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Variant: NM_000527.5(LDLR):c.440C>T (p.Thr147Ile)

Version: 1.0

CA10584919

251223 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 3519a731-8d76-4cd2-8333-2d0d1c76ac46
Approved on: 2023/4/28
Published on: 2023/4/30

HGVS expressions

NM_000527.5:c.440C>T
NM_000527.5(LDLR):c.440C>T (p.Thr147Ile)
NC_000019.10:g.11105346C>T
CM000681.2:g.11105346C>T
NC_000019.9:g.11216022C>T
CM000681.1:g.11216022C>T
NC_000019.8:g.11077022C>T
NG_009060.1:g.20966C>T
ENST00000252444.10:c.698C>T
ENST00000559340.2:c.440C>T
ENST00000560467.2:c.440C>T
ENST00000558518.6:c.440C>T
ENST00000252444.9:c.694C>T
ENST00000455727.6:c.314-2046C>T
ENST00000535915.5:c.317C>T
ENST00000545707.5:c.314-1219C>T
ENST00000557933.5:c.440C>T
ENST00000558013.5:c.440C>T
ENST00000558518.5:c.440C>T
ENST00000560467.1:c.40C>T
NM_000527.4:c.440C>T
NM_001195798.1:c.440C>T
NM_001195799.1:c.317C>T
NM_001195800.1:c.314-2046C>T
NM_001195803.1:c.314-1219C>T
NM_001195798.2:c.440C>T
NM_001195799.2:c.317C>T
NM_001195800.2:c.314-2046C>T
NM_001195803.2:c.314-1219C>T

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PP3 PM1 PM2

Not Met criteria codes 15

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BP4 BP3 BS1 BS4 BS3 BS2
PP1 PP4 PS1 PS2 PS4 BA1
PM5 PM4 PM6

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.440C>T (p.Thr147Ile) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3_Supporting, PM1, PM2, and PP3 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: PS3_Supporting: Level 3 assays: PMID 21865347: Htz Patient lymphocytes, FACS assays - results - 55-70% LDLR activity ---- results are below 85% of wild-type activity. So PS3_Supporting is met. PM1: Variant meets PM2 and is on exon 4. So PM1 is met. PM2: This variant is absent from gnomAD (gnomAD v2.1.1). So PM2 is met. PP3: REVEL = 0.811. It is above 0.75, so PP3 is met.

Met criteria codes

PS3_Supporting	✔	Level 3 assays: PMID 21865347: Htz Patient lymphocytes, FACS assays - results - 55-70% LDLR activity ---- results are below 85% of wild-type activity. So PS3_Supporting is met.
PP3	✔	REVEL = 0.811. It is above 0.75, so PP3 is met.
PM1	✔	Variant meets PM2 and is on exon 4. So PM1 is met.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1). So PM2 is met.

Not Met criteria codes

BP4	✖	REVEL = 0.811. It is above 0.5
BP3	✖	No in-frame deletions/insertions.
BS1	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS4	✖	No data available
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No data available

PP1		✖	No data available
PP4		✖	No data available
PS1		✖	No other missense variant in the same codon.
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No data available
BA1		✖	This variant is absent from gnomAD (gnomAD v2.1.1).
PM5		✖	No other missense variant in the same codon.
PM4		✖	No in-frame deletions/insertions.
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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