

Variant: NM_000527.5(LDLR):c.859G>T (p.Gly287Cys)

Version: 1.0

CA10585162 [↗](#)

251489 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: a146f460-92d1-4395-9894-8c05b643abb6

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HGVS expressions

NM_000527.5(LDLR):c.859G>T (p.Gly287Cys)

NM_000527.5:c.859G>T

NC_000019.10:g.11107433G>T

CM000681.2:g.11107433G>T

NC_000019.9:g.11218109G>T

CM000681.1:g.11218109G>T

NC_000019.8:g.11079109G>T

NG_009060.1:g.23053G>T

ENST00000252444.10:c.1117G>T

ENST00000559340.2:c.859G>T

ENST00000560467.2:c.859G>T

ENST00000558518.6:c.859G>T

ENST00000252444.9:c.1113G>T

ENST00000455727.6:c.355G>T

ENST00000535915.5:c.736G>T

ENST00000545707.5:c.478G>T

ENST00000557933.5:c.859G>T

ENST00000558013.5:c.859G>T

ENST00000558518.5:c.859G>T

ENST00000558528.1:n.374G>T

ENST00000560467.1:c.459G>T

NM_000527.4:c.859G>T

NM_001195798.1:c.859G>T

NM_001195799.1:c.736G>T

NM_001195800.1:c.355G>T

NM_001195803.1:c.478G>T

NM_001195798.2:c.859G>T

NM_001195799.2:c.736G>T

NM_001195800.2:c.355G>T

NM_001195803.2:c.478G>T

Pathogenic

Met criteria codes 5

PP1_StrongPS4PP3PP4PM2

Not Met criteria codes 3

PS3PM3PM5

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.859G>T (p.Gly287Cys) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PP4, PS4, PP1_Strong) 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: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL=0.928. PP4: Variant meets PM2 and is identified in `1 index cases who fulfil criteria for FH after alternative causes of high cholesterol were excluded. PS4: Variant meets PM2 and is identified in at least 11 unrelated index cases fulfil DLCN ≥ 6 reported in ClinGen VCI, PubMed and ClinVar: 7 cases reported in VCI, 6 of them from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France, and 1 from Research Lab of Molecular Genetics of Lipid Metabolism-Prof. M.Arca; 3 cases reported from PubMed and at least 1 additional case reported in ClinVar from U4M-Lille University, France. From PubMed, 1 case reported In PMID 12730724 by El Messal et al, 2003, from Laboratoire de Biochimie, Faculte des Sciences Ain Chock, Casablanca, Morocco; 1 case reported in PMID 17196209 by Campagna et al, 2008, from University of Rome, Italy; 1 case reported in PMID 22669020 by El Aziz et al, 2012, from Ibn Rochd University Hospital, Casablanca, Morocco. PP1_Strong: Variant segregates with FH phenotype in 6 informative meiosis from 6 families reported from different laboratories: 4 affected relatives from 4 families tested positive for the variant, reported in VCI from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 2 affected relative is positive for the variant, reported in PMID 17196209 by Campagna et al, 2008, from University of Rome, Italy, and in PMID 22669020 by El Aziz et al, 2012, from Ibn Rochd University Hospital, Casablanca, Morocco. PS3 not met: Functional data is not available. PM5 not met: One other variant at same codon: NM_000527.5(LDLR):c.859G>A (p.Gly287Ser), ClinVar ID 161280, is classified as Uncertain significance by these guidelines, therefore PM5 is not met. PM3 not met: One case reported in VCI from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France. The subject is homozygous for the variant, however patient’s LDL-C is 5.32 mmol/l and no indication of lipid lowering medication. In PMID 22669020, two brothers of 21 and 18 years old are homozygous for the variant with untreated LDL-C at 12.8 mmol/l and 10.1 mmol/l respectively, which are just below 13 mmol/l threshold for HoFH phenotype. Additionally, one of 2 brothers (21 yrs with LDL-C 12.8 mmol/l) also had Type 1 diabetes.

Met criteria codes

PP1_Strong	i ✓	Variant segregates with FH phenotype in 6 informative meiosis from 6 families reported from different laboratories: 4 affected relatives from 4 families tested positive for the variant, reported in VCI from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 2 affected relative is positive for the variant, reported in PMID 17196209 by Campagna et al, 2008, from University of Rome, Italy, and in PMID 22669020 by El Aziz et al, 2012, from Ibn Rochd University Hospital, Casablanca, Morocco.
PS4	i ✓	Variant meets PM2 and is identified in at least 11 unrelated index cases fulfil DLCN ≥ 6 reported in ClinGen VCI, PubMed and ClinVar: 7 cases reported in VCI, 6 of them from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France, and 1 from Research Lab of Molecular Genetics of Lipid Metabolism-Prof. M.Arca; 3 cases reported from PubMed and at least 1 additional case reported in ClinVar from U4M-Lille University, France.

From PubMed, 1 case reported in PMID 12730724 by El Messal et al, 2003, from Laboratoire de Biochimie, Faculté des Sciences Ain Chock, Casablanca, Morocco; 1 case reported in PMID 17196209 by Campagna et al, 2008, from University of Rome, Italy; 1 case reported in PMID 22669020 by El Aziz et al, 2012, from Ibn Rochd University Hospital, Casablanca, Morocco.

PP3			REVEL=0.928.
PP4			Variant meets PM2 and is identified in ≥1 index cases who fulfil criteria for FH after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PS3			Functional data is not available.
PM3			One case reported in VCI from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France. The subject is homozygous for the variant, however patient's LDL-C is 5.32 mmol/l and no indication of lipid lowering medication. In PMID 22669020, two brothers of 21 and 18 years old are homozygous for the variant with untreated LDL-C at 12.8 mmol/l and 10.1 mmol/l respectively, which are just below 13 mmol/l threshold for HoFH phenotype. Additionally, one of 2 brothers (21 yrs with LDL-C 12.8 mmol/l) also had Type 1 diabetes.
PM5			One other variant at same codon: NM_000527.5(LDLR):c.859G>A (p.Gly287Ser), ClinVar ID 161280, is classified as Uncertain significance by these guidelines, therefore PM5 is not met.

Curation History



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