

Variant: *NM_000527.5(LDLR):c.1322T>C (p.Ile441Thr)*

Version: 1.0

CA10585400 [↗](#)

251783 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c86aaf4e-cc4f-448f-a070-bdbdce293339

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HGVS expressions

NM_000527.5(LDLR):c.1322T>C (p.Ile441Thr)

NM_000527.5:c.1322T>C

NC_000019.10:g.11113413T>C

CM000681.2:g.11113413T>C

NC_000019.9:g.11224089T>C

CM000681.1:g.11224089T>C

NC_000019.8:g.11085089T>C

NG_009060.1:g.29033T>C

ENST00000252444.10:c.1580T>C

ENST00000559340.2:c.1322T>C

ENST00000560467.2:c.1202T>C

ENST00000558518.6:c.1322T>C

ENST00000252444.9:c.1576T>C

ENST00000455727.6:c.818T>C

ENST00000535915.5:c.1199T>C

ENST00000545707.5:c.941T>C

ENST00000557933.5:c.1322T>C

ENST00000558013.5:c.1322T>C

ENST00000558518.5:c.1322T>C

ENST00000559340.1:c.43T>C

ENST00000560173.1:n.321T>C

ENST00000560467.1:c.802T>C

NM_000527.4:c.1322T>C

NM_001195798.1:c.1322T>C

NM_001195799.1:c.1199T>C

NM_001195800.1:c.818T>C

NM_001195803.1:c.941T>C

NM_001195798.2:c.1322T>C

NM_001195799.2:c.1199T>C

NM_001195800.2:c.818T>C

NM_001195803.2:c.941T>C

Met criteria codes **6**

Pathogenic

PM2

PS3

PP3

PP4

PP1_Strong

PS4_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Not Met criteria codes 20

PM1 PM3 PM5 PM4 PM6
PS1 PS2 PP2 BA1 PVS1
BS2 BS1 BS4 BS3 BP5 BP7
BP4 BP3 BP1 BP2

Evidence Links 0

Criteria Specification Information ⓘ

🔗 Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1322T>C (p.Ile441Thr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS3, PP1_Strong, PM2, PS4_Moderate, PP3 and PP4) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PS3 - Level 1 assay - PMID:25741862 - CHO cells, WB+FACS+CLSM, 7% low-density lipoprotein particle receptor biosynthetic process; 5% low-density lipoprotein particle binding; 10% low-density lipoprotein particle clearance. PP1_strong - 6 informative meioses in 3 families identified by Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. PM2 - No population data was found for this allele in gnomAD (gnomAD v2.1.1). PS4_moderate - Variant meets PM2. Variant identified in 9 index cases. PP3 - REVEL: 0,907. PP4 - Variant meets PM2. Variant identified in 9 index cases fulfilling specific clinical criteria for FH (6 cases with Simon-Broome from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 3 cases with Simon-Broome criteria published in PMID: 20538126).

Met criteria codes

PM2	ⓘ	✓	No population data was found for this allele in gnomAD (gnomAD v2.1.1).
PS3	ⓘ	✓	Level 1 assay - PMID:25741862 - CHO cells, WB+FACS+CLSM, 7% low-density lipoprotein particle receptor biosynthetic process; 5% low-density lipoprotein particle binding; 10% low-density lipoprotein particle clearance
PP3	ⓘ	✓	REVEL: 0,907. Score is above 0,75.
PP4	ⓘ	✓	Variant meets PM2. Variant identified in 9 index cases fulfilling specific clinical criteria for FH (6 cases with Simon-Broome from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 3 cases with Simon-Broome criteria published in PMID: 20538126).
PP1_Strong	ⓘ	✓	6 informative meioses in 3 families identified by Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge.
PS4_Moderate	ⓘ	✓	Variant meets PM2. Variant identified in 9 index cases (6 cases with Simon-Broome from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; 3 cases with Simon-Broome criteria published in PMID: 20538126).

Not Met criteria codes

PM1	ⓘ	✗	Missense at codon 441. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
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PM3			Not identified in individuals with other variants.
PM5			No other missense variants classified as Pathogenic in the same codon. Two other missense variants described in the same codon (accessed 19 August 2020): (1)NM_000527.5(LDLR):c.1322T>A (p.Ile441Asn) (ClinVar ID 251782) - classified as Likely pathogenic by these guidelines. (2)NM_000527.5(LDLR):c.1323C>G (p.Ile441Met) (ClinVar ID 251784) - classified as VUS by these guidelines.
PM4			Missense variant. Not applicable.
PM6			No de novo cases were identified.
PS1			No variant described that leads to the same amino acid change.
PS2			No de novo cases were identified.
PP2			Not applicable.
BA1			No population data was found for this allele in gnomAD (gnomAD v2.1.1).
PVS1			Missense variant. Not applicable.
BS2			No unaffected individuals identified with the variant.
BS1			No population data was found for this allele in gnomAD (gnomAD v2.1.1).
BS4			Only one family with non-segregations reported - at least two families are needed.
BS3			No functional study showing non-damaging effect on protein function or splicing.
BP5			Not applicable.
BP7			Missense variant. Not applicable.
BP4			REVEL: 0,907. Score is not below 0,15.
BP3			Not applicable.
BP1			Not applicable.
BP2			

1 case has also APOE c.683G>A;p.(Trp228*) variant and has heterozygous FH phenotype (LDL not above 350mg/dl). Other family members also have the APOE variant (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge). 2nd variant is not in LDLR, APOB or PCSK9, so BP2 is Not Met at this moment.

Curation History

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