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Variant: NM_000527.5(LDLR):c.2177C>T (p.Thr726Ile)

Version: 1.0

CA023649

36461 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: cf5aea83-78f5-4c3c-8aaa-fb5df3b65938
Approved on: 2022-05-24
Published on: 2022-12-24

HGVS expressions

NM_000527.5:c.2177C>T
NM_000527.5(LDLR):c.2177C>T (p.Thr726Ile)
NC_000019.10:g.11123210C>T
CM000681.2:g.11123210C>T
NC_000019.9:g.11233886C>T
CM000681.1:g.11233886C>T
NC_000019.8:g.11094886C>T
NG_009060.1:g.38830C>T
ENST00000252444.10:c.2435C>T
ENST00000559340.2:c.*246C>T
ENST00000560467.2:c.2057C>T
ENST00000558518.6:c.2177C>T
ENST00000252444.9:c.2431C>T
ENST00000455727.6:c.1673C>T
ENST00000535915.5:c.2054C>T
ENST00000545707.5:c.1643C>T
ENST00000557933.5:c.2177C>T
ENST00000558013.5:c.2177C>T
ENST00000558518.5:c.2177C>T
NM_000527.4:c.2177C>T
NM_001195798.1:c.2177C>T
NM_001195799.1:c.2054C>T
NM_001195800.1:c.1673C>T
NM_001195803.1:c.1643C>T
NM_001195798.2:c.2177C>T
NM_001195799.2:c.2054C>T
NM_001195800.2:c.1673C>T
NM_001195803.2:c.1643C>T

Benign

Met criteria codes 2

BA1 BP4

Not Met criteria codes 20

PP1 PP3 PP4 PM6 PM2 PM1 PM3 PM5 PM4 PVS1

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

BS1 BS4 BS3 BS2 BP7 BP2
PS1 PS2 PS3 PS4

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.2177C>T (p.Thr726Ile) variant is classified as Benign for Familial Hypercholesterolemia by applying evidence codes BA1 and BP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1016/j.gim.2021.09.012). The supporting evidence is as follows: BA1 - FAF = 0.008138 (0.8138%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BA1 is Met. BP4 - REVEL = 0.454, it is below 0.50, so splicing evaluation is required. Functional data on splicing not available. A) variant not on limits B) does not create AG C) variant is exonic and there 1 an AG nearby MES scores: variant cryptic = -1.90, wt cryptic = -1.77, canonical acceptor = 8.76. Ratio variant cryptic/wt cryptic: -1.90/-1.77 = 1.07 --- it is not above 1.1 Ratio variant cryptic/canonical acceptor: -1.90/8.76 --- it is not above 0.9 --- BP4 is Met.

Met criteria codes

BA1	✔	FAF = 0.008138 (0.8138%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BA1 is Met.
BP4	✔	REVEL = 0.454, it is below 0.50, so splicing evaluation is required. Functional data on splicing not available. A) variant not on limits B) does not create AG C) variant is exonic and there 1 an AG nearby MES scores: variant cryptic = -1.90, wt cryptic = -1.77, canonical acceptor = 8.76. Ratio variant cryptic/wt cryptic: -1.90/-1.77 = 1.07 --- it is not above 1.1 Ratio variant cryptic/canonical acceptor: -1.90/8.76 --- it is not above 0.9 --- BP4 is Met.

Not Met criteria codes

PP1	✖	Segregation data not reported, so PP1 is Not Met.
PP3	✖	REVEL = 0.454, it is not above 0.75, so splicing evaluation is required. Functional data on splicing not available. A) variant not on limits B) does not create AG C) variant is exonic and there are 3 AG nearby 1) MES scores: variant cryptic = -1.90, wt cryptic = -1.77, canonical acceptor = 8.76. Ratio variant cryptic/wt cryptic: -1.90/-1.77 = 1.07 --- it is not above 1.1 Ratio variant cryptic/canonical acceptor: -1.90/8.76 --- it is not above 0.9 2) MES scores: variant cryptic = -8.77, wt cryptic = -3.45, canonical acceptor = 8.76. Ratio variant cryptic/wt cryptic: -8.77/-3.45 = 2.54 --- it is above 1.1 Ratio variant cryptic/canonical acceptor: -8.77/8.76 --- it is not above 0.9 3) MES scores: variant cryptic = -14.64, wt cryptic = -9.10, canonical acceptor = 8.76. Ratio variant cryptic/wt cryptic: -14.64/-9.10 = 1.61 --- it is above 1.1 Ratio variant cryptic/canonical acceptor: -14.647/8.76 --- it is not above 0.9 --- PP3 is not met.
PP4	✖	Variant does not meet PM2, so PP4 is Not Met.
PM6	✖	de novo occurrence data not reported, so PM6 is Not Met.
PM2	✖	PopMax MAF = 0.01123 (1.123%) in European (Finnish) exomes+genomes (gnomAD v2.1.1), so PM2 is not met.

PM1	✖	Variant does not meet PM2. Also is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3	✖	Variant does not meet PM2, so PM3 is Not Met.
PM5	✖	No more missense variants at the same codon, so PM5 is Not Met.
PM4	✖	Variant does not meet PM2 and is not due to in-frame deletions/insertions, so PM4 is not met.
PVS1	✖	Variant is not in canonical +/- 1,2 GT/AG splice site that predict a frameshift, so PVS1 is Not Met.
BS1	✖	FAF = 0.008138 (0.8138%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BS1 is not met.
BS4	✖	Lack of segregation data not reported, so BS4 is Not Met.
BS3	✖	Level 1 assays: PMID 34167030: Heterologous cells (CHO), FACS - result - Normal cell surface (91%), 86% LDL-LDLR binding and 96% uptake. ---- results are not above 90% of wild-type activity for the whole cycle (86% binding), so BS3 is not met.
BS2	✖	Not observed in 1000 normolipidemic individuals from Robarts Research Institute and in 200 non-FH alleles from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS2 is Not Met.
BP7	✖	Variant is not synonymous, so BP7 is Not Met.
BP2	✖	Variant identified in index cases with heterozygous FH phenotype and other LDLR variants, but cannot determine if these variants are in trans, so BP2 is not met.
PS1	✖	No more missense variants at the same codon, so PS1 is Not Met.
PS2	✖	de novo occurrence data not reported, so PS2 is Not Met.
PS3	✖	Level 1 assays: PMID 34167030: Heterologous cells (CHO), FACS - result - Normal cell surface (91%), 86% LDL-LDLR binding and 96% uptake. ---- functional study is consistent with no damaging effect, so PS3 is not met.
PS4	✖	Variant does not meet PM2, so PS4 is Not Met.

Curation History

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