

Variant: *NM_000527.5(LDLR):c.1945C>T (p.Pro649Ser)*

Version: 1.0

CA10585688 [↗](#)

252121 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 0969c86e-9a9e-4c83-8df7-90c415971ff2

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HGVS expressions

NM_000527.5(LDLR):c.1945C>T (p.Pro649Ser)

NM_000527.5:c.1945C>T

NC_000019.10:g.11120191C>T

CM000681.2:g.11120191C>T

NC_000019.9:g.11230867C>T

CM000681.1:g.11230867C>T

NC_000019.8:g.11091867C>T

NG_009060.1:g.35811C>T

ENST00000252444.10:c.2203C>T

ENST00000559340.2:c.*14C>T

ENST00000560467.2:c.1825C>T

ENST00000558518.6:c.1945C>T

ENST00000252444.9:c.2199C>T

ENST00000455727.6:c.1441C>T

ENST00000535915.5:c.1822C>T

ENST00000545707.5:c.1564C>T

ENST00000557933.5:c.1945C>T

ENST00000558013.5:c.1945C>T

ENST00000558518.5:c.1945C>T

ENST00000559340.1:c.526C>T

NM_000527.4:c.1945C>T

NM_001195798.1:c.1945C>T

NM_001195799.1:c.1822C>T

NM_001195800.1:c.1441C>T

NM_001195803.1:c.1564C>T

NM_001195798.2:c.1945C>T

NM_001195799.2:c.1822C>T

NM_001195800.2:c.1441C>T

NM_001195803.2:c.1564C>T

Uncertain Significance

Met criteria codes **4**

PP3

PP4

PM2

PS4_Supporting

Not Met criteria codes **22**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

BP5

BP7

BP4

BP3

BP1

BP2

PP1

PP2

PM1

PM3

PM5

PM4

BA1

PM6

BS1

BS4

BS3

BS2

PVS1

Evidence Links

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- 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.1945C>T (p.Pro649Ser) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 October 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.1.0). PP3: REVEL = 0.766. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 4 index cases who fulfill criteria for FH, after alternative causes of high cholesterol were excluded (1 case with probable FH by Simon Broome criteria and 1 case with DLCN score >=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, France; 1 case with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism, Italy - Prof. M. Arca; 1 case with DLCN score >=6 from Meshkov et al 2021, PMID 33418990).

Met criteria codes

PP3		✓	REVEL = 0.766. It is above 0.75, so PP3 is met.
PP4		✓	Variant meets PM2 and is identified in at least 1 index case fulfilling FH criteria (DLCN <=6), after alternative causes of high cholesterol were excluded, from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière)
PM2		✓	This variant is absent from gnomAD (gnomAD v2.1.1 and v4.1).
PS4_Supporting		✓	Variant meets PM2 and is identified in at least 4 index cases who fulfill criteria for FH, after alternative causes of high cholesterol were excluded: 2 index cases from Centre de Génétique Moléculaire et Chromosomique (one fullfiling SB criteria for probable FH and other fulfilling DLCN>=6) // 1 index case fulfilling DLCN>=6 from the Research Lab of Molecular Genetics of Lipid Metabolism // 1 index case fulfilling DLCN>=6 from PMID:33418990.

Not Met criteria codes

PS1		✗	No other variant with same amino acid change
PS2		✗	No de novo occurrence
PS3		✗	not met (no information or reports of functional data).

BP5			Not applicable
BP7			Missense variant
BP4			REVEL is not below 0.5
BP3			Missense variant
BP1			Not applicable
BP2			Not identified in index cases with more than one variant
PP1			Variant segregates with FH phenotype in 1 relative positive for variant with LDL-C >75th percentile from the Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) (not in at least 2 informative meiosis, so PP1 is not met)
PP2			Not applicable
PM1			Variant located on exon 13 (not exon 4) and does not affect any cysteine residues listed on the FH VCEP guidelines
PM3			Not identified in index cases with more than one variant
PM5			NM_000527.5(LDLR):c.1946C>T (p.Pro649Leu) (ClinVar ID: 252122) considered as VUS by these guidelines.
PM4			Missense variant
BA1			This variant is absent from gnomAD (gnomAD v2.1.1 and v4.1).
PM6			No de novo occurrence
BS1			This variant is absent from gnomAD (gnomAD v2.1.1 and v4.1).
BS4			No non-segregation identified.
BS3			not met (no information or reports of functional data).
BS2			Not identified in normolipidemic individuals
PVS1			Missense variant

Curation History



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