Variant: NM_000527.5(LDLR):c.2291T>C (p.Ile764Thr)

Version: 1.0

CA039387

252265 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 9f8b49ba-2fc2-42ca-92af-6bb1301e49a2
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HGVS expressions

NM_000527.5:c.2291T>C
NM_000527.5(LDLR):c.2291T>C (p.Ile764Thr)
NC_000019.10:g.11123324T>C
CM000681.2:g.11123324T>C
NC_000019.9:g.11234000T>C
CM000681.1:g.11234000T>C
NC_000019.8:g.11095000T>C
NG_009060.1:g.38944T>C
ENST00000252444.10:c.2549T>C
ENST00000559340.2:c.*360T>C
ENST00000560467.2:c.2171T>C
ENST00000558518.6:c.2291T>C
ENST00000252444.9:c.2545T>C
ENST00000455727.6:c.1787T>C
ENST00000535915.5:c.2168T>C
ENST00000545707.5:c.1757T>C
ENST00000557933.5:c.2291T>C
ENST00000558013.5:c.2291T>C
ENST00000558518.5:c.2291T>C
NM_000527.4:c.2291T>C
NM_001195798.1:c.2291T>C
NM_001195799.1:c.2168T>C
NM_001195800.1:c.1787T>C
NM_001195803.1:c.1757T>C
NM_001195798.2:c.2291T>C
NM_001195799.2:c.2168T>C
NM_001195800.2:c.1787T>C
NM_001195803.2:c.1757T>C

Likely Benign

Met criteria codes 4

PP4 PM2 BP4 BS3

Not Met criteria codes 9

PP1 PP3 PS1 PS4 BA1 PM5 BS1 BS4 BS2

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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.2291T>C (p.Ile764Thr) variant is classified as Likely Benign for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP4, BP4 and BS3 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on February 28, 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.0001337 (0.01337%) in East Asian exomes + genomes (gnomAD v4.1.0). PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills Simon Broome criteria for possible FH from Cardiovascular Research Group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal, after alternative causes of high cholesterol were excluded. BP4: REVEL = 0.352, it is below 0.50, so splicing evaluation required. Functional data on splicing not available. A) Variant not on limits. B) Does not create GT. C) There is a GT nearby. MES scores: variant cryptic = -5.73, wt cryptic = -8.16, canonical donor site = 9.06. Cryptic scores are negative, splice site not used. Variant is not predicted to alter splicing. BS3: Level 1 assay: PMID 34167030 (Alves et al., 2021): Heterologous cells (CHO), FACS; Result - > Normal cell surface LDLR (105%), LDL-LDLR binding (90%) and uptake (89%). Functional study is consistent with no damaging effect. Level 3 assay: PMID 37719435 (Graça et al., 2023): Heterologous cells (CHO), microscopy assays; Result - >100% LDLR expression and >100% LDLR activity. Functional study is consistent with no damaging effect. With the application of BP4 and BS3 and the functional evidence available, consensus was to classify this variant as Likely Benign.

Met criteria codes

PP4	✔	Variant meets PM2 and is identified in at least 1 index case who fulfills SB possible for FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, after alternative causes of high cholesterol were excluded.
PM2	✔	PopMax MAF = 0.0001337 (0.01337%) in East Asian exomes+genomes (gnomAD v4.1.0).
BP4	✔	REVEL = 0.352, it is below 0.50, so splicing evaluation required. Functional data on splicing not available. A) Variant not on limits B) Does not create GT C) There is a GT nearby. MES scores: variant cryptic = -5.73, wt cryptic = -8.16, canonical donor site = 9.06. Ratio variant cryptic/wt cryptic: -5.73/-8.16 = 0.70 --- it is not above 1.1. Ratio variant cryptic/canonical donor: -5.73/9.06 = -0.63 --- it is not above 0.9. Variant is not predicted to alter splicing.
BS3	✔	Level 1 assays: PMID 37719435: Heterologous cells (CHO), microscopy assays Result - >100% LDLR expression and >100% LDLR activity Functional study is consistent with no damaging effect. Level 1 assays: PMID 34167030: Heterologous cells (CHO), FACS Result - > Normal cell surface LDLR (105%), LDL-LDLR binding (90%) and uptake (89%) Functional study is consistent with no damaging effect.

Not Met criteria codes

PP1	✖	Variant was identified in 2 members of 1 family, but data on LDL-C was missing in one of them

PP3	ℹ	✖	REVEL = 0.352, it is below 0.50, so splicing evaluation required. Functional data on splicing not available. A) Variant not on limits B) Does not create GT C) There is a GT nearby. MES scores: variant cryptic = -5.73, wt cryptic = -8.16, canonical donor site = 9.06. Ratio variant cryptic/wt cryptic: -5.73/-8.16 = 0.70 --- it is not above 1.1. Ratio variant cryptic/canonical donor: -5.73/9.06 = -0.63 --- it is not above 0.9. Variant is not predicted to alter splicing.
PS1	ℹ	✖	1 other missense variants in the same codon: - NM_000527.5(LDLR):c.2291T>G (p.Ile764Arg) (ClinVar ID 920005) - Uncertain significance by these guidelines
PS4	ℹ	✖	Variant identified in only 1 FH case
BA1	ℹ	✖	FAF = 0.00006511 (0.006511%) in East Asian exomes (gnomAD v4.1.0).
PM5	ℹ	✖	1 other missense variants in the same codon: - NM_000527.5(LDLR):c.2291T>G (p.Ile764Arg) (ClinVar ID 920005) - Uncertain significance by these guidelines
BS1	ℹ	✖	FAF = 0.00006511 (0.006511%) in East Asian exomes (gnomAD v4.1.0).
BS4	ℹ	✖	Variant identified in only 1 family member
BS2	ℹ	✖	Variant was not identified in any controls

Curation History

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