The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000527.5(LDLR):c.1856T>C (p.Phe619Ser)

Version: 1.0

CA10585655

252084 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 9196bc02-fbc8-49f5-a381-d8aea0b91b68
Approved on: 2022/4/21
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HGVS expressions

NM_000527.5(LDLR):c.1856T>C (p.Phe619Ser)
NM_000527.5:c.1856T>C
NC_000019.10:g.11120102T>C
CM000681.2:g.11120102T>C
NC_000019.9:g.11230778T>C
CM000681.1:g.11230778T>C
NC_000019.8:g.11091778T>C
NG_009060.1:g.35722T>C
ENST00000252444.10:c.2114T>C
ENST00000559340.2:c.1716T>C
ENST00000560467.2:c.1736T>C
ENST00000558518.6:c.1856T>C
ENST00000252444.9:c.2110T>C
ENST00000455727.6:c.1352T>C
ENST00000535915.5:c.1733T>C
ENST00000545707.5:c.1475T>C
ENST00000557933.5:c.1856T>C
ENST00000558013.5:c.1856T>C
ENST00000558518.5:c.1856T>C
ENST00000559340.1:c.437T>C
NM_000527.4:c.1856T>C
NM_001195798.1:c.1856T>C
NM_001195799.1:c.1733T>C
NM_001195800.1:c.1352T>C
NM_001195803.1:c.1475T>C
NM_001195798.2:c.1856T>C
NM_001195799.2:c.1733T>C
NM_001195800.2:c.1352T>C
NM_001195803.2:c.1475T>C

Likely Pathogenic

Met criteria codes 4

PM2 PP3 PP4 PS4_Moderate

Not Met criteria codes 1

PM5

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR): c.1856T>C (p.Phe619Ser) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS4_Moderate) 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 = 0.832, which is above the threshold for 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_Moderate Met: Variant meets PM2, and is identified in 6 unrelated index cases who fulfil DLCN criteria for FH from different labs. Two index cases reported from U4M – Lille University &CHRU Lille, University de Lille – CHRU de Lille (SCV000583896.1). Four French index cases reported from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP, GH Hôpitaux Universitaires Pitié-Salpêtrière / Charles-Foix, (SCV000503427.1, PMID20809525). There are two other variants in same codon: LDLR: NM_000527:c.1855T>C (p.Phe619Leu), LDLR: NM_000527:c.1856T>G (p.Phe619Cys), which are classified as Likely Pathogenic by these guidelines. Neither variant is classified as Pathogenic, therefore PM5 is not met.

Met criteria codes

PM2	✔	This variant is absent in gnomAD (gnomAD v2.1.1)
PP3	✔	REVEL = 0.832, which is above the threshold for 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.
PS4_Moderate	✔	Variant meets PM2, and is identified in 6 unrelated index cases who fulfil DLCN criteria for FH from different labs. Two index cases reported from U4M – Lille University &CHRU Lille, University de Lille – CHRU de Lille (SCV000583896.1). Four French index cases reported from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP, GH Hôpitaux Universitaires Pitié-Salpêtrière / Charles-Foix, (SCV000503427.1, PMID20809525).

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>G (p.Phe619Cys), which are classified as Likely Pathogenic by these guidelines. Neither variant is classified as Pathogenic, therefore PM5 is not met.

Curation History

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