

Variant: NM_000527.5(LDLR):c.1211C>T (p.Thr404Ile)

Version: 1.0

CA10585360 [↗](#)

251736 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 0b713e51-bded-4ddb-a945-894590270b8f

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HGVS expressions

NM_000527.5:c.1211C>T

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NC_000019.10:g.11113302C>T

CM000681.2:g.11113302C>T

NC_000019.9:g.11223978C>T

CM000681.1:g.11223978C>T

NC_000019.8:g.11084978C>T

NG_009060.1:g.28922C>T

ENST00000252444.10:c.1469C>T

ENST00000559340.2:c.1211C>T

ENST00000560467.2:c.1091C>T

ENST00000558518.6:c.1211C>T

ENST00000252444.9:c.1465C>T

ENST00000455727.6:c.707C>T

ENST00000535915.5:c.1088C>T

ENST00000545707.5:c.830C>T

ENST00000557933.5:c.1211C>T

ENST00000558013.5:c.1211C>T

ENST00000558518.5:c.1211C>T

ENST00000560173.1:n.210C>T

ENST00000560467.1:c.691C>T

NM_000527.4:c.1211C>T

NM_001195798.1:c.1211C>T

NM_001195799.1:c.1088C>T

NM_001195800.1:c.707C>T

NM_001195803.1:c.830C>T

NM_001195798.2:c.1211C>T

NM_001195799.2:c.1088C>T

NM_001195800.2:c.707C>T

NM_001195803.2:c.830C>T

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM2 PM3
PS4_Supporting

Not Met criteria codes 20

BS2 BS1 BS4 BS3 BP4 BP3
BP1 BP2 PVS1 BP7 BA1
PS1 PS2 PS3 PP1 PP2 PM6
PM1 PM5 PM4

Evidence Links 0

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.1211C>T (p.Thr404Ile) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM3, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 October 2022. The supporting evidence is as follows: PM2: This variant is absent from gnomAD v2.1.1. PP3: REVEL = 0.928. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 2 unrelated index cases who fulfill criteria for FH after alternative causes of high cholesterol were excluded (1 case with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca, Italy; 1 case from PMID 19446849). PM3: Variant meets PM2 and is identified in an index case with homozygous FH phenotype and LDLR variant (c.428G>A (p.Cys143Tyr)) classified as Pathogenic by these guidelines, in trans (PMID 14570618, 19073363).

Met criteria codes

PP3			REVEL = 0.928
PP4			Variant meets PM2 and is identified in at least 1 index case who fulfills SB possible/definite FH/DLCN>=6 criteria for FH from PMID 28965616, 23375686, 19446849, 19073363 and the Research Lab of Molecular Genetics of Lipid Metabolism, after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD v2.1.1
PM3			Variant meets PM2 and is identified in an index case with homozygous FH phenotype and LDLR variant (c.428G>A (p.Cys143Tyr)), classified as Pathogenic by these guidelines, in trans, from PMID:14570618 and PMID:19073363.
PS4_Supporting			Variant meets PM2 and is identified in at least 2 unrelated index cases who fulfill SB possible/definite FH/DLCN>=6 criteria for FH from PMID 28965616, 23375686, 19446849, 19073363, and the Research Lab of Molecular Genetics of Lipid Metabolism.

Not Met criteria codes

BS2			Not met.
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BS1			This variant is absent from gnomAD v2.1.1
BS4			Not met.
BS3			Not met.
BP4			REVEL = 0.928
BP3			Not applicable
BP1			Not applicable
BP2			Not met.
PVS1			Not met.
BP7			Not a synonymous variant.
BA1			This variant is absent from gnomAD v2.1.1
PS1			Not met.
PS2			Not met.
PS3			Not met.
PP1			Not met.
PP2			Not applicable
PM6			Not met.
PM1			Not located in exon 4 or at a cysteine residue.
PM5			Not met.
PM4			Not an in-frame deletion or insertion.

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