

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

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HGVS expressions

NM_000527.5:c.1328G>C

NM_000527.5(LDLR):c.1328G>C (p.Trp443Ser)

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**

PM5

PM2

PS4_Moderate

PP3

PP4

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

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)
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.

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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