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.1328G>C (p.Trp443Ser)

Version: 1.0

CA10585407

251790 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 774f269e-0cbd-4842-85ed-9fd5e3b5ac31
Approved on: 2025/1/31
Published on: 2025/2/3

HGVS expressions

NM_000527.5(LDLR):c.1328G>C (p.Trp443Ser)
NM_000527.5:c.1328G>C
NC_000019.10:g.11113419G>C
CM000681.2:g.11113419G>C
NC_000019.9:g.11224095G>C
CM000681.1:g.11224095G>C
NC_000019.8:g.11085095G>C
NG_009060.1:g.29039G>C
ENST00000252444.10:c.1586G>C
ENST00000559340.2:c.1328G>C
ENST00000560467.2:c.1208G>C
ENST00000558518.6:c.1328G>C
ENST00000252444.9:c.1582G>C
ENST00000455727.6:c.824G>C
ENST00000535915.5:c.1205G>C
ENST00000545707.5:c.947G>C
ENST00000557933.5:c.1328G>C
ENST00000558013.5:c.1328G>C
ENST00000558518.5:c.1328G>C
ENST00000559340.1:c.49G>C
ENST00000560173.1:n.327G>C
ENST00000560467.1:c.808G>C
NM_000527.4:c.1328G>C
NM_001195798.1:c.1328G>C
NM_001195799.1:c.1205G>C
NM_001195800.1:c.824G>C
NM_001195803.1:c.947G>C
NM_001195798.2:c.1328G>C
NM_001195799.2:c.1205G>C
NM_001195800.2:c.824G>C
NM_001195803.2:c.947G>C

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM5 PM2 PS4_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP

Not Met criteria codes 1

PM3

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.1328G>C (p.Trp443Ser) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM5, PS4_Moderate, PP3 and PP4 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: PopMax MAF = 0.0000006841 (0.00006841 %) in European (non-Finnish) exomes (gnomAD version 4.1.0). PP3: REVEL = 0.934. 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_Moderate, PP4: Variant meets PM2 and is identified in at least 9 unrelated index cases who fulfill criteria for FH: 1 case meeting Simon Broome criteria from PMID 17142622 (Humphries et al., 2006), UK; 1 case meeting Simon Broome possible FH criteria from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; 3 cases with DLCN >=6 from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille, France; 4 cases with DLCN >=6 from PMID 34871818 (Tada et al., 2022), Japan.

Met criteria codes

PP3	✔	REVEL = 0.934
PP4	✔	Variant meets PM2 and is identified in at least 1 index case who fulfills DLCN>=6 (PMID: 19318025) after alternative causes of high cholesterol were excluded.
PM5	✔	- 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.
PM2	✔	PopMax MAF = 0.0000006841 (0.00006841 %) in European (non-Finnish) exomes (gnomAD version 4.1.0).
PS4_Moderate	✔	Variant meets PM2 and is identified in at least 9 unrelated index cases who fulfill SB possible/definite FH/DLCN>=6 criteria for FH: (1): 1 FH patient meeting Simon Broome FH criteria was reported to carry this variant (PMID: 17142622) (2): 1 Patient with variant met Simon Broome possible FH criteria (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies; APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) (3): 3 FH patients meeting DLCN>=6 were reported to carry this variant (U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille) (4): 4 FH patients meeting DLCN>=6 were reported to carry this variant (PMID: 34871818)

Not Met criteria codes

PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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