous variant
BP3			No in-frame deletions/insertions.

BP2			No data available.
PP1			No data available.
PP3			REVEL=0.244. It is below 0.75, so splicing evaluation is required. A) not on limits B) does not create AG C) there is a AG nearby. MES scores: variant cryptic = 1.45, wt cryptic = 2.52, canonical acceptor = 11.36. Ratio variant cryptic/wt cryptic: 0.57 --- it is below 1.1 Ratio variant cryptic/canonical acceptor: 0.12--- it is below 0.9
PP4			No data available.
PM1			Not on exon 4. Not a cysteine residue.
PM3			No data available.
PM5			1 other missense variant in the same codon: - NM_000527.5(LDLR):c.2323G>A (p.Val775Ile) (ClinVar ID 630377) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No in-frame deletions/insertions.
BA1			FAF = 0.00001663 (0.0016%) in European (non-Finnish) exomes+genomes (gnomAD v2.4.0).
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			FAF = 0.00001663 (0.0016%) in European (non-Finnish) exomes+genomes (gnomAD v2.4.0).
BS4			No data available.
BS3			No data available.
BS2			No data available.
PVS1			Not a null variant

Curation History 

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