

Variant: *NM_000527.5(LDLR):c.1216C>A (p.Arg406=)*

Version: 1.0

CA023436 [↗](#)

3746 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 1bb8fe4b-fd4a-4ab2-952f-71ea0f6664c5

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HGVS expressions

NM_000527.5(LDLR):c.1216C>A (p.Arg406=)

NM_000527.5:c.1216C>A

NC_000019.10:g.11113307C>A

CM000681.2:g.11113307C>A

NC_000019.9:g.11223983C>A

CM000681.1:g.11223983C>A

NC_000019.8:g.11084983C>A

NG_009060.1:g.28927C>A

ENST00000252444.10:c.1474C>A

ENST00000559340.2:c.1216C>A

ENST00000560467.2:c.1096C>A

ENST00000558518.6:c.1216C>A

ENST00000252444.9:c.1470C>A

ENST00000455727.6:c.712C>A

ENST00000535915.5:c.1093C>A

ENST00000545707.5:c.835C>A

ENST00000557933.5:c.1216C>A

ENST00000558013.5:c.1216C>A

ENST00000558518.5:c.1216C>A

ENST00000560173.1:n.215C>A

ENST00000560467.1:c.696C>A

NM_000527.4:c.1216C>A

NM_001195798.1:c.1216C>A

NM_001195799.1:c.1093C>A

NM_001195800.1:c.712C>A

NM_001195803.1:c.835C>A

NM_001195798.2:c.1216C>A

NM_001195799.2:c.1093C>A

NM_001195800.2:c.712C>A

NM_001195803.2:c.835C>A

Likely Pathogenic

Met criteria codes **5**

PS3_Moderate

PP4

PM3

PM2

PS4_Supporting

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes **21**

PS1 PS2 BA1 PP1 PP2 PP3
PM1 PM5 PM4 PM6 BS1
BS4 BS3 BS2 BP5 BP7 BP4
BP3 BP1 BP2 PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links **0**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1216C>A (p.Arg406=) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PM3, PS3_Moderate, PP4 and PS4_Supportive) 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 = 0.00005441 (0.005%) in East Asian exomes (gnomAD v2.1.1). PM3 - Variant meets PM2 and is identified in one compound heterozygote with a homozygous FH phenotype published in PMID 28028493 (Patient F3 compound with NM_000527.5(LDLR):c.760C>T (p.Gln254Ter) (ClinVar ID 251436), LDLc: 18.21 mmol/l). Additional variant classified as Pathogenic by these guidelines. PS3_moderate - Level 2 FS: PMID: 19371225 - Htz patient's Epstein-Barr virus transformed lymphocytes. RNA assays. Mutant mRNA 25%-45% of total amount. PP4 - Variant meets PM2. Variant identified in 2 index cases. PS4_supporting - Variant meets PM2. Variant identified in 2 index cases.

Met criteria codes

PS3_Moderate			Level 2 FS: PMID: 19371225 - Htz patient's Epstein-Barr virus transformed lymphocytes. RNA assays. Mutant mRNA 25%-45% of total amount. Level 3 FS: PMID: 17335829 - Htz patient's Epstein-Barr virus transformed lymphocytes, RNA assays - skipping of 31nts from exon 9 (p.Ser397Thrfs*6).
PP4			Variant meets PM2. Variant identified in 2 index cases (1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with DLCN criteria; 1 case in PMID 28028493 (EAS FH criteria used)).
PM3			Variant meets PM2 and is identified in one compound heterozygote with a homozygous FH phenotype published in PMID 28028493 (Patient F3 compound with NM_000527.5(LDLR):c.760C>T (p.Gln254Ter) (ClinVar ID 251436), LDLc: 18.21 mmol/l). Additional variant classified as Pathogenic by these guidelines
PM2			PopMax MAF = 0.00005441 (0.005%) in East Asian exomes (gnomAD v2.1.1). MAF is under 0.02%.
PS4_Supporting			Variant meets PM2. Variant identified in 2 index cases (1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with DLCN criteria; 1 case in PMID 28028493 (EAS FH criteria used)).

Not Met criteria codes

PS1			Synonymous variant. Not applicable.
PS2			No de novo cases were identified.
BA1			no FAF, just total MAF = 0.000003983 (0.0004%) in East Asian exomes (gnomAD v2.1.1). MAF is not above 0.5%.
PP1			No family members tested.
PP2			Not applicable.
PP3			Functional splicing data available. Not applicable.

PM1			Synonymous variant. Not applicable.
PM5			Synonymous variant. Not applicable.
PM4			Not applicable.
PM6			No de novo cases were identified.
BS1			no FAF, just total MAF = 0.000003983 (0.0004%) in East Asian exomes (gnomAD v2.1.1). MAF is not above 0.2%.
BS4			No family members tested.
BS3			Level 3 FS: PMID: 19371225 - Htz patient's Epstein-Barr virus transformed lymphocytes. RNA assays. Mutant mRNA 25%-45% of total amount. Level 3 FS: PMID: 17335829 - Htz patient's Epstein-Barr virus transformed lymphocytes, RNA assays - skipping of 31nts from exon 9 (p.Ser397Thrfs*6).
BS2			No unaffected individuals identified with the variant.
BP5			Not applicable.
BP7			MES ratio: 7.59016393442623. MES is > 0,8.
BP4			Functional splicing data available. Not applicable.
BP3			Not applicable.
BP1			Not applicable.
BP2			Not applicable.
PVS1			Synonymous variant. Not applicable.

Curation History [↗](#)

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