

Variant: *NM_000527.5(LDLR):c.1856T>G (p.Phe619Cys)*

Version: 1.0

CA10585656 [↗](#)

252085 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 828e15e9-c755-4c90-bf79-2e2d5b7bca86

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HGVS expressions

NM_000527.5(LDLR):c.1856T>G (p.Phe619Cys)

NM_000527.5:c.1856T>G

NC_000019.10:g.11120102T>G

CM000681.2:g.11120102T>G

NC_000019.9:g.11230778T>G

CM000681.1:g.11230778T>G

NC_000019.8:g.11091778T>G

NG_009060.1:g.35722T>G

ENST00000252444.10:c.2114T>G

ENST00000559340.2:c.1716T>G

ENST00000560467.2:c.1736T>G

ENST00000558518.6:c.1856T>G

ENST00000252444.9:c.2110T>G

ENST00000455727.6:c.1352T>G

ENST00000535915.5:c.1733T>G

ENST00000545707.5:c.1475T>G

ENST00000557933.5:c.1856T>G

ENST00000558013.5:c.1856T>G

ENST00000558518.5:c.1856T>G

ENST00000559340.1:c.437T>G

NM_000527.4:c.1856T>G

NM_001195798.1:c.1856T>G

NM_001195799.1:c.1733T>G

NM_001195800.1:c.1352T>G

NM_001195803.1:c.1475T>G

NM_001195798.2:c.1856T>G

NM_001195799.2:c.1733T>G

NM_001195800.2:c.1352T>G

NM_001195803.2:c.1475T>G

Likely Pathogenic

Met criteria codes **5**

PP1

PP3

PP4

PM2

PS4_Supporting

Not Met criteria codes **1**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR): c.1856T>G (p.Phe619Cys) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS4_Supporting, PP1) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows: PM2 Met: This variant is absent in gnomAD (gnomAD v2.1.1). PP3 Met: REVEL = 0.856, which is above the threshold of 0.75. PP4 Met: This variant meets PM2 and is identified >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PS4_Supporting Met: Variant meets PM2, and is identified in 2 unrelated index cases who fulfil DLCN criteria for FH diagnosis from different labs. One index case is from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583897.1), another index case is reported from Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (PMID16250003, SCV000295717.2). PP1 Met: Variant segregates with FH phenotype in 2 informative meioses in one family reported from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583897.1). There are two other variants in same codon: LDLR: NM_000527:c.1855T>C (p.Phe619Leu), LDLR: NM_000527:c.1856T>C (p.Phe619Ser), which are classified as Likely Pathogenic by these guidelines. Neither variant is classified as Pathogenic, therefore PM5 is not met.

Met criteria codes

PP1			Variant segregates with FH phenotype in 2 informative meioses in one family reported from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583897.1).
PP3			REVEL = 0.856, which is above the threshold of 0.75.
PP4			This variant meets PM2 and is identified >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2			This variant is absent in gnomAD (gnomAD v2.1.1).
PS4_Supporting			Variant meets PM2, and is identified in 2 unrelated index cases fulfil DLCN criteria for FH diagnosis from different labs. One index case is from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583897.1), another index case is reported from Department of Vascular Medicine, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands (PMID16250003, SCV000295717.2).

Not Met criteria codes

PM5			There are two other variants in same codon: LDLR: NM_000527:c.1855T>C (p.Phe619Leu), LDLR: NM_000527:c.1856T>C (p.Phe619Ser), which are classified as Likely Pathogenic by these guidelines. Neither variant is classified as Pathogenic, therefore PM5 is not met.
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