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>C (p.Asp356Ala)

Version: 1.0

CA10585287

251645 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 3cb94032-782f-4eb2-b705-a27547228f7e
Approved on: 2023/4/28
Published on: 2023/5/1

HGVS expressions

NM_000527.5(LDLR):c.1067A>C (p.Asp356Ala)
NM_000527.5:c.1067A>C
NC_000019.10:g.11111520A>C
CM000681.2:g.11111520A>C
NC_000019.9:g.11222196A>C
CM000681.1:g.11222196A>C
NC_000019.8:g.11083196A>C
NG_009060.1:g.27140A>C
ENST00000252444.10:c.1325A>C
ENST00000559340.2:c.1067A>C
ENST00000560467.2:c.947A>C
ENST00000558518.6:c.1067A>C
ENST00000252444.9:c.1321A>C
ENST00000455727.6:c.563A>C
ENST00000535915.5:c.944A>C
ENST00000545707.5:c.686A>C
ENST00000557933.5:c.1067A>C
ENST00000558013.5:c.1067A>C
ENST00000558518.5:c.1067A>C
ENST00000560173.1:n.66A>C
ENST00000560467.1:c.547A>C
NM_000527.4:c.1067A>C
NM_001195798.1:c.1067A>C
NM_001195799.1:c.944A>C
NM_001195800.1:c.563A>C
NM_001195803.1:c.686A>C
NM_001195798.2:c.1067A>C
NM_001195799.2:c.944A>C
NM_001195800.2:c.563A>C
NM_001195803.2:c.686A>C

Likely Pathogenic

Met criteria codes 5

PP1 PP3 PP4 PM5 PM2

Not Met criteria codes 1

PS4

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>C (p.Asp356Ala) is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PM5, PP1, PP3, 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). PP1 - variant segregates with FH phenotype in 2 informative meiosis in 1 family from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obeste et des Dyslipidemies (APHP Sorbonne Univeristie Hopitalde la Pitie-Salpetriere): 2 affected family members have the variant. PP3 - REVEL=0.947 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>T (p.Asp356Val) (ClinVar ID 440623) - 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

PP1	✔	variant segregates with FH phenotype in 2 informative meiosis in 1 family from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obeste et des Dyslipidemies (APHP Sorbonne Univeristie Hopitalde la Pitie-Salpetriere): 2 affected family members have the variant.
PP3	✔	REVEL=0.947
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>T (p.Asp356Val) (ClinVar ID 440623) - 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.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PS4 ✖ variant meets PM2 and but is identified in only 1 index cases with DLCN criteria>=6 from Centre de Genetique Moleculaire et Chromosomique, Unite de genetique de l'Obeste et des Dyslipidemies (APHP Sorbonne Univeristie Hopitalde la Pitie-Salpetriere)

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.1067A>C (p.Asp...	Likely Pathogenic	Hypercholesterolemia, Familial	2023-05-01	1.0	ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2	LDLR

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