

Variant: NM_000527.5(LDLR):c.1361C>A (p.Thr454Asn)

Version: 1.1

CA10585425 [↗](#)

251812 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: bceb5fe5-d799-4bbe-9625-e9eea69def7f

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HGVS expressions

NM_000527.5:c.1361C>A

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NC_000019.10:g.11113537C>A

CM000681.2:g.11113537C>A

NC_000019.9:g.11224213C>A

CM000681.1:g.11224213C>A

NC_000019.8:g.11085213C>A

NG_009060.1:g.29157C>A

ENST00000252444.10:c.1619C>A

ENST00000559340.2:c.1361C>A

ENST00000560467.2:c.1241C>A

ENST00000558518.6:c.1361C>A

ENST00000252444.9:c.1615C>A

ENST00000455727.6:c.857C>A

ENST00000535915.5:c.1238C>A

ENST00000545707.5:c.980C>A

ENST00000557933.5:c.1361C>A

ENST00000558013.5:c.1361C>A

ENST00000558518.5:c.1361C>A

ENST00000559340.1:c.82C>A

ENST00000560467.1:c.841C>A

NM_000527.4:c.1361C>A

NM_001195798.1:c.1361C>A

NM_001195799.1:c.1238C>A

NM_001195800.1:c.857C>A

NM_001195803.1:c.980C>A

NM_001195798.2:c.1361C>A

NM_001195799.2:c.1238C>A

NM_001195800.2:c.857C>A

NM_001195803.2:c.980C>A

Likely Pathogenic

Met criteria codes 3

PS3PP4PM2

Not Met criteria codes 23

PS1PS2PS4PP1PP2PP3BA1PM6BS1BS4BS3PM1PM3PM5PM4BS2BP5BP7BP4BP3BP1BP2PVS1

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

[Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1](#)[PDF](#)[Criteria Specification Approval History](#)[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1361C>A (p.Thr454Asn) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3, PM2 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: PS3 - Level 1 FS: Etxebarria et al. 2015 (PMID 25378237): Heterologous cells (CHO) with FACS - results: 65% LDL-LDLR binding, uptake and cell surface LDLR --- activity is below 70% of wild-type, so PS3 is met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PP4 - variant meets PM2 and was identified in 1 index case with MEDPED clinical criteria of FH (45 year old female with TC 398mg/dl) from PMID: 19007590 (Civeira et al. 2008), Spain; so PP4 is met.

Met criteria codes

PS3		✓	Level 1 FS: Etxebarria et al. 2015 (PMID 25378237): Heterologous cells (CHO) with FACS - results: 65% LDL-LDLR binding, uptake and cell surface LDLR --- activity is below 70% of wild-type, so PS3 is met
PP4		✓	variant meets PM2 and was identified in - 9 cases (but paper just states with clinical diagnosis of FH, but does not specify criteria used) from PMID 25378237 (Etxebarria et al. 2015), Spain; - 1 index case (but does not specify clearly if DLCN>6) from PMID: 15241806 (Mozas et al. 2004), Spain; - 1 index case with MEDPED clinical criteria of FH (45 year old female with TC 398mg/dl) from PMID: 19007590 (Civeira et al. 2008), Spain; --- since 1 index case clearly fulfills clinical criteria of FH, PP4 is met
PM2		✓	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met

Not Met criteria codes

PS1		✗	there are no other missense variants described in the same codon, so not met
PS2		✗	no de novo occurrence
PS4		✗	variant meets PM2 and was identified in - 9 cases (but paper just states with clinical diagnosis of FH, but does not specify criteria used) from PMID 25378237 (Etxebarria et al. 2015), Spain; - 1 index case (but does not specify clearly if DLCN>6) from PMID: 15241806 (Mozas et al. 2004), Spain; - 1 index case with MEDPED clinical criteria of

FH (45 year old female with TC 398mg/dl) from PMID: 19007590 (Civeira et al. 2008), Spain; --- since only 1 index case clearly fulfills clinical criteria of FH, PS4_Supporting is not met

PP1			no segregation data
PP2			not applicable
PP3			REVEL = 0.473, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. A) variant located at -20 to +3 bases from canonical acceptor splice site MES scores: canonical site variant (CTTCTCTCCTCCTGCCTCAGCAA) = 6.40; canonical site wt (CTTCTCTCCTCCTGCCTCAGCAC) = 6.76. Ratio variant/wt canonical acceptor: 6.40/6.76 = 0.947 ---- It is not below 0.8 Variant is predicted to not alter splicing, so PP3 is not met
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
PM6			no de novo occurrence
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
BS4			no segregation data
BS3			Level 1 FS: Etxebarria et al. 2015 (PMID 25378237): Heterologous cells (CHO) with FACS - results: 65% LDL-LDLR binding, uptake and cell surface LDLR --- activity is not above 90% of wild-type, so BS3 is not met
PM1			variant is missense and meets PM2, but it is not in exon 4 and does not alter Cys, so not met
PM3			not identified in index cases with more than 1 variant
PM5			there are no other missense variants described in the same codon, so not met
PM4			variant is missense, so not met
BS2			not identified in normolipidemic individuals, so not met
BP5			not applicable
BP7			variant is missense, so not met
BP4			REVEL = 0.473, it is below 0.50, splicing evaluation required. Functional data on splicing not available. A) variant located at -20 to +3 bases from canonical acceptor splice site MES scores: canonical site variant (CTTCTCTCCTCCTGCCTCAGCAA) = 6.40; canonical site wt (CTTCTCTCCTCCTGCCTCAGCAC) = 6.76. Ratio variant/wt canonical acceptor: 6.40/6.76 = 0.947 ---- It is not above 1.0 Variant is not predicted to not alter splicing, so BP4 is not met

BP3			not applicable
BP1			not applicable
BP2			not identified in index cases with more than 1 variant
PVS1			variant is missense and not in initiation codon, so not met

Curation History 		
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