

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

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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

PP1PP3PP4PM5PM2

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 meioses 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 meioses 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 $\geq$ 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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