

Variant: NM_000527.5(LDLR):c.1588T>G (p.Phe530Val)

Version: 1.0

CA10576310 [↗](#)

226361 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 2b7fbe35-134c-4858-acb1-2057d42276b8

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HGVS expressions

NM_000527.5:c.1588T>G

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NC_000019.10:g.11116095T>G

CM000681.2:g.11116095T>G

NC_000019.9:g.11226771T>G

CM000681.1:g.11226771T>G

NC_000019.8:g.11087771T>G

NG_009060.1:g.31715T>G

ENST00000252444.10:c.1846T>G

ENST00000559340.2:c.1588T>G

ENST00000560467.2:c.1468T>G

ENST00000558518.6:c.1588T>G

ENST00000252444.9:c.1842T>G

ENST00000455727.6:c.1084T>G

ENST00000535915.5:c.1465T>G

ENST00000545707.5:c.1207T>G

ENST00000557933.5:c.1588T>G

ENST00000558013.5:c.1588T>G

ENST00000558518.5:c.1588T>G

ENST00000559340.1:c.309T>G

NM_000527.4:c.1588T>G

NM_001195798.1:c.1588T>G

NM_001195799.1:c.1465T>G

NM_001195800.1:c.1084T>G

NM_001195803.1:c.1207T>G

NM_001195798.2:c.1588T>G

NM_001195799.2:c.1465T>G

NM_001195800.2:c.1084T>G

NM_001195803.2:c.1207T>G

Uncertain Significance

Met criteria codes **4**

PM2

PS4_Supporting

PP3

PP4

Not Met criteria codes **2**

PM5

BP4

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

- [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.1588T>G (p.Phe530Val) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PS4_Supporting, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 20 February 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.00001891 (0.001891%) in European (non-Finnish) exomes/genomes (gnomAD v4.1.0). PP3: REVEL = 0.868. PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN>=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; 1 case fulfilling Japan Atherosclerosis Society criteria for FH reported in PMID 36229376 (Tada et al., 2022)), after alternative causes of high cholesterol were excluded.

Met criteria codes

PM2			PopMax MAF = 0.00001891 (0.001891%) in European (non-Finnish) exomes/genomes (gnomAD v4.1.0).
PS4_Supporting			Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN>=6 criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA, Australia); 1 case fulfilling Japan Atherosclerosis Society criteria for FH reported in PMID: 36229376, after alternative causes of high cholesterol were excluded.
PP3			REVEL = 0.868.
PP4			Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN>=6 criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA, Australia); 1 case fulfilling Japan Atherosclerosis Society criteria for FH reported in PMID: 36229376, after alternative causes of high cholesterol were excluded.

Not Met criteria codes

PM5			One other missense variant at the same codon: NM_000527.5(LDLR):c.1590C>A (p.Phe530Leu) (ClinVar ID 3073518) is classified as a variant of uncertain significance by these guidelines.
BP4			REVEL = 0.868.

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