

Variant: NM\_000527.5(LDLR):c.1217G>A (p.Arg406Gln)

Version: 1.0

CA033088 [↗](#)

228798 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** Semidominant inheritance

**UUID:** 85b170dc-d751-4e93-90df-66867783e4f0

**Approved on:** 2021/6/9

**Published on:** 2021/6/24

### HGVS expressions

**NM\_000527.5:c.1217G>A**

**NM\_000527.5(LDLR):c.1217G>A (p.Arg406Gln)**

NC\_000019.10:g.11113308G>A

CM000681.2:g.11113308G>A

NC\_000019.9:g.11223984G>A

CM000681.1:g.11223984G>A

NC\_000019.8:g.11084984G>A

NG\_009060.1:g.28928G>A

ENST00000252444.10:c.1475G>A

ENST00000559340.2:c.1217G>A

ENST00000560467.2:c.1097G>A

ENST00000558518.6:c.1217G>A

ENST00000252444.9:c.1471G>A

ENST00000455727.6:c.713G>A

ENST00000535915.5:c.1094G>A

ENST00000545707.5:c.836G>A

ENST00000557933.5:c.1217G>A

ENST00000558013.5:c.1217G>A

ENST00000558518.5:c.1217G>A

ENST00000560173.1:n.216G>A

ENST00000560467.1:c.697G>A

NM\_000527.4:c.1217G>A

NM\_001195798.1:c.1217G>A

NM\_001195799.1:c.1094G>A

NM\_001195800.1:c.713G>A

NM\_001195803.1:c.836G>A

NM\_001195798.2:c.1217G>A

NM\_001195799.2:c.1094G>A

NM\_001195800.2:c.713G>A

NM\_001195803.2:c.836G>A

Likely Pathogenic

Met criteria codes **5**

PP3

PP4

PM5

PM2

PS4\_Supporting

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes **21**

BP5 BP7 BP4 BP3 BP1 BP2  
BS1 BS4 BS3 BS2 PP1 PP2  
PS1 PS2 PS3 BA1 PM1  
PM3 PM4 PM6 PVS1

Evidence Links **0**

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

### ***Familial Hypercholesterolemia VCEP***

**NM\_000527.5(LDLR):c.1217G>A (p.Arg406Gln) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PM5, PP3, PP4, PS4\_Supporting) 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 = 0.00006164 (0.006%) in African/African American (gnomAD v2.1.1). PM5 - Two other missense variants described in the same codon (accessed 19 August 2020): --- 1 variant classified as Pathogenic by these guidelines. PP3 - REVEL: 0,809. PP4 - Variant meets PM2. Variant identified in 2 index cases fulfilling Simon-Broome criteria. PS4\_supporting - Variant meets PM2. Variant identified in 2 index cases (PMID: 10882754 - 1 case with Simon-Broome criteria; PMID: 17094996 - 1 case with Simon-Broome criteria).**

#### **Met criteria codes**

|                       |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PP3</b>            |   |   | REVEL: 0,809. Score is above 0,75.                                                                                                                                                                                                                                                                                                                                                                         |
| <b>PP4</b>            |  |  | Variant meets PM2. Variant identified in 2 index cases fulfilling Simon-Broome criteria (PMID: 10882754; PMID: 17094996).                                                                                                                                                                                                                                                                                  |
| <b>PM5</b>            |  |  | Two other missense variants described in the same codon (accessed 19 August 2020):<br>(1)NM_000527.5(LDLR):c.1216C>T (p.Arg406Trp) (ClinVar ID226351) - classified as Pathogenic by these guidelines.<br>(2)NM_000527.5(LDLR):c.1217G>C (p.Arg406Pro) (ClinVar ID 226352) - classified as Likely pathogenic by these guidelines. --- 1 variant classified as Pathogenic by these guidelines, so PM5 is met |
| <b>PM2</b>            |  |  | PopMax MAF = 0.00006164 (0.006%) in African/African American (gnomAD v2.1.1). MAF is below 0.02%.                                                                                                                                                                                                                                                                                                          |
| <b>PS4_Supporting</b> |  |  | Variant meets PM2. Variant identified in 2 index cases (PMID: 10882754 - 1 case with Simon-Broome criteria; PMID: 17094996 - 1 case with Simon-Broome criteria).                                                                                                                                                                                                                                           |

#### **Not Met criteria codes**

|            |                                                                                     |                                                                                     |                                        |
|------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------|
| <b>BP5</b> |  |  | Not applicable.                        |
| <b>BP7</b> |  |  | Missense variant. Not applicable.      |
| <b>BP4</b> |  |  | REVEL: 0,809. Score is not below 0,15. |

|             |                                                                                     |                                                                                     |                                                                                                                  |
|-------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| <b>BP3</b>  |      |      | Not applicable.                                                                                                  |
| <b>BP1</b>  |    |    | Not applicable.                                                                                                  |
| <b>BP2</b>  |    |    | Not identified in individuals with other variants.                                                               |
| <b>BS1</b>  |    |    | no FAF, just total MAF = 0.00001593 (0.0016%) in African/African American (gnomAD v2.1.1). MAF is not above 0.2% |
| <b>BS4</b>  |    |    | No family members tested.                                                                                        |
| <b>BS3</b>  |    |    | No functional assays performed/found - not applicable.                                                           |
| <b>BS2</b>  |    |    | No unaffected individuals identified with the variant.                                                           |
| <b>PP1</b>  |    |    | No family members tested.                                                                                        |
| <b>PP2</b>  |    |    | Not applicable.                                                                                                  |
| <b>PS1</b>  |    |    | No variant described that leads to the same amino acid change.                                                   |
| <b>PS2</b>  |  |  | No de novo cases were identified.                                                                                |
| <b>PS3</b>  |  |  | No functional assays performed/found - not applicable.                                                           |
| <b>BA1</b>  |  |  | no FAF, just total MAF = 0.00001593 (0.0016%) in African/African American (gnomAD v2.1.1). MAF is not above 0.5% |
| <b>PM1</b>  |  |  | Missense at codon 406. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.    |
| <b>PM3</b>  |  |  | Not identified in individuals with other variants.                                                               |
| <b>PM4</b>  |  |  | Missense variant. Not applicable.                                                                                |
| <b>PM6</b>  |  |  | No de novo cases were identified.                                                                                |
| <b>PVS1</b> |  |  | Missense variant. Not applicable.                                                                                |

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