The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.1301C>G (p.Thr434Arg)

Version: 1.0

CA10585393

251774 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e7fe2f7c-172d-4122-83bc-6fa3cc271b27
Approved on: 2022/10/28
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HGVS expressions

NM_000527.5(LDLR):c.1301C>G (p.Thr434Arg)
NM_000527.5:c.1301C>G
NC_000019.10:g.11113392C>G
CM000681.2:g.11113392C>G
NC_000019.9:g.11224068C>G
CM000681.1:g.11224068C>G
NC_000019.8:g.11085068C>G
NG_009060.1:g.29012C>G
ENST00000252444.10:c.1559C>G
ENST00000559340.2:c.1301C>G
ENST00000560467.2:c.1181C>G
ENST00000558518.6:c.1301C>G
ENST00000252444.9:c.1555C>G
ENST00000455727.6:c.797C>G
ENST00000535915.5:c.1178C>G
ENST00000545707.5:c.920C>G
ENST00000557933.5:c.1301C>G
ENST00000558013.5:c.1301C>G
ENST00000558518.5:c.1301C>G
ENST00000559340.1:c.22C>G
ENST00000560173.1:n.300C>G
ENST00000560467.1:c.781C>G
NM_000527.4:c.1301C>G
NM_001195798.1:c.1301C>G
NM_001195799.1:c.1178C>G
NM_001195800.1:c.797C>G
NM_001195803.1:c.920C>G
NM_001195798.2:c.1301C>G
NM_001195799.2:c.1178C>G
NM_001195800.2:c.797C>G
NM_001195803.2:c.920C>G

Pathogenic

Met criteria codes 5

PP4 PM2 PM3 PP1_Strong PS4

Expert Panel

Familial Hypercholesterolemia VCEP

Not Met criteria codes 17

PP3 BA1 PM6 PM1 PM5 PM4 BS2 BS1 BS4 BS3 PS1 PS2 PS3 BP4 BP3 BP2 PVS1

Evidence Links 0

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1301C>G (p.Thr434Arg) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4, PM2, PM3, PP1_Strong, and PP4 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: PS4: Variant meets PM2 and is identified in 10 unrelated cases, as follows: 6 patients with DLCN >=6 and 2 patients with Simon-Broome criteria of possible FH from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obesite et des Dyslipidies; 1 case with MedPed criteria from PMID 21868016 (Garcia-Garcia et al., 2011); 1 case with DLCN>6 from PMID 10634824 (Deiana et al., 2000). So PS4 is met. PM2: This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PM3: Variant meets PM2 and is identified in 2 siblings from PMID 29306853 with childhood total cholesterol levels >700 mg/dL and homozygous for this variant. So PM3 is met. PP1_Strong: Variant segregates with FH phenotype in >1 families, as follows: 6 affected family members from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obesite et des Dyslipidies; 10 affected members tested positive and 7 unaffected members tested negative in one family in 17 informative meiosis from PMID 21868016, so PP1_Strong is met. PP4: Variant meets PM2 and is identified in 10 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details).

Met criteria codes

PP4	✔	Variant meets PM2 and is identified in 10 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details).
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met.
PM3	✔	Variant meets PM2 and is identified in 2 siblings from PMID 29306853 with childhood total cholesterol levels >700 mg/dL and homozygous for this variant. So PM3 is met.
PP1_Strong	✔	Variant segregates with FH phenotype in >1 families, as follows: 6 affected family members from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obesite et des Dyslipidies; 10 affected members tested positive and 7 unaffected members tested negative in one family in 17 informative meiosis from PMID 21868016, so PP1_Strong is met.
PS4	✔	Variant meets PM2 and is identified in 10 unrelated cases, as follows: 6 patients with DLCN >=6 and 2 patients with Simon-Broome criteria of possible FH from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obesite et des Dyslipidies; 1 case with MedPed criteria from PMID 21868016 (Garcia-Garcia et al., 2011); 1 case with DLCN>6 from PMID 10634824 (Deiana et al., 2000). So PS4 is met.

Not Met criteria codes

PP3	ℹ	✖	REVEL = 0.652. It is not above 0.75, so splicing evaluation required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp upstream from the canonical donor site and creates AG. Wild type score= 6.59, Variant score= 5.74; Var/Wt ratio = 0.87. It is below 0.9. C) there is an AG nearby. Variant cryptic score= -13.46, Wild type cryptic score= -10.76; Var criptic/Wt criptic= 1.25, Var criptic/Wt score= -2.04. It is below 0.9. Variant is not predicted to alter splicing.
BA1	ℹ	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	ℹ	✖	Not in exon 4. Not a cysteine residue.
PM5	ℹ	✖	3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1301C>T (p.Thr434Met)(ClinVar ID 251775) - Unknown significance by these guidelines - NM_000527.5(LDLR):c.1300A>C (p.Thr434Pro)(ClinVar ID 496018) - Unknown significance by these guidelines - NM_000527.5(LDLR):c.1301C>A (p.Thr434Lys) (ClinVar ID 251773) - Likely pathogenic by these guidelines There is no other missense variant in the same codon classified as pathogenic by these guidelines.
PM4	ℹ	✖	No In-frame deletions/insertions
BS2	ℹ	✖	Variant identified in 1 heterozygous non-affected (LDL<50th percentile) family member (PMID 21868016).
BS1	ℹ	✖	This variant is absent from gnomAD (gnomAD v2.1.1).
BS4	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	ℹ	✖	PMID 21868016: Heterologous cells (COS7), ELISA and western blot assays - result - Normal LDLR expression (no assessment of the whole LDLR cycle).
PS1	ℹ	✖	No missense variant in the same codon resulting in the same amino acid change
PS2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3	ℹ	✖	PMID 21868016: Heterologous cells (COS7), ELISA and western blot assays - result - Normal LDLR expression
BP4	ℹ	✖	REVEL = 0.652. It is not above 0.75, so splicing evaluation required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp upstream from the canonical donor site and creates AG. Wild type score= 6.59, Variant score= 5.74; Var/Wt ratio = 0.87. It is below 0.9. C) there is an AG nearby. Variant cryptic score= -13.46, Wild type cryptic score= -10.76; Var criptic/Wt criptic= 1.25, Var criptic/Wt score= -2.04. It is below 0.9. Variant is not predicted to alter splicing.

BP3		✖	No In-frame deletions/insertions
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1		✖	Not a null variant.

Curation History

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