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.1067A>T (p.Asp356Val)

Version: 1.0

CA404083112

440623 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 046269d8-56c2-4e2e-be65-f77fb906fca4
Approved on: 2023/4/28
Published on: 2023/5/1

HGVS expressions

NM_000527.5:c.1067A>T
NM_000527.5(LDLR):c.1067A>T (p.Asp356Val)
NC_000019.10:g.11111520A>T
CM000681.2:g.11111520A>T
NC_000019.9:g.11222196A>T
CM000681.1:g.11222196A>T
NC_000019.8:g.11083196A>T
NG_009060.1:g.27140A>T
ENST00000252444.10:c.1325A>T
ENST00000559340.2:c.1067A>T
ENST00000560467.2:c.947A>T
ENST00000558518.6:c.1067A>T
ENST00000252444.9:c.1321A>T
ENST00000455727.6:c.563A>T
ENST00000535915.5:c.944A>T
ENST00000545707.5:c.686A>T
ENST00000557933.5:c.1067A>T
ENST00000558013.5:c.1067A>T
ENST00000558518.5:c.1067A>T
ENST00000560173.1:n.66A>T
ENST00000560467.1:c.547A>T
NM_000527.4:c.1067A>T
NM_001195798.1:c.1067A>T
NM_001195799.1:c.944A>T
NM_001195800.1:c.563A>T
NM_001195803.1:c.686A>T
NM_001195798.2:c.1067A>T
NM_001195799.2:c.944A>T
NM_001195800.2:c.563A>T
NM_001195803.2:c.686A>T

Likely Pathogenic

Met criteria codes 5

PM5 PM2 PP3 PP4 PS4_Supporting

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 variant NM_000527.5(LDLR):c.1067A>T (p.Asp356Val) is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PM5, PP3, PS4_Supporting and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1016/j.gim.2021.09.012). The supporting evidence is as follows: PM2 - This variant is absent from gnomAD (gnomAD v2.1.1). PP3 - REVEL = 0.903 PS4_Supporting: Variant meets PM2, and is identified in 2 unrelated cases: 1 case with DLCN>6 from PMID: 30745730; 1 case with Simon-Broome criteria of possible FH from Color Health. So, PS4_Supporting is met. PP4 - Variant meets PM2 and is identified in at least 1 index case meeting clinical diagnostic criteria for FH, after alternative causes of high cholesterol were excluded. PM5 - 4 other missense variants in the same codon: 1) NM_000527.5(LDLR):c.1066G>T (p.Asp356Tyr) (ClinVar ID 226345) - Pathogenic by these guidelines. 2) NM_000527.5(LDLR):c.1066G>C (p.Asp356His) (ClinVar ID 251644) - Likely Pathogenic by these guidelines. 3) NM_000527.5(LDLR):c.1066G>A (p.Asp356Asn) (ClinVar ID 251643) - Unknown Significance by these guidelines. 4) NM_000527.5(LDLR):c.1067A>C (p.Asp356Ala) (ClinVar ID 251645) - Likely Pathogenic by these guidelines. There is 1 variant (p.Asp356Tyr) in the same codon classified as Pathogenic by these guidelines. So PM5 is met.

Met criteria codes

PM5	✔	4 other missense variants in the same codon: - NM_000527.5(LDLR):c.1066G>T (p.Asp356Tyr) (ClinVar ID 226345) - Pathogenic by these guidelines. - NM_000527.5(LDLR):c.1066G>C (p.Asp356His) (ClinVar ID 251644) - Likely Pathogenic by these guidelines. - NM_000527.5(LDLR):c.1066G>A (p.Asp356Asn) (ClinVar ID 251643) - Unknown Significance by these guidelines. - NM_000527.5(LDLR):c.1067A>C (p.Asp356Ala) (ClinVar ID 251645) - Likely Pathogenic by these guidelines. There is 1 variant in the same codon classified as Pathogenic by these guidelines. So PM5 is met.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).
PP3	✔	REVEL = 0.903
PP4	✔	Variant meets PM2 and is identified in at least 1 index case meeting clinical diagnostic criteria for FH, after alternative causes of high cholesterol were excluded.
PS4_Supporting	✔	Variant meets PM2 and is identified in two unrelated index cases: 1 case with DLCN>6 from PMID 30745730; 1 case with Simon-Broome criteria of possible FH from Color Health.

Curation History

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.