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.1216C>T (p.Arg406Trp)

Version: 2.0

CA033073

226351 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 20341145-6ce8-4ebf-bf2f-1b567994c9fb
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HGVS expressions

NM_000527.5(LDLR):c.1216C>T (p.Arg406Trp)
NM_000527.5:c.1216C>T
NC_000019.10:g.11113307C>T
CM000681.2:g.11113307C>T
NC_000019.9:g.11223983C>T
CM000681.1:g.11223983C>T
NC_000019.8:g.11084983C>T
NG_009060.1:g.28927C>T
ENST00000252444.10:c.1474C>T
ENST00000559340.2:c.1216C>T
ENST00000560467.2:c.1096C>T
ENST00000558518.6:c.1216C>T
ENST00000252444.9:c.1470C>T
ENST00000455727.6:c.712C>T
ENST00000535915.5:c.1093C>T
ENST00000545707.5:c.835C>T
ENST00000557933.5:c.1216C>T
ENST00000558013.5:c.1216C>T
ENST00000558518.5:c.1216C>T
ENST00000560173.1:n.215C>T
ENST00000560467.1:c.696C>T
NM_000527.4:c.1216C>T
NM_001195798.1:c.1216C>T
NM_001195799.1:c.1093C>T
NM_001195800.1:c.712C>T
NM_001195803.1:c.835C>T
NM_001195798.2:c.1216C>T
NM_001195799.2:c.1093C>T
NM_001195800.2:c.712C>T
NM_001195803.2:c.835C>T

Pathogenic

Met criteria codes 6

PM2 PP1_Strong PS3 PS4 PP3 PP4

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Not Met criteria codes 16

PM1 PM3 PM5 PM4 PM6
BA1 BS2 BS1 BS4 BS3 BP7
BP4 BP2 PVS1 PS1 PS2

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c1216C>T (p.Arg406Trp) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PS3, PS4, PP1_Strong, and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1101/2021.03.17.21252755). The supporting evidence is as follows: PM2 - PopMax MAF = 0.000097 (0.0097%) in Ashkenazi Jewish exomes+genomes (gnomAD v2.1.1). PP3 - REVEL = 0.88, which is above the threshold of 0.75. PS3 – Level 1 functional studies: PMID: 2574186; Heterologous cells (CHO), FACS assays - variant results in 60-65% LDLR expression/biosynthesis, LDL binding and LDL internalization compared to wild-type; results meet <70% threshold. PS4 – Variant meets PM2 and is identified in at least 19 unrelated index cases who fulfill clinical criteria for FH (1 case with DLCN criteria from PathWest Laboratory Medicine WA – FH VCEP member lab; 18 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – FH VCEP member lab). PP1_Strong – Variant segregates with phenotype in 31 informative meioses from 15 families in data provided by FH VCEP member labs (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – 11 families: 23 affected with the variant and 1 unaffected without the variant; Laboratory of Genetics and Molecular Cardiology – 4 families: 4 affected with the variant and 3 unaffected without the variant). PP4 - Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded. Note: two other missense variants at this same codon have been reported: 1) NM_000527.5(LDLR):c.1217G>A (p.Arg406Gln) – Likely pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) – Likely pathogenic by these guidelines. -PM5 not applicable as such variants must be Pathogenic.

Met criteria codes

PM2	✔	PopMax MAF = 0.000097 (0.0097%) in Ashkenazi Jewish exomes+genomes (gnomAD v2.1.1).
PP1_Strong	✔	Variant segregates with phenotype in 31 informative meioses from 15 families in data provided by FH VCEP member labs (Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – 11 families: 23 affected with the variant and 1 unaffected without the variant; Laboratory of Genetics and Molecular Cardiology – 4 families: 4 affected with the variant and 3 unaffected without the variant)
PS3	✔	Level 1 studies performed: PMID: 2574186; Heterologous cells (CHO), FACS assays - variant results in 60-65% LDLR expression/biosynthesis, LDL binding AND LDL internalization compared to wild-type; results meet <70% threshold.
PS4	✔	Variant meets PM2 and is identified in at least 19 unrelated index cases who fulfill clinical criteria for FH (1 case with DLCN criteria from PathWest Laboratory Medicine WA – FH VCEP member lab; 18 cases with SB criteria from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge – FH VCEP member lab).
PP3	✔	REVEL = 0.88
PP4	✔	Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.

Not Met criteria codes

PM1	✖	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	✖	2 other missense variants in the same codon: 1) NM_000527.5(LDLR):c.1217G>A (p.Arg406Gln) – Likely pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) - Likely pathogenic by these guidelines.
PM4	✖	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
BA1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	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 genotype-positive, phenotype-negative cases, which are required for BS4.
BS3	✖	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
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
PVS1	✖	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

Curation History

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