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.1A>T (p.Met1Leu)

Version: 2.1

CA10584720

250968 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: be29245c-5ccb-4a73-8acb-9d5bb0810775
Approved on: 2022/3/17
Published on: 2022/7/12

HGVS expressions

NM_000527.5(LDLR):c.1A>T (p.Met1Leu)
NM_000527.5:c.1A>T
NC_000019.10:g.11089549A>T
CM000681.2:g.11089549A>T
NC_000019.9:g.11200225A>T
CM000681.1:g.11200225A>T
NC_000019.8:g.11061225A>T
NG_009060.1:g.5169A>T
ENST00000559340.2:c.1A>T
ENST00000560467.2:c.1A>T
ENST00000558518.6:c.1A>T
ENST00000455727.6:c.1A>T
ENST00000535915.5:c.1A>T
ENST00000545707.5:c.1A>T
ENST00000557933.5:c.1A>T
ENST00000557958.1:n.87A>T
ENST00000558013.5:c.1A>T
ENST00000558518.5:c.1A>T
ENST00000560502.5:n.87A>T
NM_000527.4:c.1A>T
NM_001195798.1:c.1A>T
NM_001195799.1:c.1A>T
NM_001195800.1:c.1A>T
NM_001195803.1:c.1A>T
NM_001195798.2:c.1A>T
NM_001195799.2:c.1A>T
NM_001195800.2:c.1A>T
NM_001195803.2:c.1A>T
NR_163945.1:n.111T>A

Pathogenic

Met criteria codes 6

PM2 PVS1_Moderate PS4_Supporting PS1 PS3 PP4

Not Met criteria codes 20

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM1 PM3 PM5 PM4 PM6
BA1 BS2 BS1 BS4 BS3 BP5
BP7 BP4 BP3 BP1 BP2 PS2
PP1 PP2 PP3

Evidence Links 0

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.1A>T (p.Met1Leu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS1, PS3, PM2, PVS1_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: PS1 - One more missense variant that leads to the same amino acid change: (1)NM_000527.5(LDLR):c.1A>C (p.Met1Leu) (ClinVar ID 250966) - Pathogenic by these guidelines --- variant is classified as Pathogenic, so PS1 is Met. PS3 - Level 1 (and other levels) FS: Graça et al., 2021 (PMID 34572405) Heterologous cells (CHO), FACS, luciferase and microscopy assays: FACS: 10% cell surface LDLR, 3% binding and 8% uptake; luciferase : 1% luciferase construct activity; microscopy: 5-10% LDLR expression and 5-10% LDLR activity. --- functional study in heterologous cells results in expression, binding and uptake less than 70% of wild-type, so PS3 is met. PM2 - This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met. PVS1_moderate - Variant is in initiation codon, so PVS1_Moderate is Met. PS4_supporting - Variant meets PM2 and was identified in: - 1 index case with DLCN score above 6 from University of British Columbia, Canada; - 1 index case with Simon-Broome criteria of possible 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), France; - 1 index case with Simon-Broome criteria of possible FH (Inclusion: LDL-C level>95th percentile for age and gender and autosomal dominant inheritance pattern of hypercholesterolemia, and a family history of hypercholesterolemia and cardiovascular disease) from PMID: 21382890 (van der Graaf et al., 2011), The Netherlands; - 1 index case with Simon-Broome criteria of at least possible FH from PMID: 17094996 (Tosi et al., 2007), UK. --- 4 cases, so PS4_Supporting is Met PP4 - Variant meets PM2 and was identified in 4 unrelated index cases who fulfill clinical FH criteria from different labs (see PS4 for details), so PP4 is Met.

