

Variant: *NM_000527.5(LDLR):c.1747C>T (p.His583Tyr)*

Version: 1.0

CA023567 [↗](#)

200921 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: de63ac3f-3eb4-4eeb-bdc2-12f22ab90103

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HGVS expressions

NM_000527.5(LDLR):c.1747C>T (p.His583Tyr)

NM_000527.5:c.1747C>T

NC_000019.10:g.11116900C>T

CM000681.2:g.11116900C>T

NC_000019.9:g.11227576C>T

CM000681.1:g.11227576C>T

NC_000019.8:g.11088576C>T

NG_009060.1:g.32520C>T

ENST00000252444.10:c.2005C>T

ENST00000559340.2:c.1705+688C>T

ENST00000560467.2:c.1627C>T

ENST00000558518.6:c.1747C>T

ENST00000252444.9:c.2001C>T

ENST00000455727.6:c.1243C>T

ENST00000535915.5:c.1624C>T

ENST00000545707.5:c.1366C>T

ENST00000557933.5:c.1747C>T

ENST00000558013.5:c.1747C>T

ENST00000558518.5:c.1747C>T

ENST00000559340.1:c.426+688C>T

NM_000527.4:c.1747C>T

NM_001195798.1:c.1747C>T

NM_001195799.1:c.1624C>T

NM_001195800.1:c.1243C>T

NM_001195803.1:c.1366C>T

NM_001195798.2:c.1747C>T

NM_001195799.2:c.1624C>T

NM_001195800.2:c.1243C>T

NM_001195803.2:c.1366C>T

Pathogenic

Met criteria codes **7**

PP1_Strong

PP3

PP4

PS3

PS4

PM2

PM3

Not Met criteria codes **16**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PVS1

BA1

BP4

BP3

BP1

BP5

BP7

BS1

BS3

PP2

PS1

PS2

PM6

PM1

PM5

PM4

Evidence Links 0

- [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.1747C>T (p.His583Tyr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PS4, PP1_Strong, PM2, PM3, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 7 November 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.001203 (0.12%) in East Asian (gnomAD v2.1.1). PopMax MAF > 0.02% (PM2 is "not met"), however, after reviewing literature cases, a founder effect - mostly Asian ancestry - seems to be associated (PMID 27206935 - Chiou et al. 2016; several case reports used for PS4). This variant was also found in other populations: PopMax MAF = 0.016% in South Asian (gnomAD v2.1.1). PP3: REVEL = 0.884. PS3: Functional studies reported in PMID 32695144 (Dušková et al., 2020) performed using heterologous cells (CHO), WB and FACS - results - 52% expression and 44% internalization. The variant showed a deleterious effect on the protein localization and function, and was associated with the accumulation of the protein in the ER. Results are below 70%, so PS3 is met. // Functional studies reported in PMID 21511053 (Zhao et al., 2011) performed using retrovirus transfected LDLR-/- fibroblasts, FACS and 125I-LDL assays - results - approximately 50% cell surface LDLR, 50-60% LDL-LDLR uptake and normal LDL-LDLR binding. Results are below 70%, so PS3 is met. ----- Overall, both functional studies are consistent with damaging effect. PS4, PP4: Variant meets PM2 and is identified in at least 17 unrelated index cases fulfilling criteria for FH (2 index cases 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; at least 15 cases from PMID 20538126, 22353362, 21376320, 25846081, 19318025). PP1_Strong: Variant segregates with FH phenotype in at least 9 informative meioses (minimum 6) from 3 families from different PMIDs (23155708, 2923363, 22353362): 9 affected family members have the variant. PM3: Variant meets PM2 and is identified in 1 index case (PMID 7903864) with homozygous FH phenotype and a deletion of LDLR exons 4-11, confirmed in trans, classified as Pathogenic by these guidelines; 1 index case (PMID 23155708) with homozygous FH phenotype and the LDLR c.2054C>T, p.(Pro685Leu) variant, confirmed in trans, classified as Pathogenic by these guidelines; 1 index case (PMID 29233637) with homozygous FH phenotype and the LDLR c.724C>T, p.(Gln242*) variant, confirmed in trans, classified as Pathogenic by these guidelines.

