

Variant: NM_000527.5(LDLR):c.1738T>C (p.Ser580Pro)

Version: 1.0

CA16602336 [↗](#)

375822 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: dbe69dff-fc05-4b5e-bb6a-5c4520cdc0a0

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HGVS expressions

NM_000527.5:c.1738T>C

NM_000527.5(LDLR):c.1738T>C (p.Ser580Pro)

NC_000019.10:g.11116891T>C

CM000681.2:g.11116891T>C

NC_000019.9:g.11227567T>C

CM000681.1:g.11227567T>C

NC_000019.8:g.11088567T>C

NG_009060.1:g.32511T>C

ENST00000252444.10:c.1996T>C

ENST00000559340.2:c.1705+679T>C

ENST00000560467.2:c.1618T>C

ENST00000558518.6:c.1738T>C

ENST00000252444.9:c.1992T>C

ENST00000455727.6:c.1234T>C

ENST00000535915.5:c.1615T>C

ENST00000545707.5:c.1357T>C

ENST00000557933.5:c.1738T>C

ENST00000558013.5:c.1738T>C

ENST00000558518.5:c.1738T>C

ENST00000559340.1:c.426+679T>C

NM_000527.4:c.1738T>C

NM_001195798.1:c.1738T>C

NM_001195799.1:c.1615T>C

NM_001195800.1:c.1234T>C

NM_001195803.1:c.1357T>C

NM_001195798.2:c.1738T>C

NM_001195799.2:c.1615T>C

NM_001195800.2:c.1234T>C

NM_001195803.2:c.1357T>C

Uncertain Significance

Met criteria codes **3**

PP3

PP4

PM2

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BA1	BP4	BP3	BP2	BS1	BS4
BS3	BS2	PP1	PM6	PM1	
PM3	PM5	PM4	PS1	PS2	
PS3	PS4	PVS1			

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1738T>C (p.Ser580Pro) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, 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: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL=0.911. PP4: Variant meets PM2 and is identified in 1 index case 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, after alternative causes of high cholesterol were excluded.

Met criteria codes

PP3			REVEL=0.911. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2. Identified in 1 FH case fromCentre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) with Simon Broome criteria of possible FH, after alternative causes of high cholesterol were excluded. So, PP4 is met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1). So, PM2 is met.

Not Met criteria codes

BA1			This variant is absent from gnomAD (gnomAD v2.1.1).
BP4			REVEL=0.911. It is above 0.5
BP3			No in-frame deletions/insertions
BP2			No data available
BS1			This variant is absent from gnomAD (gnomAD v2.1.1).
BS4			No data available

BS3			No data available
BS2			No data available.
PP1			No data available
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			Not in exon 4. Not a cysteine residue.
PM3			No data available
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1739C>T (p.Ser580Phe) (ClinVar ID 438325) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.1739C>G (p.Ser580Cys) (ClinVar ID 921461) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No in-frame deletions/insertions
PS1			No other missense variants with the same amino acid change.
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No data available
PS4			Variant meets PM2. Identified in 1 FH case fromCentre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) with Simon Broome criteria of possible FH, after alternative causes of high cholesterol were excluded.
PVS1			Not a null variant

Curation History 

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