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.1327T>C (p.Trp443Arg)

Version: 1.0

CA033596

998052 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 49662f67-017a-43b6-904e-709de915230e
Approved on: 2025/1/31
Published on: 2025/2/3

HGVS expressions

NM_000527.5(LDLR):c.1327T>C (p.Trp443Arg)
NM_000527.5:c.1327T>C
NC_000019.10:g.11113418T>C
CM000681.2:g.11113418T>C
NC_000019.9:g.11224094T>C
CM000681.1:g.11224094T>C
NC_000019.8:g.11085094T>C
NG_009060.1:g.29038T>C
ENST00000252444.10:c.1585T>C
ENST00000559340.2:c.1327T>C
ENST00000560467.2:c.1207T>C
ENST00000558518.6:c.1327T>C
ENST00000252444.9:c.1581T>C
ENST00000455727.6:c.823T>C
ENST00000535915.5:c.1204T>C
ENST00000545707.5:c.946T>C
ENST00000557933.5:c.1327T>C
ENST00000558013.5:c.1327T>C
ENST00000558518.5:c.1327T>C
ENST00000559340.1:c.48T>C
ENST00000560173.1:n.326T>C
ENST00000560467.1:c.807T>C
NM_000527.4:c.1327T>C
NM_001195798.1:c.1327T>C
NM_001195799.1:c.1204T>C
NM_001195800.1:c.823T>C
NM_001195803.1:c.946T>C
NM_001195798.2:c.1327T>C
NM_001195799.2:c.1204T>C
NM_001195800.2:c.823T>C
NM_001195803.2:c.946T>C

Likely Pathogenic

Met criteria codes 6

PS4_Supporting PP3 PP4 PM2 PM3 PM5

Expert Panel

Familial Hypercholesterolemia VCEP

Not Met criteria codes 1

PP1

Evidence Links 0

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.1327T>C (p.Trp443Arg) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM3, PM5, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 31 January 2025. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.1.0). PP3: REVEL = 0.951. PM5: 1 other missense variant in the same codon: NM_000527.5(LDLR):c.1329G>C (p.Trp443Cys) (ClinVar ID 251792)- Pathogenic by these guidelines. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 4 unrelated index cases who fulfill criteria for FH: 1 patient with DLCN >=6 from PMID 28458923 (Korneva et al., 2017), Russia; 1 patient with DLCN >=6 from PMID 32423031 (Semenova et al., 2020), Russia; 2 patients with DLCN >=6 from PMID 33418990 (Meshkov et al., 2021), Russia. PM3: Variant meets PM2 and is identified in an index case with homozygous FH phenotype (treated LDL-C > 15.2 mmol/L). This patient also carries the c.2141-954_2390-318del variant, classified as Likely Pathogenic by these guidelines, in trans (PMID 36901902, Nazarenko et al., 2023).

Met criteria codes

PS4_Supporting	✔	Variant meets PM2 and is identified in at least 4 unrelated index cases who fulfill SB definite FH or DLCN>=6: (1): PMID 28458923- 1 FH patient carrying variant who meets definite FH criteria (2): PMID 32423031- 1 unrelated FH patient carrying variant who meets DLCN>6 criteria (3): PMID 33418990- 2 unrelated FH patient carrying variant who meets DLCN>6 criteria
PP3	✔	REVEL = 0.951
PP4	✔	Variant meets PM2 and is identified in at least 1 index case who fulfills DLCN>=6 criteria for FH after alternative causes of high cholesterol were excluded (PMID: 28458923).
PM2	✔	This variant is absent from gnomAD (gnomAD v4.1.0).
PM3	✔	Variant meets PM2 and is identified in an index case with homozygous FH phenotype (treated LDL-C > 15.2 mmol/L). This patient also carries the c.2141-954_2390-318del variant, classified as Likely Pathogenic by these guidelines, in trans (PMID: 36901902).
PM5	✔	1 other missense variant in the same codon: - NM_000527.5(LDLR):c.1329G>C (p.Trp443Cys) variant (ClinVar ID 251792) - Pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines.

Not Met criteria codes

PP1		✖	PMID 28458923 - table states 1 family with 3 patients, but gave no data.

Curation History

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