

Variant: *NM_000527.5(LDLR):c.1855T>C (p.Phe619Leu)*

Version: 1.0

CA037227 [↗](#)

252083 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 0295e6fb-e527-4826-a143-03161d46853d

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HGVS expressions

NM_000527.5(LDLR):c.1855T>C (p.Phe619Leu)

NM_000527.5:c.1855T>C

NC_000019.10:g.11120101T>C

CM000681.2:g.11120101T>C

NC_000019.9:g.11230777T>C

CM000681.1:g.11230777T>C

NC_000019.8:g.11091777T>C

NG_009060.1:g.35721T>C

ENST00000252444.10:c.2113T>C

ENST00000559340.2:c.1715T>C

ENST00000560467.2:c.1735T>C

ENST00000558518.6:c.1855T>C

ENST00000252444.9:c.2109T>C

ENST00000455727.6:c.1351T>C

ENST00000535915.5:c.1732T>C

ENST00000545707.5:c.1474T>C

ENST00000557933.5:c.1855T>C

ENST00000558013.5:c.1855T>C

ENST00000558518.5:c.1855T>C

ENST00000559340.1:c.436T>C

NM_000527.4:c.1855T>C

NM_001195798.1:c.1855T>C

NM_001195799.1:c.1732T>C

NM_001195800.1:c.1351T>C

NM_001195803.1:c.1474T>C

NM_001195798.2:c.1855T>C

NM_001195799.2:c.1732T>C

NM_001195800.2:c.1351T>C

NM_001195803.2:c.1474T>C

Likely Pathogenic

Met criteria codes **5**

PP3

PP4

PM2

PS4_Supporting

PS3_Supporting

Not Met criteria codes **21**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**



[Criteria Specifications for this VCEP](#)

Evidence Links 1

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1855T>C (p.Phe619Leu) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS3_Supporting, PS4_Supporting) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PM2 - PopMax MAF = 0.00003266 (0.003266%) in East Asian (gnomAD v2.1.1). PP3 - REVEL: 0,857. PP4 - Variant meets PM2. Variant identified in 2 index cases fulfilling validated clinical criteria for FH from different labs. PS3_supporting - PMID: 9409298 - Level 3 assay - study on htz patient's cultured lymphoblasts, immunoblotting + I125-LDL assay, no precursor detectable, degradation of 125I-LDL 63%. ---- functional study is consistent with damaging effect. PS4_supporting - Variant meets PM2. Variant identified in 2 index cases (1 case with Simon-Broome from Color laboratory; 1 case with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)).

Met criteria codes

PP3			REVEL: 0,857. Score is above 0,75.
PP4			Variant meets PM2. Variant identified in 2 index cases fulfilling validated clinical criteria for FH (1 case with Simon-Broome from Color laboratory; 1 case with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)).
PM2			PopMax MAF = 0.00003266 (0.003266%) in East Asian (gnomAD v2.1.1). MAF is below 0.02%.
PS4_Supporting			Variant meets PM2. Variant identified in 2 index cases (1 case with Simon-Broome from Color laboratory; 1 case with DLCN criteria from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)).
PS3_Supporting			PMID: 9409298 - Level 3 assay - study on htz patient's cultured lymphoblasts, immunoblotting + I125-LDL assay, no precursor detectable, degradation of 125I-LDL 63%. ---- functional study is consistent with damaging effect
			study on htz patient's cultured lymphoblasts, immunoblotting + I125-LDL assay, no precursor detectable, degradation of 125I-LDL 63% PubMed:9409298 

Not Met criteria codes

PS1			No variant described that leads to the same amino acid change.
PS2			No de novo cases were identified.

PP1			No family members tested.
PP2			Not applicable.
PM6			No de novo cases were identified.
PM1			Missense at codon 619. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3			Not identified in individuals with other variants.
PM5			No other missense variants classified as Pathogenic by these guidelines. Two other missense variants described in the same codon:(1)NM_000527.5(LDLR):c.1856T>G (p.Phe619Cys) (ClinVar ID 252085) - VUS by these guidelines. (2)NM_000527.5(LDLR):c.1856T>C (p.Phe619Ser) (ClinVar ID 252084) - VUS by these guidelines.
PM4			Missense variant. Not applicable.
BA1			no FAF, just total MAF = 0.000003976 (0.0004%) in East Asian (gnomAD v2.1.1). MAF is not above 0.5%
BS2			No unaffected individuals identified with the variant.
PVS1			Missense variant. Not applicable.
BS1			no FAF, just total MAF = 0.000003976 (0.0004%) in East Asian (gnomAD v2.1.1). MAF is not above 0.2%
BS4			No family members tested.
BS3			No in vitro or in vivo functional studies showing no damaging effect on protein function or splicing.
BP4			REVEL: 0,857. Score is not below 0,50.
BP3			Not applicable.
BP1			Not applicable.
BP2			Not identified in individuals with other variants.
BP5			Not applicable.
BP7			Missense variant. Not applicable.

Curation History 		
Showing 1 to 1 of 1 rows		

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