

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

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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

PP3

PP4

PM2

PM5

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

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.

PM2



This variant is absent from gnomAD (gnomAD v2.1.1).

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.

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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