

Variant: *NM_000527.5(LDLR):c.1444G>C (p.Asp482His)*

Version: 1.0

CA10585454 [↗](#)

251844 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c4514ebd-5f3b-4eb3-b62b-68702b42de00

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HGVS expressions

NM_000527.5:c.1444G>C

NM_000527.5(LDLR):c.1444G>C (p.Asp482His)

NC_000019.10:g.11113620G>C

CM000681.2:g.11113620G>C

NC_000019.9:g.11224296G>C

CM000681.1:g.11224296G>C

NC_000019.8:g.11085296G>C

NG_009060.1:g.29240G>C

ENST00000252444.10:c.1702G>C

ENST00000559340.2:c.1444G>C

ENST00000560467.2:c.1324G>C

ENST00000558518.6:c.1444G>C

ENST00000252444.9:c.1698G>C

ENST00000455727.6:c.940G>C

ENST00000535915.5:c.1321G>C

ENST00000545707.5:c.1063G>C

ENST00000557933.5:c.1444G>C

ENST00000558013.5:c.1444G>C

ENST00000558518.5:c.1444G>C

ENST00000559340.1:c.165G>C

ENST00000560467.1:c.924G>C

NM_000527.4:c.1444G>C

NM_001195798.1:c.1444G>C

NM_001195799.1:c.1321G>C

NM_001195800.1:c.940G>C

NM_001195803.1:c.1063G>C

NM_001195798.2:c.1444G>C

NM_001195799.2:c.1321G>C

NM_001195800.2:c.940G>C

NM_001195803.2:c.1063G>C

Likely Pathogenic

Met criteria codes **6**

PM5 PM2 PS4_Supporting
PS3_Moderate PP3 PP4

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 16

PM1 PM3 PM4 PM6 BS1
BS4 BS3 BS2 PVS1 PS1
PS2 BP4 BP3 BP2 BA1 PP1

Evidence Links 1

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1444G>C (p.Asp482His) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3_Moderate, PM2, PM5, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL=0.993. PM5: 3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1444G>A (p.Asp482Asn) (ClinVar ID 161284) - Pathogenic by these guidelines; - NM_000527.5(LDLR):c.1444G>T (p.Asp482Tyr) (ClinVar ID 251845) - Uncertain significance by these guidelines; - NM_000527.5(LDLR):c.1445A>G (p.Asp482Gly) (ClinVar ID 251846) - Likely Pathogenic by these guidelines; There is 1 variant in the same codon classified as Pathogenic by these guidelines. PS3_Moderate: Level 2 assay: PMID 31587492 (Kizhakke P et al., 2019) - HEK-293T cells. In immunoblots of the mutants, only the precursor form was observed (~120 kDa) and the mature receptor form was absent. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 2 index cases who fulfill Simon Broome criteria for FH (1 case in PMID 11313767 (Heath KE et al., 2001), 1 case in PMID 10559517 (Graham CA et al., 1999)).

Met criteria codes

PM5			3 other missense variants in the same codon: - NM_000527.5(LDLR):c.1444G>A (p.Asp482Asn) (ClinVar ID 161284) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1444G>T (p.Asp482Tyr) (ClinVar ID 251845) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.1445A>G (p.Asp482Gly) (ClinVar ID 251846) - Likely Pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1). So, PM2 is met.
PS4_Supporting			Variant meets PM2 and is identified in 2 index cases (1 case with Simon-Broome criteria of FH in PMID: 11313767 (Heath KE et al., 2001), 1 case with Simon-Broome criteria of FH in PMID: 10559517 (Graham CA et al., 1999)). So, PS4_Supporting is met.
PS3_Moderate			Level 2 assays PMID 31587492- HEK-293T cells. In immunoblots of the mutants, only the precursor form was observed (~120 kDa) and the mature receptor form was absent. So, PS3_Moderate was met. Level 2 assay- HeLa cells and HEK-293T cells. In immunoblots of the mutants D482H, only the precursor form was observed (~120 kDa) and the mature receptor form was absent. PubMed:31587492 
PP3			REVEL=0.993. It is above 0.75, so PP3 is met.
PP4			Variant meets PM2 and is identified in 2 unrelated index cases who fulfill clinical criteria for FH (see PS4 for details), after alternative causes of high cholesterol were excluded.

Not Met criteria codes

PM1			Not in exon 4. Not a cysteine residue.
PM3			No evidence available
PM4			No in-frame deletions/insertions
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			This variant is absent from gnomAD (gnomAD v2.1.1).
BS4			No evidence available
BS3			No evidence available
BS2			No evidence available
PVS1			Not a null variant
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
BP4			REVEL=0.993.
BP3			No in-frame deletions/insertions
BP2			No evidence available
BA1			This variant is absent from gnomAD (gnomAD v2.1.1).
PP1			No evidence available

Showing 1 to 1 of 1 rows

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