

Variant: *NM_000527.5(LDLR):c.311G>T (p.Cys104Phe)*

Version: 1.0

CA10584839 [↗](#)

251130 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c11bda52-74fa-4a86-85c5-2790d8ebd5bf

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HGVS expressions

NM_000527.5:c.311G>T

NM_000527.5(LDLR):c.311G>T (p.Cys104Phe)

NC_000019.10:g.11102784G>T

CM000681.2:g.11102784G>T

NC_000019.9:g.11213460G>T

CM000681.1:g.11213460G>T

NC_000019.8:g.11074460G>T

NG_009060.1:g.18404G>T

ENST00000252444.10:c.569G>T

ENST00000559340.2:c.311G>T

ENST00000560467.2:c.311G>T

ENST00000558518.6:c.311G>T

ENST00000252444.9:c.565G>T

ENST00000455727.6:c.311G>T

ENST00000535915.5:c.191-2436G>T

ENST00000545707.5:c.311G>T

ENST00000557933.5:c.311G>T

ENST00000557958.1:n.397G>T

ENST00000558013.5:c.311G>T

ENST00000558518.5:c.311G>T

NM_000527.4:c.311G>T

NM_001195798.1:c.311G>T

NM_001195799.1:c.191-2436G>T

NM_001195800.1:c.311G>T

NM_001195803.1:c.311G>T

NM_001195798.2:c.311G>T

NM_001195799.2:c.191-2436G>T

NM_001195800.2:c.311G>T

NM_001195803.2:c.311G>T

Likely Pathogenic

Met criteria codes **4**

PM1 PM2 PP3 PP4

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM3

PM5

PM4

PM6

BS1

BS4

BS3

BS2

PVS1

PS1

PS2

PS3

PS4

BP5

BP7

BP4

BP3

BP1

BP2

BA1

PP1

PP2

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.311G>T (p.Cys104Phe) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.0.0). PP3: REVEL = 0.882. PM1: Variant meets PM2 and alters Cys104, one of the cysteine residues listed. PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills clinical criteria for FH from PMID 16159606 (Graham et al., 2005), after alternative causes of high cholesterol were excluded.

Met criteria codes

PM1			PM1 - Variant meets PM2 and alters Cys104, one of the cysteine residues listed;
PM2			PM2 - This variant is absent from gnomAD (gnomAD v4.0.0);
PP3			PP3 - REVEL = 0.882;
PP4			PP4 - Variant meets PM2 and is identified in at least 1 index case who fulfills clinical criteria for FH (PMID: 16159606), after alternative causes of high cholesterol were excluded

Not Met criteria codes

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.
PM5			PM5 - The variant already meets PM1, so PM5 cannot be applied.
PM4			Not applicable
PM6			No de novo cases were identified
BS1			Not applicable
BS4			no family members tested

BS3			BS3_Not Met: Functional studies are not available.
BS2			Variant not identified in normolipidemic individuals
PVS1			Not applicable
PS1			Not applicable
PS2			No de novo cases were identified
PS3			PS3 - Functional studies are not available.
PS4			PS4 - Variant meets PM2 but was found in only 1 patient with definite FH following Simon Broome criteria (PMID: 16159606).
BP5			Not applicable
BP7			Not applicable
BP4			REVEL = 0.882. Score is not below 0.50.
BP3			Not applicable
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.
BA1			Not applicable
PP1			no family members tested
PP2			Not applicable

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