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.1436T>A (p.Leu479Gln)

Version: 1.0

CA404086021

992900 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: cfded3a1-2932-4f02-9c54-0a202f10c204
Approved on: 2024/2/23
Published on: 2025/2/24

HGVS expressions

NM_000527.5:c.1436T>A
NM_000527.5(LDLR):c.1436T>A (p.Leu479Gln)
NC_000019.10:g.11113612T>A
CM000681.2:g.11113612T>A
NC_000019.9:g.11224288T>A
CM000681.1:g.11224288T>A
NC_000019.8:g.11085288T>A
NG_009060.1:g.29232T>A
ENST00000252444.10:c.1694T>A
ENST00000559340.2:c.1436T>A
ENST00000560467.2:c.1316T>A
ENST00000558518.6:c.1436T>A
ENST00000252444.9:c.1690T>A
ENST00000455727.6:c.932T>A
ENST00000535915.5:c.1313T>A
ENST00000545707.5:c.1055T>A
ENST00000557933.5:c.1436T>A
ENST00000558013.5:c.1436T>A
ENST00000558518.5:c.1436T>A
ENST00000559340.1:c.157T>A
ENST00000560467.1:c.916T>A
NM_000527.4:c.1436T>A
NM_001195798.1:c.1436T>A
NM_001195799.1:c.1313T>A
NM_001195800.1:c.932T>A
NM_001195803.1:c.1055T>A
NM_001195798.2:c.1436T>A
NM_001195799.2:c.1313T>A
NM_001195800.2:c.932T>A
NM_001195803.2:c.1055T>A

Likely Pathogenic

Met criteria codes 6

PS4_Supporting PP3 PP4 PM2 PM3 PP1_Moderate

Not Met criteria codes 16

BA1 PM6 PM1 PM5 PM4 BS2 BS1 BS4 BS3 PS1 PS2 PS3 BP4 BP2 PVS1 BP7

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.1436T>A (p.Leu479Gln) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM3, PP1_Moderate, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD v4.0.0. PP3: REVEL= 0.938. PS4_Supporting, PP4: Identified in two index cases who fulfil FH criteria, reported in PMID 33732287 (Moradi et al., 2021; LDLC 391 mg/dl at age of 24 years) and PMID 29213121 (Fairoozy et al., 2017; LDL-C 15 mmol/L at age of 15 years). Both index cases are homozygous for the variant. PP1_Moderate: Variant segregates with FH phenotype in five informative meiosis in two families, the affected relatives are positive for the variant, reported in PMID 33732287 and 29213121. PM3: Variant observed in a true homozygous case who had HoFH phenotype with LDLC of 15 mmol/L, reported in PMID 29213121.

Met criteria codes

PS4_Supporting	✔	Identified in two index cases who fulfil FH criteria, reported in PMID 33732287 (LDLC 391 mg/dl at age of 24) and PMID 29213121 (LDL-C 15 mmol/L at age of 15). Both index cases are homozygous for the variant.
PP3	✔	REVEL= 0.938
PP4	✔	Identified in two index cases who fulfil FH criteria, reported in PMID 33732287 (LDLC 391 mg/dl at age of 24) and PMID 29213121 (LDL-C 15 mmol/L at age of 15). Both index cases are homozygous for the variant.
PM2	✔	This variant is absent from gnomAD v4.0.0
PM3	✔	Variant observed in a true homozygous case who had HoFH phenotype with LDLC of 15 mmol/l, reported in PMID 29213121
PP1_Moderate	✔	Variant segregates with FH phenotype in five informative meiosis in two families, the affected relatives are positive for the variant, reported in PMID 33732287 and 29213121.

Not Met criteria codes

BA1		✖	Variant absent from gnomAD v2.1.1
PM6		✖	Not met.
PM1		✖	Not located in exon 4 or at a cysteine residue.
PM5		✖	No other pathogenic variants at same codon leading to different amino acid change.
PM4		✖	Not an in-frame deletion/insertion.
BS2		✖	Not met.
BS1		✖	Variant absent from gnomAD v2.1.1
BS4		✖	Not met.
BS3		✖	No data available.
PS1		✖	No other pathogenic variants at same codon leading to same amino acid change.
PS2		✖	Not met.
PS3		✖	No data available.
BP4		✖	REVEL= 0.938
BP2		✖	Not met.
PVS1		✖	Not a null variant.
BP7		✖	Not a synonymous variant.

Curation History

nowing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.