Met criteria codes

PP1_Strong			Variant segregates with FH phenotype in 9 informative meioses (minimum 6) from 3 families from different PMIDs: (F1) two relatives of a CpHtz FH patien from PMID:23155708: father (TC 7.7 nmol/L and LDL-c 4.9 nmol/L) and grandmother (TC 11.2 nmol/L and LDL-c 7.61 nmol/L) who were htz for the variant under curation // (F2) two relatives of a CpHtz FH patien from PMID:29233637: mother (LDL-c 231 mg/dL) and grandfather (LDL-c 229 mg/dL) who were htz for the variant under curation // (F3) five relatives of a Htz patient from PMID: 22353362 positives for the variant and with LDL-C>75th percentile. (one family) only one relative (father) from PMID:7903864 of a CpHtz FH patient, who was htz for the variant under curation (TC of 4.9 nmol/L and LDL-c of 2.97 nmol/L)
PP3			REVEL = 0.884. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2 and was Identified in 1 FH case fullfiling SB criteria and 1 FH case with clinical Dutch Lipid Clinic Network Criteria score ≥ 6 after alternative causes of high cholesterol were excluded, both from Centre de Génétique Moléculaire et Chromosomique (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière).

PS3			Functional studies (PMID: 32695144) performed using Heterologous cells (CHO), WB and FACS - results - 52% expression and 44% internalisation. The variant showed a deleterious effect on the protein localization and function, and was associated with the accumulation of the protein on ER. Results are below 70%, so PS3 is met. // Functional studies (PMID: 21511053) performed using retrovirus transfected LDLR-/- fibroblasts, FACS and 125I-LDL assays - results - approximately 50% cell surface LDLR, 50-60% LDL-LDLR uptake and normal LDL-LDLR binding. Results are below 70%, so PS3 is met. ----- Overall, both functional studies are consistent with damaging effect. (not considered): Funtional studies (PMID: 7903864) performed using heterologous cells (COS), immunoblot - results - approximately 50% mature protein and binds LDL. No specific information regarding % activity, binding or uptake. Therefore this study was not considered towards PS3.
PS4			Variant meets PM2 and was identified in 17 unrelated index cases - 2 index cases (one fullfiling SB criteria and one with clinical DLCN $\geq$ 6 after alternative causes of high cholesterol were excluded, both from Centre de Génétique Moléculaire et Chromosomique, Hôpital de la Pitié-Salpêtrière) // (5+1+7+1) 14 index cases fullfling SB criteria for FH, after alternative causes of high cholesterol are excluded (PMID:20538126, 22353362, 21376320, 25846081) // at least 1 index case (PMID:19318025) with the variant and DLCN criteria $\geq$ 6.
PM2			PopMax MAF = 0.001203 (0.12%) in East Asian (gnomAD v2.1.1). PopMax MAF > 0.02% (PM2 "is not met"), however, after reviewing literature cases, a founder effect - mostly asian ancestry - seems to be associated (PMID:27206935 and several case reports used for PS4). This variant was also found in other populations: PopMax MAF = 0.016% in South Asian (gnomAD v2.1.1).
PM3			Variant was identified in 1 CpHtz index case (PMID:7903864) with homozygous FH phenotype (TC 15.76 nmol/L and LDL 14 nmol/L, xanthomas) presenting, in trans, the deletion of LDLR exons 4-11, classified as Pathogenic by these guidelines // 1 CpHtz index case (PMID:23155708) with homozygous FH phenotype (TC 13.95 nmol/L and LDL11.25 nmol/L, xanthomata) presenting, in trans, the variant c.2054C>T/p.(Pro685Leu) in the LDLR, classified as Pathogenic by these guidelines // 1 CpHtz index case (PMID:29233637) with homozygous FH phenotype (TC 785 mg/dL and LDL 575mg/dL, xanthomas) presenting, in trans, the variant c.724C>T/p.(Gln242*) in the LDLR, classified as Pathogenic by these guidelines.

Not Met criteria codes

PVS1			The variant is missense, therefore PVS1 is not applied
BA1			BA1 / BS1: FAF = 0.0008091 (0.0809%) in gnomAD v2.1.1. The FAF is not above 0.5%, so BA1 not met; and is not between 0.2-0.5%, so BS1 is not met.
BP4			REVEL = 0.884. It not under 0.50, so BP4 is not met.
BP3			N/A according to FHVCEP guidelines
BP1			N/A according to FHVCEP guidelines
BP5			N/A according to FHVCEP guidelines
BP7			Variant is not synonymous and does not met BP4.

BS1			BA1 / BS1: FAF = 0.0008091 (0.0809%) in gnomAD v2.1.1. The FAF is not above 0.5%, so BA1 not met; and is not between 0.2-0.5%, so BS1 is not met.
BS3			Not met, no reports
PP2			N/A according to FHVCEP guidelines
PS1			No other variant giving same amino acid change identified
PS2			No de novo cases identified
PM6			No de novo cases identified
PM1			Variant in exon 12 of the LDLR gene (not located at exon 4)
PM5			Other variants identified, but none are pathogenic
PM4			The variant is missense, therefore PM4 is not applied

Curation History 		
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