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.1217G>C (p.Arg406Pro)

Version: 1.0

CA10576302

226352 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: a4cb57c2-99f7-4f49-9061-443b0d7a8f88
Approved on: 2022/4/22
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HGVS expressions

NM_000527.5:c.1217G>C
NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro)
NC_000019.10:g.11113308G>C
CM000681.2:g.11113308G>C
NC_000019.9:g.11223984G>C
CM000681.1:g.11223984G>C
NC_000019.8:g.11084984G>C
NG_009060.1:g.28928G>C
ENST00000252444.10:c.1475G>C
ENST00000559340.2:c.1217G>C
ENST00000560467.2:c.1097G>C
ENST00000558518.6:c.1217G>C
ENST00000252444.9:c.1471G>C
ENST00000455727.6:c.713G>C
ENST00000535915.5:c.1094G>C
ENST00000545707.5:c.836G>C
ENST00000557933.5:c.1217G>C
ENST00000558013.5:c.1217G>C
ENST00000558518.5:c.1217G>C
ENST00000560173.1:n.216G>C
ENST00000560467.1:c.697G>C
NM_000527.4:c.1217G>C
NM_001195798.1:c.1217G>C
NM_001195799.1:c.1094G>C
NM_001195800.1:c.713G>C
NM_001195803.1:c.836G>C
NM_001195798.2:c.1217G>C
NM_001195799.2:c.1094G>C
NM_001195800.2:c.713G>C
NM_001195803.2:c.836G>C

Likely Pathogenic

Met criteria codes 6

PM5 PM2 PS4_Supporting PP1 PP3 PP4

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Not Met criteria codes 16

PM1 PM3 PM4 PM6 BA1 BS2 BS1 BS4 BS3 BP7 BP4 BP2 PVS1 PS1 PS2 PS3

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c1217G>C (p.Arg406Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PM5, PS4_Supporting, PP1, 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 - This variant is absent from gnomAD (gnomAD v2.1.1). PP3 - REVEL = 0.89, which is above the threshold of 0.75. 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.Arg406Trp) – Pathogenic by these guidelines. There is 1 variant in the same codon classified as Pathogenic by these guidelines. – therefore PM5 is met. PS4_Supporting - Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (1 case with SB criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation– FH VCEP member lab; 1 case with DLCN criteria from PMID: 16250003) PP1 - Variant segregates with phenotype in 2 informative meioses from 2 families in data provided by FH VCEP member labs (Laboratory of Genetics and Molecular Cardiology – 1 family: 1 affected family member with the variant; Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation – 1 family: 1 affected family member with the variant). PP4 - Variant meets PM2. Identified in >1 case who met clinical criteria for FH after alternative causes for high cholesterol were excluded.

Met criteria codes

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.Arg406Trp) – Pathogenic by these guidelines - therefore PM5 is met.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).
PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (1 case with SB criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation– FH VCEP member lab; 1 case with DLCN criteria from PMID: 16250003).
PP1	✔	Variant segregates with phenotype in 2 informative meioses from 2 families in data provided by FH VCEP member labs (Laboratory of Genetics and Molecular Cardiology – 1 family: 1 affected family member with the variant; Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation – 1 family: 1 affected family member with the variant).
PP3	✔	REVEL = 0.89
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
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 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
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
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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