The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2024/2/23
Published on: 2024/10/7

HGVS expressions

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

PP3 PP4 PM2 PM1

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP1 PP2 PM6 PM3 PM5
PM4 BA1 BS2 PVS1 BS1
BS4 BS3 BP5 BP7 BP4 BP3
BP1 BP2 PS1 PS2 PS3 PS4

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

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
PM2	✔	PM2 - This variant is absent from gnomAD (gnomAD v4.0.0);
PM1	✔	PM1 - Variant meets PM2 and alters Cys104, one of the cysteine residues listed;

Not Met criteria codes

PP1	✖	no family members tested
PP2	✖	Not applicable
PM6	✖	No de novo cases were identified
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

BA1	✖	Not applicable
BS2	✖	Variant not identified in normolipidemic individuals
PVS1	✖	Not applicable
BS1	✖	Not applicable
BS4	✖	no family members tested
BS3	✖	BS3_Not Met: Functional studies are not available.
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.
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).

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.311G>T (p.Cys1…	Likely Pathogenic	Hypercholesterolemia, Familial	2024-10-07	1.0	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR

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