Variant: NM_000527.5(LDLR):c.1429G>A (p.Asp477Asn)

Version: 1.0

CA034365

251838 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 67035374-a991-4cff-9029-85f5f5475192
Approved on: 2025-02-28
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HGVS expressions

NM_000527.5:c.1429G>A
NM_000527.5(LDLR):c.1429G>A (p.Asp477Asn)
NC_000019.10:g.11113605G>A
CM000681.2:g.11113605G>A
NC_000019.9:g.11224281G>A
CM000681.1:g.11224281G>A
NC_000019.8:g.11085281G>A
NG_009060.1:g.29225G>A
ENST00000252444.10:c.1687G>A
ENST00000559340.2:c.1429G>A
ENST00000560467.2:c.1309G>A
ENST00000558518.6:c.1429G>A
ENST00000252444.9:c.1683G>A
ENST00000455727.6:c.925G>A
ENST00000535915.5:c.1306G>A
ENST00000545707.5:c.1048G>A
ENST00000557933.5:c.1429G>A
ENST00000558013.5:c.1429G>A
ENST00000558518.5:c.1429G>A
ENST00000559340.1:c.150G>A
ENST00000560467.1:c.909G>A
NM_000527.4:c.1429G>A
NM_001195798.1:c.1429G>A
NM_001195799.1:c.1306G>A
NM_001195800.1:c.925G>A
NM_001195803.1:c.1048G>A
NM_001195798.2:c.1429G>A
NM_001195799.2:c.1306G>A
NM_001195800.2:c.925G>A
NM_001195803.2:c.1048G>A

Uncertain Significance

Met criteria codes 4

PP4 PM2 PS3_Supporting PS4_Supporting

Not Met criteria codes 7

BP4 PP1 PP3 PM5 BA1 BS1 PS1

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2*

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1429G>A (p.Asp477Asn) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP4 and PS3_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on February 28, 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.00003294 (0.003294%) in South Asian exomes + genomes (gnomAD v4.1.0). PS3_Supporting: Level 3 assays: PMID 39114568 (Jawabri et al., 2024); heterologous cells (CHO-ldlA7 and HeLa), immunocytochemistry, confocal microscopy. Result --> Normal cell surface LDLR, LDL internalization (~35%). Results of LDL internalization are below 85% of wild-type, so functional study is consistent with damaging effect. PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated index cases with DLCN score >=6 (1 case from Brunham Lab, Centre for Heart and Lung Innovation (University of British Columbia), Canada; 1 case from PMID 16250003 (Fouchier SW. et. al., 2005), Netherlands).

Met criteria codes

PP4	✔	Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN criteria >=6 from Brunham Lab, Centre for Heart and Lung Innovation (University of British Columbia), Canada; 1 case with DLCN criteria >=6 from PMID 16250003 (Fouchier SW. et. al., 2005), Netherlands).
PM2	✔	PopMax MAF = 0.00003294 (0.003294%) in South Asian exomes+genomes (gnomAD v4.1.0)
PS3_Supporting	✔	Level 1 assays: PMID 39114568 Heterologous cells (CHO-ldlA7 and HeLa), Immunocytochemistry, confocal microscopy Result --> Normal cell surface LDLR, LDL internalization (~35%) activity is below 85% of wild-type, so functional study is consistent with damaging effect.
PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases (1 case with DLCN criteria >=6 from Brunham Lab, Centre for Heart and Lung Innovation (University of British Columbia), Canada; 1 case with DLCN criteria >=6 from PMID 16250003 (Fouchier SW. et. al., 2005), Netherlands).

Not Met criteria codes

BP4	✖	REVEL = 0.745, it is not below 0.5

PP1		✖	Variant was only identified in 1 individual
PP3		✖	REVEL = 0.745. It is not above 0.75, so splicing evaluation required. Functional data on splicing not available. A) Variant not on limits B) Does not create AG/GT C) There is no AG/GT nearby. Variant is not predicted to alter splicing
PM5		✖	1 other missense variant in the same codon - NM_000527.5(LDLR):c.1431C>G (p.Asp477Glu) (ClinVar ID 1713361) - Uncertain significance - insuficient evidence by these guidelines. There is no variant in the same codon classified as Pathogenic by these guidelines
BA1		✖	FAF = 0.000009240 (0.0009240%) in South Asian exomes (gnomAD v4.1.0)
BS1		✖	FAF = 0.000009240 (0.0009240%) in South Asian exomes (gnomAD v4.1.0)
PS1		✖	1 other missense variant in the same codon - NM_000527.5(LDLR):c.1431C>G (p.Asp477Glu) (ClinVar ID 1713361) - Uncertain significance - insuficient evidence by these guidelines. There is no variant in the same codon classified as Pathogenic by these guidelines

Curation History

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