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.1475A>G (p.Asp492Gly)

Version: 1.0

CA10585475

251865 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 00b89750-e18b-4cbd-9fd6-a690ccbbdcd3
Approved on: 2023/11/7
Published on: 2024/10/3

HGVS expressions

NM_000527.5(LDLR):c.1475A>G (p.Asp492Gly)
NM_000527.5:c.1475A>G
NC_000019.10:g.11113651A>G
CM000681.2:g.11113651A>G
NC_000019.9:g.11224327A>G
CM000681.1:g.11224327A>G
NC_000019.8:g.11085327A>G
NG_009060.1:g.29271A>G
ENST00000252444.10:c.1733A>G
ENST00000559340.2:c.1475A>G
ENST00000560467.2:c.1355A>G
ENST00000558518.6:c.1475A>G
ENST00000252444.9:c.1729A>G
ENST00000455727.6:c.971A>G
ENST00000535915.5:c.1352A>G
ENST00000545707.5:c.1094A>G
ENST00000557933.5:c.1475A>G
ENST00000558013.5:c.1475A>G
ENST00000558518.5:c.1475A>G
ENST00000559340.1:c.196A>G
NM_000527.4:c.1475A>G
NM_001195798.1:c.1475A>G
NM_001195799.1:c.1352A>G
NM_001195800.1:c.971A>G
NM_001195803.1:c.1094A>G
NM_001195798.2:c.1475A>G
NM_001195799.2:c.1352A>G
NM_001195800.2:c.971A>G
NM_001195803.2:c.1094A>G

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM2 PM5 PS4_Supporting

Not Met criteria codes 1

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS3

Criteria Specifications for this VCEP

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1475A>G (p.Asp492Gly) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes 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 7 November 2023. The supporting evidence is as follows: PM2: Variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL=0.994. PM5: Two other missense variants in the same codon: NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn), ClinVar 161285, classified as Pathogenic by these guidelines; NM_000527.5(LDLR):c.1474G>C (p.Asp492His), ClinVar 251846, classified as Likely Pathogenic by these guidelines. Therefore PM5 is met. PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated cases who fulfil DLCN criteria for FH clinical diagnosis: 1 case from PMID 16250003 (Fouchier et al., 2005), the Netherlands; 1 case from PMID 30270055 (Corral et al., 2018), Argentina.

Met criteria codes

PP3	✔	REVEL=0.994.
PP4	✔	Variant meets PM2 and is identified in >1 index cases who fulfil DLCN criteria for FH diagnosis after alternative causes of high cholesterol were excluded.
PM2	✔	Variant is absent from gnomAD (gnomAD v2.1.1).
PM5	✔	Two other missense variants in the same codon: NM_000527.5(LDLR):c.1474G>A(p.Asp492Asn (ClinVarID 161285) classified as Pathogenic by these guidelines. NM_000527.5(LDLR):c.1474G>C(p.Asp492His (ClinVarID 251846) classified as Likely Pathogenic by these guidelines. Therefore PM5 is met.
PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated cases who fulfil DLCN criteria for FH clinical diagnosis. One case each reported in PMID 16250003 by Fouchier et al, 2005, from University of Amsterdam, The Netherlands, and in PMID 30270055 by Corral et al, 2018, from Universidad FASTA, Buenos Aires, Argentina.

Not Met criteria codes

PS3	✖	Functional data is not available.

Curation History

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