Met criteria codes

PM2	✔	This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met.
PVS1_Moderate	✔	Variant is in initiation codon, so PVS1_Moderate is Met
PS4_Supporting	✔	Variant meets PM2 and was identified in: - 1 index case with DLCN score above 6 from University of British Columbia, Canada; - 1 index case with Simon-Broome criteria of possible 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), France; - 1 index case with Simon-Broome criteria of possible FH (Inclusion: LDL-C level>95th percentile for age and gender and autosomal dominant inheritance pattern of hypercholesterolemia, and a family history of hypercholesterolemia and cardiovascular disease) from PMID: 21382890 (van der Graaf et al., 2011), The Netherlands; - 1 index case with Simon-Broome criteria of at least possible FH from PMID: 17094996 (Tosi et al., 2007), UK. --- 4 cases, so PS4_Supporting is Met
PS1	✔	One more missense variant that leads to the same amino acid change: (1)NM_000527.5(LDLR):c.1A>C (p.Met1Leu) (ClinVar ID 250966) - Pathogenic by these guidelines --- variant is classified as Pathogenic, so PS1 is Met
PS3	✔	

Level 1 (and other levels) FS: Graça et al., 2021 (PMID 34572405) Heterologous cells (CHO), FACS, luciferase and microscopy assays: FACS: 10% cell surface LDLR, 3% binding and 8% uptake; luciferase : 1% luciferase construct activity; microscopy: 5-10% LDLR expression and 5-10% LDLR activity. --- functional study in heterologous cells results in expression, binding and uptake less than 70% of wild-type, so PS3 is met.

PP4			Variant meets PM2 and was identified in: - 1 index case with DLCN score above 6 from University of British Columbia, Canada; - 1 index case with Simon-Broome criteria of possible 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), France; - 1 index case with Simon-Broome criteria of possible FH (Inclusion: LDL-C level>95th percentile for age and gender and autosomal dominant inheritance pattern of hypercholesterolemia, and a family history of hypercholesterolemia and cardiovascular disease) from PMID: 21382890 (van der Graaf et al., 2011), The Netherlands; - 1 index case with Simon-Broome criteria of at least possible FH from PMID: 17094996 (Tosi et al., 2007), UK. --- so PP4 is Met

Not Met criteria codes

PM1			Variant is missense and PM2 is Met, but it is not in exon 4 nor changes any of the 60 Cys residues listed, so PM1 is Not Met
PM3			not identified in individuals with other variants, so PM3 is Not Met
PM5			Four more missense variants described in same codon, that lead to different amino acid changes: (1)NM_000527.5(LDLR):c.1A>G (p.Met1Val) (ClinVar ID 250967) - Likely pathogenic by these guidelines (2)NM_000527.4(LDLR):c.2T>C (p.Met1Thr) (ClinVar ID 441174) - Likely pathogenic by these guidelines (3)NM_000527.4(LDLR):c.3G>A (p.Met1Ile) (ClinVar ID 440536) - Likely pathogenic by these guidelines (4)NM_000527.5(LDLR):c.3G>T (p.Met1Ile) (ClinVar ID 250969) - Likely pathogenic by these guidelines --- no other variant is classified as Pathogenic by these guidelines, so PM5 is Not Met.
PM4			Variant is missense, so not applicable
PM6			no de novo cases were identified, so PM6 is Not Met
BA1			This variant was not identified in gnomAD (gnomAD v2.1.1), so BA1 is not met.
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
BS1			This variant was not identified in gnomAD (gnomAD v2.1.1), so BS1 is not met.
BS4			no lack of segregation was observed, so BS4 is Not Met
BS3			Level 1 (and other levels) FS: Graça et al., 2021 (PMID 34572405) Heterologous cells (CHO), FACS, luciferase and microscopy assays: FACS: 10% cell surface LDLR, 3% binding and 8% uptake; luciferase : 1% luciferase construct activity; microscopy: 5-10% LDLR expression and 5-10% LDLR activity. --- functional study in heterologous cells results in expression, binding and uptake not more than 90% of wild-type, so BS3 is not met

BP5		✖	Not applicable
BP7		✖	Missense variant, so BP7 is not applicable
BP4		✖	PVS1_Moderate is Met, so BP4 is not applicable.
BP3		✖	Not applicable
BP1		✖	Not applicable
BP2		✖	not identified in individuals with other variants, so BP2 is Not Met
PS2		✖	no de novo cases were identified, so PS2 is Not Met
PP1		✖	Variant segregates with FH phenotype in - 1 informative meiosis 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 relative has the variant and the phenotype. --- not enough for PP1, so not met
PP2		✖	Not applicable
PP3		✖	PVS1_Moderate is Met, so PP3 is not applicable.

Curation History

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