

Variant: *NM_000527.5(LDLR):c.1975A>C (p.Thr659Pro)*

Version: 1.0

CA037634 [↗](#)

252140 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 9a4d98e9-5d76-4b32-9b73-d49180628bf2

Approved on: 2023/5/15

Published on: 2025/2/13

HGVS expressions

NM_000527.5:c.1975A>C

NM_000527.5(LDLR):c.1975A>C (p.Thr659Pro)

NC_000019.10:g.11120221A>C

CM000681.2:g.11120221A>C

NC_000019.9:g.11230897A>C

CM000681.1:g.11230897A>C

NC_000019.8:g.11091897A>C

NG_009060.1:g.35841A>C

ENST00000252444.10:c.2233A>C

ENST00000559340.2:c.*44A>C

ENST00000560467.2:c.1855A>C

ENST00000558518.6:c.1975A>C

ENST00000252444.9:c.2229A>C

ENST00000455727.6:c.1471A>C

ENST00000535915.5:c.1852A>C

ENST00000545707.5:c.1594A>C

ENST00000557933.5:c.1975A>C

ENST00000558013.5:c.1975A>C

ENST00000558518.5:c.1975A>C

ENST00000559340.1:c.556A>C

NM_000527.4:c.1975A>C

NM_001195798.1:c.1975A>C

NM_001195799.1:c.1852A>C

NM_001195800.1:c.1471A>C

NM_001195803.1:c.1594A>C

NM_001195798.2:c.1975A>C

NM_001195799.2:c.1852A>C

NM_001195800.2:c.1471A>C

NM_001195803.2:c.1594A>C

Likely Pathogenic

Met criteria codes **4**

PP4

PP1_Strong

PM2

PS4_Supporting

Not Met criteria codes **18**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BP7

BP4

BP2

BS1

BS4

BS3

BS2

PP3

PS1

PS2

PS3

BA1

PM1

PM3

PM5

PM4

PM6

PVS1

Evidence Links

0

- 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.1975A>C (p.Thr659Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PP1_Strong, PM2, PS4_Supporting and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 15 May 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.0001853 (0.01853%) in European (Finnish) exomes (gnomAD v2.1.1). PS4_Supporting, PP4: Variant meets PM2 and is identified in 4 unrelated index cases with criteria for FH (TC and LDL >95th percentile and autosomal dominant transmission of hypercholesterolemia in the family) from France (PMID 20809525, Marduel et al. 2010). PP1_Strong: Variant segregates with FH phenotype in at least 6 informative meioses from 3 families 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: 6 affected family members have the variant.

Met criteria codes

PP4			Variant meets PM2 and is identified in 4 unrelated index cases with criteria for FH (TC and LDL >95th percentile and autosomal dominant transmission of hypercholesterolemia in the family) from France (PMID: 20809525), so PP4 is Met.
PP1_Strong			Variant segregates with FH phenotype in at least 6 informative meioses from 3 families from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 6 affected family members have the variant.
PM2			PopMax MAF = 0.0001853 (0.01853%) in European (Finnish) exomes (gnomAD v2.1.1), so PM2 is Met.
PS4_Supporting			Variant meets PM2 and is identified in 4 unrelated index cases with criteria for FH (TC and LDL >95th percentile and autosomal dominant transmission of hypercholesterolemia in the family) from France (PMID: 20809525), that possibly are the same 4 index cases with DLCN>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), so give PS4_Supporting to be conservative.

Not Met criteria codes

BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.652. It is not below 0.50, so BP4 is Not Met.
BP2			Not observed in trans with other LP/P variants, so BP2 is Not Met.
BS1			FAF = 0.00001686 (0.001686%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BS1 is not met.
BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			There are no functional studies reported for this variant, so BS3 is not met.
BS2			Case-control data not reported, so BS2 is Not Met.

PP3		✖	REVEL = 0.652 It is not above 0.75, splicing evaluation needed. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp downstream from the canonical acceptor site, but it does not create GT. C) there is no a GT nearby. --- PP3 is not met.
PS1		✖	No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2		✖	de novo occurrence data not reported, so PS2 is Not Met.
PS3		✖	There are no functional studies reported for this variant, so PS3 is not met.
BA1		✖	FAF = 0.00001686 (0.001686%) in European (non-Finnish) exomes (gnomAD v2.1.1), so BA1 is not met.
PM1		✖	Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3		✖	Not observed in trans with other LP/P variants, so PM3 is Not Met.
PM5		✖	1 other missense variant in the same codon: - NM_000527.5(LDLR):c.1976C>A (p.Thr659Asn) (ClinVar ID 252141) - Uncertain significance - insufficient evidence by these guidelines There are no more variants in the same codon classified as Pathogenic by these guidelines, so PM5 is Not Met.
PM4		✖	Variant meets PM2 and is missense, so PM4 is Not Met.
PM6		✖	de novo occurrence data not reported, so PM6 is Not Met.
PVS1		✖	Variant is missense, so PVS1 is Not Met.

Curation History 		
Showing 1 to 1 of 1 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

[ClinGen Terms of Use.](#)

[✕ Powered by BCM's Genboree.](#)