

Variant: *NM_000527.5(LDLR):c.1329G>C (p.Trp443Cys)*

Version: 1.0

CA10585409 [↗](#)

251792 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: a2f5cf0c-e5f9-4215-a7eb-690c2673a2de

Approved on: 2025/1/31

Published on: 2025/2/3

HGVS expressions

NM_000527.5(LDLR):c.1329G>C (p.Trp443Cys)

NM_000527.5:c.1329G>C

NC_000019.10:g.11113420G>C

CM000681.2:g.11113420G>C

NC_000019.9:g.11224096G>C

CM000681.1:g.11224096G>C

NC_000019.8:g.11085096G>C

NG_009060.1:g.29040G>C

ENST00000252444.10:c.1587G>C

ENST00000559340.2:c.1329G>C

ENST00000560467.2:c.1209G>C

ENST00000558518.6:c.1329G>C

ENST00000252444.9:c.1583G>C

ENST00000455727.6:c.825G>C

ENST00000535915.5:c.1206G>C

ENST00000545707.5:c.948G>C

ENST00000557933.5:c.1329G>C

ENST00000558013.5:c.1329G>C

ENST00000558518.5:c.1329G>C

ENST00000559340.1:c.50G>C

ENST00000560173.1:n.328G>C

ENST00000560467.1:c.809G>C

NM_000527.4:c.1329G>C

NM_001195798.1:c.1329G>C

NM_001195799.1:c.1206G>C

NM_001195800.1:c.825G>C

NM_001195803.1:c.948G>C

NM_001195798.2:c.1329G>C

NM_001195799.2:c.1206G>C

NM_001195800.2:c.825G>C

NM_001195803.2:c.948G>C

Met criteria codes **5**

Pathogenic

PP3

PP4

PP1_Strong

PS4

PM2

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Not Met criteria codes **1**

PM5

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.1329G>C (p.Trp443Cys) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PP1_Strong, PM2, 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 = 0.0000007200 (0.00007200%) in European (non-Finnish) exomes (gnomAD v4.1.0). PP3: REVEL = 0.961. PS4, PP4: Variant meets PM2 and is identified in at least 14 unrelated index cases who fulfill FH criteria from different labs (5 cases with DLCN score >=6 and 5 cases with possible FH by Simon Broome 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; 2 cases with DLCN score >=6 and 2 cases with possible FH by Simon Broome criteria from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France). PP1_Strong: Variant segregates with FH phenotype in at least 6 informative meioses from 5 families from different labs (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France): 6 affected family members have the variant.

Met criteria codes

PP3			REVEL = 0.961
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 (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière).
PP1_Strong			Variant segregates with FH phenotype in at least 6 informative meioses from 5 families from different labs: - Data from 3 families. P3 family : 1 family member positive for variant with LDL-C >75th percentile. P6 family : 1 family member positive for variant with LDL-C >75th percentile. P7 family : 1 family member positive for variant with LDL-C >75th percentile (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) - Data from 2 families. Family 1 : 2 family members positive for variant with LDL-C >75th percentile ; Family 2: 1 family member positive for variant with LDL-C >75th percentile (Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France).
PS4			Variant meets PM2 and is identified in at least 14 unrelated index cases who fulfill SB possible or DLCN>=6 criteria for FH from different labs: - 5 unrelated probands with Dutch lipid clinic network >=6 and 5 unrelated probands with Simon Broome possible (Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière). - 2 unrelated probands with DLCN >or = 6 and 2 unrelated probands with Simon Broome possible (Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France).

PM2			PopMax MAF = 0.0000007200 (0.00007200%) in European (non-Finnish) exomes (gnomAD v4.1.0).
Not Met criteria codes			
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 			
			    
Showing 1 to 1 of 1 rows			

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