

Variant: *NM_000527.5(LDLR):c.44T>C (p.Leu15Pro)*

Version: 1.0

CA10584732 [↗](#)

250981 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 5a4acf2a-a4d4-4d21-b7ac-83ea18a248e0

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HGVS expressions

NM_000527.5(LDLR):c.44T>C (p.Leu15Pro)

NM_000527.5:c.44T>C

NC_000019.10:g.11089592T>C

CM000681.2:g.11089592T>C

NC_000019.9:g.11200268T>C

CM000681.1:g.11200268T>C

NC_000019.8:g.11061268T>C

NG_009060.1:g.5212T>C

ENST00000559340.2:c.44T>C

ENST00000560467.2:c.44T>C

ENST00000558518.6:c.44T>C

ENST00000455727.6:c.44T>C

ENST00000535915.5:c.44T>C

ENST00000545707.5:c.44T>C

ENST00000557933.5:c.44T>C

ENST00000557958.1:n.130T>C

ENST00000558013.5:c.44T>C

ENST00000558518.5:c.44T>C

ENST00000560502.5:n.130T>C

NM_000527.4:c.44T>C

NM_001195798.1:c.44T>C

NM_001195799.1:c.44T>C

NM_001195800.1:c.44T>C

NM_001195803.1:c.44T>C

NM_001195798.2:c.44T>C

NM_001195799.2:c.44T>C

NM_001195800.2:c.44T>C

NM_001195803.2:c.44T>C

NR_163945.1:n.68A>G

Likely Pathogenic

Met criteria codes 4

PS3_Moderate

PP4

PM2

PS4_Supporting

Not Met criteria codes 22

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BS2

BS1

BS4

BS3

BP4

BP3

BP1

BP2

PVS1

BP5

BP7

BA1

PS1

PS2

PP1

PP2

PP3

PM6

PM1

PM3

PM5

PM4

Evidence Links

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- Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.44T>C (p.Leu15Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PS3_Moderate, PP4, and PS4_Supporting 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), so PM2 is met. PS3_moderate - Level 2 Assay: PMID:27175606: Heterologous cells (CHO), CLSM assays: LDLR retained in ER, no LDL-LDLR binding. LDL binding <70% wild type activity, so PS3_Moderate is met. PS4_supporting - Variant meets PM2 and is identified in - 2 unrelated index cases who fulfill Simon-Broome possible criteria for FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), - 1 case from PMID: 12052488 with LDL-C above 10 mmol/L (DLCN>6), from Sweden. 3 cases, so PS4_Supporting is met. PP4 - Variant meets PM2 and is identified in 3 unrelated index cases who fulfill FH clinical criteria (see PS4 for details).

Met criteria codes

PS3_Moderate			Level 2 Assay: PMID:27175606 Heterologous cells (CHO), CLSM assays: LDLR retained in ER, no LDL-LDLR binding LDL binding <70% wild type activity, so PS3_Moderate is met
PP4			Variant meets PM2 and is identified in - 2 unrelated index cases who fulfill Simon-Broome possible criteria for FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), - 1 case from PMID: 12052488 with LDL-C above 10 mmol/L (DLCN>6), from Sweden. so PP4 is met
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met.
PS4_Supporting			Variant meets PM2 and is identified in - 2 unrelated index cases who fulfill Simon-Broome possible criteria for FH from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), - 1 case from PMID: 12052488 with LDL-C above 10 mmol/L (DLCN>6), from Sweden. 3 cases, so PS4_Supporting is met

Not Met criteria codes

BS2			there is no data on normolipidemic individuals, so not met
BS1			This variant is absent from gnomAD (gnomAD v2.1.1)
BS4			there is no segregation data
BS3			Level 2 Assay: PMID:27175606 Heterologous cells (CHO), CLSM assays: LDLR retained in ER, no LDL-LDLR binding LDL binding <70% wild type activity, so BS3 is not met
BP4			REVEL = 0.675. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable

BP2			no index cases with other variants were identified
PVS1			variant is missense and not in initiation codon, so not met
BP5			not applicable
BP7			variant is missense, so not applicable
BA1			This variant is absent from gnomAD (gnomAD v2.1.1)
PS1			There is no other missense variant that leads to the same amino acid change, so not met
PS2			no de novo occurrence was identified
PP1			there is no segregation data
PP2			not applicable
PP3			REVEL = 0.675. It is not above 0.75, so PP3 is not met
PM6			no de novo occurrence was identified
PM1			variant is missense and meets PM2, but it is in exon 1 and does not alter Cys, so not met
PM3			no index cases with other variants were identified
PM5			there is 1 more missense variant in the same codon: NM_000527.5(LDLR):c.44T>A (p.Leu15His) (ClinVar ID 250980) - classified as VUS by these guidelines, so PM5 is not met
PM4			variant is missense, so not applicable

Curation History [↗](#)

Showing 1 to 1 of 1 rows

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