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>C (p.Met1Leu)

Version: 2.0

CA10584718

250966 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e7450868-fc21-439a-949f-f84feae9c98d
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HGVS expressions

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

Pathogenic

Met criteria codes 6

PS4_Supporting PP4 PM2 PVS1_Moderate PP1_Moderate PS3

Not Met criteria codes 14

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PP3 BA1 PM6 PM3 PM5
PM4 BS1 BS4 BS3 PS1
PS2 BP4 BP2 BP7

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1A>C (p.Met1Leu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes as PM2, PVS1_Moderate, PS3, PS4_Supporting, PP1_Moderate, and PP4 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 - variant is absent from gnomAD (v2.1.1). PVS1_Moderate – variant is predicted to affect the initiation codon. PS3 - Level 1 functional studies performed - Heterologous cells (CHO), FACS: results of 60% cell surface LDLR, 59% LDL binding and 66% LDL uptake, compared to wild-type. Note - Level 3 luciferase reporter assays were also performed: results of 5% luciferase construct activity compared to wild-type. Both studies performed in PMID: 34572405. PS4_Supporting - variant meets PM2 and is identified in 4 unrelated index cases who fulfill clinical criteria for FH (4 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – FH VCEP member lab). PP1_Moderate – variant segregates with phenotype in 4 informative meioses in 3 families (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – 3 families: 4 affected relatives with the variant). PP4 - variant meets PM2 and is identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded. Note: four other missense variants at this same codon have been reported: 1) NM_000527.5(LDLR):c.1A>G (p.Met1Val) – Likely pathogenic by these guidelines. 2) NM_000527.4(LDLR):c.2T>C (p.Met1Thr) - Likely pathogenic by these guidelines. 3) NM_000527.4(LDLR):c.3G>A (p.Met1Ile) - Likely pathogenic by these guidelines. 4) NM_000527.5(LDLR):c.3G>T (p.Met1Ile) - Likely pathogenic by these guidelines. -PM5 not applicable as such variants must be Pathogenic.

Met criteria codes

PS4_Supporting	✔	Variant meets PM2 and is identified in 4 unrelated index cases who fulfill clinical criteria for FH (4 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – FH VCEP member lab).
PP4	✔	Variant meets PM2 and is identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.
PM2	✔	This variant is absent from gnomAD (v2.1.1).
PVS1_Moderate	✔	This variant is predicted to affect the initiation codon.
PP1_Moderate	✔	Variant segregates with phenotype in 4 informative meioses in 3 families (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – 3 families: 4 relatives affected with the variant)
PS3	✔	Level 1 functional studies performed - Heterologous cells (CHO), FACS: results of 60% cell surface LDLR, 59% LDL binding and 66% LDL uptake, compared to wild-type. Note - Level 3 luciferase reporter assays were also performed: results of 5% luciferase construct activity compared to wild-type. Both studies performed in PMID: 34572405.

Not Met criteria codes

PP3	✖	REVEL = 0.63, which is below the threshold of 0.75.
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	Four other missense variants at this same codon have been reported: 1) NM_000527.5(LDLR):c.1A>G (p.Met1Val) – Likely pathogenic by these guidelines. 2) NM_000527.4(LDLR):c.2T>C (p.Met1Thr) - Likely pathogenic by these guidelines. 3) NM_000527.4(LDLR):c.3G>A (p.Met1Ile) - Likely pathogenic by these guidelines. 4) NM_000527.5(LDLR):c.3G>T (p.Met1Ile) - Likely pathogenic by these guidelines. -PM5 not applicable as such variants must be Pathogenic.
PM4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

owing 1 to 3 of 3 rows

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