

Variant: NM_000527.5(LDLR):c.1957G>A (p.Val653Ile)

Version: 1.0

CA404093185 [↗](#)

628891 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: ea1ab271-3d8b-4108-8df4-94bcbdeb55c3

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HGVS expressions

NM_000527.5:c.1957G>A

NM_000527.5(LDLR):c.1957G>A (p.Val653Ile)

NC_000019.10:g.11120203G>A

CM000681.2:g.11120203G>A

NC_000019.9:g.11230879G>A

CM000681.1:g.11230879G>A

NC_000019.8:g.11091879G>A

NG_009060.1:g.35823G>A

ENST00000252444.10:c.2215G>A

ENST00000559340.2:c.*26G>A

ENST00000560467.2:c.1837G>A

ENST00000558518.6:c.1957G>A

ENST00000252444.9:c.2211G>A

ENST00000455727.6:c.1453G>A

ENST00000535915.5:c.1834G>A

ENST00000545707.5:c.1576G>A

ENST00000557933.5:c.1957G>A

ENST00000558013.5:c.1957G>A

ENST00000558518.5:c.1957G>A

ENST00000559340.1:c.538G>A

NM_000527.4:c.1957G>A

NM_001195798.1:c.1957G>A

NM_001195799.1:c.1834G>A

NM_001195800.1:c.1453G>A

NM_001195803.1:c.1576G>A

NM_001195798.2:c.1957G>A

NM_001195799.2:c.1834G>A

NM_001195800.2:c.1453G>A

NM_001195803.2:c.1576G>A

Uncertain Significance

Met criteria codes **3**

BP4

PP4

PM2

Not Met criteria codes **2**

PS3

PM5

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

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.1957G>A (p.Val653Ile) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP4 and BP4 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 in all specified genetic ancestry groups (gnomAD v2.1.1). PP4: Variant meets PM2 and is identified in 1 index case who meets Simon Broome criteria for FH after alternative causes of high cholesterol were excluded, 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. BP4: REVEL=0.372, it is below 0.5, splicing evaluation required. MES: A) variant not on limits. B) Variant not on limit creating de novo acceptor; variant is on limit however does not create GT. C) there is not a GT nearby. Variant is not predicted to alter splicing, and result is confirmed by SpliceAI, therefore BP4 is met.

Met criteria codes

BP4			REVEL=0.372, it is below 0.5, splicing evaluation required. MES: A) variant not on limits. B) Variant not on limit creating de novo acceptor; variant is on limit however does not create GT. C) there is not a GT nearby. Variant is not predicted to alter splicing, and result is confirmed by SpliceAI, therefore BP4 is met.
PP4			Variant meets PM2, and is identified in 1 index cases who fulfil Simon Broome criteria for FH after alternative causes of high cholesterol were excluded, 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).
PM2			This variant is absent in all specified genetic ancestry groups (gnomAD v2.1.1).

Not Met criteria codes

PS3			Functional data not available.
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>T (p.Val653Phe) (ClinVar ID 252129), 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.

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