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.2446A>C (p.Lys816Gln)

Version: 1.0

CA404098844

440697 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 8b2fda49-2957-482c-985e-3acbe1cc2fc4
Approved on: 2023/4/28
Published on: 2023/4/28

HGVS expressions

NM_000527.5(LDLR):c.2446A>C (p.Lys816Gln)
NM_000527.5:c.2446A>C
NC_000019.10:g.11129569A>C
CM000681.2:g.11129569A>C
NC_000019.9:g.11240245A>C
CM000681.1:g.11240245A>C
NC_000019.8:g.11101245A>C
NG_009060.1:g.45189A>C
ENST00000252444.10:c.2704A>C
ENST00000559340.2:c.*515A>C
ENST00000560467.2:c.2326A>C
ENST00000558518.6:c.2446A>C
ENST00000252444.9:c.2700A>C
ENST00000455727.6:c.1942A>C
ENST00000535915.5:c.2323A>C
ENST00000545707.5:c.1912A>C
ENST00000557933.5:c.2508A>C
ENST00000558013.5:c.2446A>C
ENST00000558518.5:c.2446A>C
ENST00000560628.1:n.108+1915A>C
NM_000527.4:c.2446A>C
NM_001195798.1:c.2446A>C
NM_001195799.1:c.2323A>C
NM_001195800.1:c.1942A>C
NM_001195803.1:c.1912A>C
NM_001195798.2:c.2446A>C
NM_001195799.2:c.2323A>C
NM_001195800.2:c.1942A>C
NM_001195803.2:c.1912A>C

Uncertain Significance

Met criteria codes 1

PM2

Not Met criteria codes 7

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BA1 BS1 BP4 PVS1 PS1 PP3 PM5

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.2446A>C (p.Lys816Gln) variant is classified as Uncertain significance - insufficient evidence, for Familial Hypercholesterolemia by applying evidence code PM2 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: . PM2: This variant is absent from gnomAD (gnomAD v2.1.1)

Met criteria codes

PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1)

Not Met criteria codes

BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	REVEL = 0.552. It is not below 0.5, splicing evaluation needed. Functional data on splicing not available. A) variant is not on limits B) Variant does not create GT Variant is not predicted to affect splicing.
PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	2 other missense variants in the same codon: . NM_000527.5(LDLR):c.2447A>G (p.Lys816Arg) (ClinVar ID 440698) Conflicting interpretations of pathogenicity by these guidelines . NM_000527.5(LDLR):c.2447A>G (p.Lys816Arg) (ClinVar ID 1791406) Uncertain significance by these guidelines There are no variant in the same codon classified as Pathogenic by these guidelines.
PP3	✖	REVEL = 0.552. It is not above 0.75, splicing evaluation needed. Functional data on splicing not available. A) variant is not on limits B) Variant does not create GT C) There is an AG nearby: . MES scores: wt cryptic= -5.82, variant cryptic= -1.26, canonical acceptor= 8.21. . MES scores: wt cryptic= -4.18, variant cryptic= -2.41, canonical acceptor= 8.21. Variant is not predicted to affect splicing.
PM5	✖	

2 other missense variants in the same codon: . NM_000527.5(LDLR):c.2447A>G (p.Lys816Arg) (ClinVar ID 440698) Conflicting interpretations of pathogenicity by these guidelines . NM_000527.5(LDLR):c.2447A>G (p.Lys816Arg) (ClinVar ID 1791406) Uncertain significance by these guidelines There are no variant in the same codon classified as Pathogenic by these guidelines.

Curation History

owing 1 to 1 of 1 rows

ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.2446A>C (p.Lys...	Uncertain Significance	Hypercholesterolemia, Familial	2023-04-28	1.0	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR

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