

Variant: NM_000527.5(LDLR):c.1957G>T (p.Val653Phe)

Version: 1.0

CA10585695 [↗](#)

252129 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: a144e629-27a6-411b-9541-dd30a4ea5262

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HGVS expressions

NM_000527.5:c.1957G>T

NM_000527.5(LDLR):c.1957G>T (p.Val653Phe)

NC_000019.10:g.11120203G>T

CM000681.2:g.11120203G>T

NC_000019.9:g.11230879G>T

CM000681.1:g.11230879G>T

NC_000019.8:g.11091879G>T

NG_009060.1:g.35823G>T

ENST00000252444.10:c.2215G>T

ENST00000559340.2:c.*26G>T

ENST00000560467.2:c.1837G>T

ENST00000558518.6:c.1957G>T

ENST00000252444.9:c.2211G>T

ENST00000455727.6:c.1453G>T

ENST00000535915.5:c.1834G>T

ENST00000545707.5:c.1576G>T

ENST00000557933.5:c.1957G>T

ENST00000558013.5:c.1957G>T

ENST00000558518.5:c.1957G>T

ENST00000559340.1:c.538G>T

NM_000527.4:c.1957G>T

NM_001195798.1:c.1957G>T

NM_001195799.1:c.1834G>T

NM_001195800.1:c.1453G>T

NM_001195803.1:c.1576G>T

NM_001195798.2:c.1957G>T

NM_001195799.2:c.1834G>T

NM_001195800.2:c.1453G>T

NM_001195803.2:c.1576G>T

Uncertain Significance

Met criteria codes **3**

PS4_Supporting

PP4

PM2

Not Met criteria codes **6**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1957G>T (p.Val653Phe) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 February 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 5 unrelated index cases fulfilling criteria for FH (3 cases with DLCN score >=6 from reported in VCI by Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case meeting Simon Broome criteria reported in VCI by Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP. Sorbonne Université, Hospital de la Pitié-Salpêtrière, France; 1 case meeting Simon Broome criteria in PMID 14974088 (Dedoussis et al., 2004), from Harokopio University of Athens, Greece).

Met criteria codes

PS4_Supporting			Variant meets PM2, and is identified in 5 unrelated index cases fulfil FH criteria. Three cases fulfil DLCN ≥6 reported in VCI by Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France. Two cases fulfil Simon Broome criteria, one case reported in VCI by Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP. Sorbonne Université, Hospital de la Pitié-Salpêtrière); one case reported in PMID 14974088 by Dedoussis et al, 2004, from Harokopio University of Athens, Greece.
PP4			Variant meets PM2, and is identified in >1 index cases who fulfil FH criteria after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

BP4			REVEL=0.69, it is not above 0.75, splicing evaluation required. MES: A) Variant not on limits. B) Variant not on limit creating de novo acceptor; variant on limit and created GT, Var de novo score/Wt score = -18.11/10.28 = -1.76, which is less than 0.8. C) There is not a GT nearby. Variant is not predicted to alter splicing, and result is confirmed by SpliceAI. REVEL score for the variant is between 0.5 and 0.75, therefore PP3/BP4 is not met.
BP2			Variant identified in a patient with heterozygous FH phenotype who also carries NM_000527.5 (LDLR):c.1171G>A (p.Ala391Thr) and confirmed in trans. However LDLR: p.A391T is classified as Benign by these guidelines, therefore BP2 is not met. This index case is reported in PMID 14974088 by Dedoussis et al, 2004, from Harokopio University of Athens, Greece.

PS3			Functional data not available.
PP1			Variant segregates with FH phenotype in 1 (less than 2) informative meiosis, one affected relative tested positive for the variant from 1 family, reported in PMID 14974088 by Dedoussis et al, 2004, from Harokopio University of Athens, Greece.
PP3			REVEL=0.69, it is not above 0.75, splicing evaluation required. MES: A) Variant not on limits. B) Variant not on limit creating de novo acceptor; variant on limit and created GT, Var de novo score/Wt score = -18.11/10.28 = -1.76, which is less than 0.8. C) There is not a GT nearby. Variant is not predicted to alter splicing, and result is confirmed by SpliceAI. REVEL score for the variant is between 0.5 and 0.75, therefore PP3/BP4 is not met.
PM5			Three other missense variants in the same codon: NM_000527.5 (LDLR):c.1958T>G (p.Val653Gly) (ClinVar ID 252130), classified as VUS; NM_000527.5 (LDLR):c.1957G>A (p.Val653Ile) (ClinVar ID 628891), classified as VUS; NM_000527.5 (LDLR):c.1958_1959delinsCC (p.Val653Ala) (ClinVar ID 1008168), classified as VUS by these guidelines, therefore PM5 is not met.

Curation History 		
    		
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