

Variant: NM_000527.5(LDLR):c.1279A>C (p.Arg427=)

Version: 1.0

CA033384 [↗](#)

251764 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e1a0ec5e-a3f6-416d-b5d0-f502d242d549

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HGVS expressions

NM_000527.5:c.1279A>C

NM_000527.5(LDLR):c.1279A>C (p.Arg427=)

NC_000019.10:g.11113370A>C

CM000681.2:g.11113370A>C

NC_000019.9:g.11224046A>C

CM000681.1:g.11224046A>C

NC_000019.8:g.11085046A>C

NG_009060.1:g.28990A>C

ENST00000252444.10:c.1537A>C

ENST00000559340.2:c.1279A>C

ENST00000560467.2:c.1159A>C

ENST00000558518.6:c.1279A>C

ENST00000252444.9:c.1533A>C

ENST00000455727.6:c.775A>C

ENST00000535915.5:c.1156A>C

ENST00000545707.5:c.898A>C

ENST00000557933.5:c.1279A>C

ENST00000558013.5:c.1279A>C

ENST00000558518.5:c.1279A>C

ENST00000560173.1:n.278A>C

ENST00000560467.1:c.759A>C

NM_000527.4:c.1279A>C

NM_001195798.1:c.1279A>C

NM_001195799.1:c.1156A>C

NM_001195800.1:c.775A>C

NM_001195803.1:c.898A>C

NM_001195798.2:c.1279A>C

NM_001195799.2:c.1156A>C

NM_001195800.2:c.775A>C

NM_001195803.2:c.898A>C

Likely Benign

Met criteria codes 5

BP7 BP4 BP2 PP4 PM2

Not Met criteria codes 20

BA1 BP3 BP1 BS1 BS4 BS3
BS2 PP1 PP2 PP3 PM6
PM1 PM3 PM5 PM4 PS1
PS2 PS3 PS4 PVS1

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 1.2
- PDF
- Criteria Specification Approval History
- Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1279A>C (p.Arg427=) variant is classified as Likely Benign for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes BP2, BP4, BP7, PM2 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 27 January 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.00006976 (0.006976%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1). BP4: No REVEL, splicing evaluation required. Functional data on splicing not available. A) variant not on limits B) does not create AG/GT C) variant is exonic and there is no AG/GT nearby Variant is not predicted to alter splicing. --- BP4 is met. BP7: Variant is synonymous and meets BP4. BP2: Variant identified in an index case with heterozygous FH phenotype (LDL-C=170mg/dL on statins) and LDLR c.530C>T (p.Ser177Leu) (confirmed in trans), classified as Pathogenic by these guidelines, from Cardiovascular Research Group, Instituto Nacional de Saúde Dr. Ricardo Jorge, Portugal. PP4: Variant meets PM2 and is identified in 1 index case with possible FH by Simon Broome criteria from Cardiovascular Research Group, Instituto Nacional de Saúde Dr. Ricardo Jorge, Portugal. Variant has 3 Supporting evidence codes towards Benign, enough to classify as Likely Benign and only 1 Moderate plus 1 Supporting evidence codes towards Pathogenic, so we are confident in classifying this variant as Likely Benign.

Met criteria codes

BP7		✓	Variant is synonymous and meets BP4.
BP4		✓	No REVEL, splicing evaluation required. Functional data on splicing not available. A) variant not on limits B) does not create AG/GT C) variant is exonic and there is no AG/GT nearby Variant is not predicted to alter splicing. --- BP4 is Met.
BP2		✓	Variant identified in an index case with heterozygous FH phenotype (LDL-C=170mg/dl under statins) and LDLR: c.530C>T (p.Ser177Leu), confirmed in trans, classified as Pathogenic by these guidelines, from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BP2 is met.
PP4		✓	Variant meets PM2 and is identified in 1 index cases who fulfills SB possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so PP4 is met.
PM2		✓	PopMax MAF = 0.00006976 (0.006976%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so PM2 is met.

Not Met criteria codes			
BA1		✖	FAF = 0.00003422 (0.003422%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BA1 is not met.
BP3		✖	Not applicable
BP1		✖	Not applicable
BS1		✖	FAF = 0.00003422 (0.003422%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BS1 is not met.
BS4		✖	Variant does not segregate with FH phenotype in only 1 informative meiosis from 1 family from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS4 is not met.
BS3		✖	There are no functional studies reported for this variant, so BS3 is not met.
BS2		✖	Variant identified in only 1 heterozygous non-affected (LDL<50th percentile) family member from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS2 is not met.
PP1		✖	Segregation data not reported, so PP1 is Not Met.
PP2		✖	Not applicable
PP3		✖	No REVEL, splicing evaluation required. Functional data on splicing not available. A) variant not on limits B) does not create AG/GT C) variant is exonic and there is no AG/GT nearby Variant is not predicted to alter splicing. --- PP3 is not met.
PM6		✖	de novo occurrence data not reported, so PM6 is Not Met.
PM1		✖	Variant meets PM2 but is not a missense variant in exon 4 and is not one of the highly conserved cysteine residues.
PM3		✖	Variant identified in an index case with heterozygous FH phenotype (LDL-C=170mg/dl under statins) and LDLR: c.530C>T (p.Ser177Leu), confirmed in trans, classified as Pathogenic by these guidelines, from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so PM3 is not met.
PM5		✖	Variant is synonymous, so PM5 is Not Met.
PM4		✖	Variant does not meet PM2 and is synonymous, so PM4 is Not Met.
PS1		✖	Variant is synonymous, so PS1 is Not Met.
PS2		✖	de novo occurrence data not reported, so PS2 is Not Met.

PS3			There are no functional studies reported for this variant, so PS3 is not met.
PS4			Variant meets PM2 and is identified in only 1 index cases who fulfills SB possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so PS4 is not met.
PVS1			Variant is synonymous, so PVS1 is Not Met.

Curation History 		
Showing 1 to 1 of 1 rows		

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