

Variant: *NM_000527.5(LDLR):c.1444G>A (p.Asp482Asn)*

Version: 1.0

CA023502 [↗](#)

161284 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 80bb5f03-87c5-45e6-9b97-a70014c29afa

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HGVS expressions

NM_000527.5(LDLR):c.1444G>A (p.Asp482Asn)

NM_000527.5:c.1444G>A

NC_000019.10:g.11113620G>A

CM000681.2:g.11113620G>A

NC_000019.9:g.11224296G>A

CM000681.1:g.11224296G>A

NC_000019.8:g.11085296G>A

NG_009060.1:g.29240G>A

ENST00000252444.10:c.1702G>A

ENST00000559340.2:c.1444G>A

ENST00000560467.2:c.1324G>A

ENST00000558518.6:c.1444G>A

ENST00000252444.9:c.1698G>A

ENST00000455727.6:c.940G>A

ENST00000535915.5:c.1321G>A

ENST00000545707.5:c.1063G>A

ENST00000557933.5:c.1444G>A

ENST00000558013.5:c.1444G>A

ENST00000558518.5:c.1444G>A

ENST00000559340.1:c.165G>A

ENST00000560467.1:c.924G>A

NM_000527.4:c.1444G>A

NM_001195798.1:c.1444G>A

NM_001195799.1:c.1321G>A

NM_001195800.1:c.940G>A

NM_001195803.1:c.1063G>A

NM_001195798.2:c.1444G>A

NM_001195799.2:c.1321G>A

NM_001195800.2:c.940G>A

NM_001195803.2:c.1063G>A

Pathogenic

Met criteria codes **5**

PP1_Strong

PS4

PP3

PP4

PM2

Not Met criteria codes **16**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

PS1

PS2

PS3

BA1

PM6

BS1

BS4

BS3

PM1

PM3

PM5

PM4

BP4

BP3

BP2

PVS1

[Criteria Specifications for this VCEP](#)

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1444G>A (p.Asp482Asn) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PP1_Strong, PM2, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.00009 (0.009%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). PP3: REVEL=0.945. PS4, PP4: Variant meets PM2 and is identified in at least 14 unrelated index cases who fulfill criteria for FH (3 cases with Simon-Broome criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; 3 cases with DLCN score >=6 and 1 case with Simon-Broome criteria from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 3 cases with DLCN score >=6 from Robarts Research Institute, Canada; 3 cases with DLCN score >=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; 1 case with DLCN score>=6 from Color Health, Inc, USA). PP1_Strong: Variant segregates with FH phenotype in at least 11 informative meioses in 4 families from different labs (Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic and Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France): 8 affected family members have the variant and 3 unaffected family members do not have the variant.

Met criteria codes

PP1_Strong			Variant segregates with FH phenotype in 11 informative meioses in 4 families from different labs (Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) and Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France): 8 affected family members have the variant and 3 non-affected family members do not have the variant. So, PP1_Strong is met.
PS4			Variant meets PM2 and is identified in 14 unrelated cases (3 cases with Simon-Broome criteria of FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 3 cases with DLCN criteria and 1 case with Simon-Broome criteria of FH from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 3 cases with DLCN criteria of FH from Robarts Research Institute; 3 cases with DLCN criteria of FH from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 1 case with DLCN criteria of FH from Color Health, Inc). So, PS4 is met.
PP3			REVEL=0.945. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2 and is identified in 14 unrelated index cases who fulfill clinical criteria for FH from several labs (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2			PopMax MAF = 0.00009 (0.009%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1). So, PM2 is met.

Not Met criteria codes

PS1		✖	No other missense variant in the same codon with the same amino acid change,
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No data available
BA1		✖	PopMax MAF = 0.00009 (0.009%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
PM6		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1		✖	PopMax MAF = 0.00009 (0.009%) in European (Non-Finnish) exomes+genomes (gnomAD v2.1.1).
BS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No data available
PM1		✖	Not in exon 4. Not a cysteine residue.
PM3		✖	No data available
PM5		✖	3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1444G>T (p.Asp482Tyr) (ClinVar ID 251845) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1444G>C (p.Asp482His) (ClinVar ID 251844) - Likely Pathogenic by these guidelines - NM_000527.5(LDLR):c.1445A>G (p.Asp482Gly) (ClinVar ID 251846) - Likely Pathogenic by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4		✖	No in-frame deletions/insertions
BP4		✖	REVEL=0.945.
BP3		✖	No in-frame deletions/insertions
BP2		✖	No data available
PVS1		✖	Not a null variant

Showing 1 to 1 of 1 rows

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