

Variant: *NM_000527.5(LDLR):c.1796T>C (p.Leu599Ser)*

Version: 1.0

CA10585616 [↗](#)

252035 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 2b248b47-0882-4bbf-ad0b-7a7d02443545

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HGVS expressions

NM_000527.5(LDLR):c.1796T>C (p.Leu599Ser)

NM_000527.5:c.1796T>C

NC_000019.10:g.11116949T>C

CM000681.2:g.11116949T>C

NC_000019.9:g.11227625T>C

CM000681.1:g.11227625T>C

NC_000019.8:g.11088625T>C

NG_009060.1:g.32569T>C

ENST00000252444.10:c.2054T>C

ENST00000559340.2:c.1705+737T>C

ENST00000560467.2:c.1676T>C

ENST00000558518.6:c.1796T>C

ENST00000252444.9:c.2050T>C

ENST00000455727.6:c.1292T>C

ENST00000535915.5:c.1673T>C

ENST00000545707.5:c.1415T>C

ENST00000557933.5:c.1796T>C

ENST00000558013.5:c.1796T>C

ENST00000558518.5:c.1796T>C

ENST00000559340.1:c.426+737T>C

NM_000527.4:c.1796T>C

NM_001195798.1:c.1796T>C

NM_001195799.1:c.1673T>C

NM_001195800.1:c.1292T>C

NM_001195803.1:c.1415T>C

NM_001195798.2:c.1796T>C

NM_001195799.2:c.1673T>C

NM_001195800.2:c.1292T>C

NM_001195803.2:c.1415T>C

Likely Pathogenic

Met criteria codes 4

PS4_Moderate PP3 PP4 PM2

Not Met criteria codes 3

PS3 PP1 PM5

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1796T>C (p.Leu599Ser) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PS4_Moderate, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 22 July 2022. The supporting evidence is as follows: PM2: Variant is absent from gnomAD v2.1.1. PP3: REVEL = 0.779. PS4, PP4: Variant meets PM2 and is identified in 9 unrelated index cases fulfilling FH clinical criteria (5 cases with DLCN score ≥6 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; 1 meeting Simon Broome criteria from PMID 12436241 (Amsellem et al., 2002), APHP Saint Antoine Hospital, Paris, France; 1 meeting Simon Broome criteria from PMID 17094996 (Tosi et al., 2007), UK; 1 with DLCN score ≥6 from PMID 19318025 (Alonso et al., 2009), Spain; and 1 with DLCN score ≥6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France).

Met criteria codes

PS4_Moderate			PS4: Variant meets PM2 and is identified in 9 unrelated index cases fulfilling FH clinical criteria (5 with DLCN > 6 from Centre de Génétique Moléculaire et Chromosomique, 1 fulfilling SB clinical criteria for FH from PMID 12436241, 1 fulfilling SB clinical criteria for FH from PMID 17094996, 1 with DLCN>6 from PMID 19318025, and 1 with DLCN>6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon
PP3			REVEL = 0.779. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2 and is identified in at least 5 index case who fulfills criteria for FH from Centre de Génétique Moléculaire et Chromosomique, after alternative causes of high cholesterol were excluded.
PM2			Variant is absent from gnomAD v2.1.1

Not Met criteria codes

PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			1 other missense variants in the same codon: - NM_000527.5(LDLR):c.1796T>G (p.Leu599Trp) (ClinVar ID 252036) - Uncertain significance by these guidelines There are no variants in the same codon classified as Pathogenic by these guidelines.

Curation History [↗](#)

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