The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2023/6/23
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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

PP3 PP4 PM2 PM5 PS4_Supporting PS3_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Not Met criteria codes 16

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

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 (Kizhakkedath 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

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.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1). So, PM2 is met.
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.
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

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

Curation History

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