

Variant: *NM_000527.5(LDLR):c.1222G>A (p.Glu408Lys)*

Version: 1.0

CA023437 [↗](#)

36453 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: e08d34fe-2556-4636-864a-0cc996c545c4

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HGVS expressions

NM_000527.5:c.1222G>A

NM_000527.5(LDLR):c.1222G>A (p.Glu408Lys)

NC_000019.10:g.11113313G>A

CM000681.2:g.11113313G>A

NC_000019.9:g.11223989G>A

CM000681.1:g.11223989G>A

NC_000019.8:g.11084989G>A

NG_009060.1:g.28933G>A

ENST00000252444.10:c.1480G>A

ENST00000559340.2:c.1222G>A

ENST00000560467.2:c.1102G>A

ENST00000558518.6:c.1222G>A

ENST00000252444.9:c.1476G>A

ENST00000455727.6:c.718G>A

ENST00000535915.5:c.1099G>A

ENST00000545707.5:c.841G>A

ENST00000557933.5:c.1222G>A

ENST00000558013.5:c.1222G>A

ENST00000558518.5:c.1222G>A

ENST00000560173.1:n.221G>A

ENST00000560467.1:c.702G>A

NM_000527.4:c.1222G>A

NM_001195798.1:c.1222G>A

NM_001195799.1:c.1099G>A

NM_001195800.1:c.718G>A

NM_001195803.1:c.841G>A

NM_001195798.2:c.1222G>A

NM_001195799.2:c.1099G>A

NM_001195800.2:c.718G>A

NM_001195803.2:c.841G>A

Likely Pathogenic

Met criteria codes **6**

PS3_Moderate

PP1

PP3

PP4

PM2

PS4_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 20

BP5 BP7 BP4 BP3 BP1 BP2
PS1 PS2 PP2 PM6 PM1
PM3 PM5 PM4 PVS1 BA1
BS2 BS1 BS4 BS3

Evidence Links 0

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.1222G>A (p.Glu408Lys) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PS3_Moderate, PS4_Moderate, PP1, PP3 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 = 0.00001763 (0.0018%) in European non-Finnish exomes (gnomAD v2.1.1). PS3_moderate - Level 2 assay: PMID:1301956 - study on hmz patient's fibroblasts, 125I-LDL assay, effect value reported as <2%; Level 2 assay: PMID: 9026534 - Epstein-Barr virus-transformed lymphoblasts from hmz patient, 125I-LDL assays - Results - 5-10% LDLR activity. PS4_moderate - Variant meets PM2. Variant identified in 8 index cases (1 case from Center of molecular biology and gene therapy with Simon-Broome criteria; 1 case from GeneDx laboratory with Simon Broome criteria, 1 case from Color laboratory with Simon Broome criteria, 1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with Simon Broome criteria, 1 case from University of British Columbia with DLCN criteria, 1 case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge with Simon-Broome criteria, 2 cases from Ambry Genetics with Simon-Broome criteria). PP1 - Variant segregates with phenotype in 2 members of family (2 meioses) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. PP3 - REVEL: 0,879. Score is above 0,75. PP4 - Variant meets PM2. Variant identified in 8 index cases (see PS4_Moderate).

Met criteria codes

PS3_Moderate			Level 2 assay: PMID:1301956 - study on hmz patient's fibroblasts, 125I-LDL assay, effect value reported as <2%; Level 2 assay: PMID: 9026534 - Epstein-Barr virus-transformed lymphoblasts from hmz patient, 125I-LDL assays - Results - 5-10% LDLR activity.
PP1			Variant segregates with phenotype in 2 members of family (2 meioses) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge.
PP3			REVEL: 0,879. Score is above 0,75.
PP4			Variant meets PM2. Variant identified in 8 index cases (see PS4_Moderate).
PM2			PopMax MAF = 0.00001763 (0.0018%) in European non-Finnish exomes (gnomAD v2.1.1). MAF is below 0.02%.
PS4_Moderate			Variant meets PM2. Variant identified in 8 index cases (1 case from Center of molecular biology and gene therapy with Simon-Broome criteria; 1 case from GeneDx laboratory with Simon Broome criteria, 1 case from Color laboratory with Simon Broome criteria, 1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) with Simon Broome criteria, 1 case from University of British Columbia with DLCN criteria, 1 case from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge with Simon-Broome criteria, 2 cases from Ambry Genetics with Simon-Broome criteria).

Not Met criteria codes

BP5			Not applicable.
BP7			Missense variant. Not applicable.
BP4			REVEL: 0,879. Score is not below 0,15.
BP3			Not applicable.
BP1			Not applicable.
BP2			Not identified in individuals with other variants.
PS1			No variant described that leads to the same amino acid change.
PS2			No de novo cases were identified.
PP2			Not applicable.
PM6			No de novo cases were identified.
PM1			Missense at codon 408. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3			Not identified in individuals with other variants.
PM5			No other missense variants in the same codon classified as Pathogenic by these guidelines. Four missense variants described in the same codon (accessed 19 August 2020): (1)NM_000527.4(LDLR):c.1222G>C (p.Glu408Gln) (ClinVar ID 373430) - classified as VUS by these guidelines; (2)NM_000527.5(LDLR):c.1223A>T (p.Glu408Val) (ClinVar ID 251740) - classified as Likely pathogenic by these guidelines; (3)NM_000527.5(LDLR):c.1223A>C (p.Glu408Ala) (ClinVar ID 251739) - classified as Likely pathogenic by these guidelines; (4)NM_000527.4(LDLR):c.1224G>C (p.Glu408Asp) (ClinVar ID 431524) - classified as VUS by these guidelines.
PM4			Missense variant. Not applicable.
PVS1			Missense variant. Not applicable.
BA1			FAF = 0.000002930 (0.0002930%) in European non-Finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%.
BS2			No unaffected individuals identified with the variant.

