

Variant: NM_000527.5(LDLR):c.1085A>C (p.Asp362Ala)

Version: 1.0

CA023415 [↗](#)

36452 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))

Condition: hypercholesterolemia, familial ([MONDO:0007750](#))

Inheritance Mode: Semidominant inheritance

UUID: 40987225-c315-4693-9ec1-385b38754699

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HGVS expressions

NM_000527.5(LDLR):c.1085A>C (p.Asp362Ala)

NM_000527.5:c.1085A>C

NC_000019.10:g.11111538A>C

CM000681.2:g.11111538A>C

NC_000019.9:g.11222214A>C

CM000681.1:g.11222214A>C

NC_000019.8:g.11083214A>C

NG_009060.1:g.27158A>C

ENST00000252444.10:c.1343A>C

ENST00000559340.2:c.1085A>C

ENST00000560467.2:c.965A>C

ENST00000558518.6:c.1085A>C

ENST00000252444.9:c.1339A>C

ENST00000455727.6:c.581A>C

ENST00000535915.5:c.962A>C

ENST00000545707.5:c.704A>C

ENST00000557933.5:c.1085A>C

ENST00000558013.5:c.1085A>C

ENST00000558518.5:c.1085A>C

ENST00000560173.1:n.84A>C

ENST00000560467.1:c.565A>C

NM_000527.4:c.1085A>C

NM_001195798.1:c.1085A>C

NM_001195799.1:c.962A>C

NM_001195800.1:c.581A>C

NM_001195803.1:c.704A>C

NM_001195798.2:c.1085A>C

NM_001195799.2:c.962A>C

NM_001195800.2:c.581A>C

NM_001195803.2:c.704A>C

Uncertain Significance

Met criteria codes3

PS4_ModeratePP4PM2

Not Met criteria codes23

BA1BP5BP7BP4BP3BP1BP2BS1BS4BS3BS2PP1PP2PP3PM6PM1PM3PM5PM4PS1PS2PS3PVS1

Evidence Links0

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 NM_000527.5(LDLR):c.1085A>C (p.Asp362Ala) variant is classified as **Uncertain significance - insufficient evidence for Familial Hypercholesterolemia** by applying evidence codes (PM2, PP4 and PS4_Moderate) 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 - PopMax MAF = 0.0001782 (0.01782%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1). PS4_Moderate - Variant meets PM2 and is identified in 8 unrelated index cases (5 cases with Simon-Broome criteria of definite/possible FH published in PMID: 16542394, Denmark; at least 1 case with DLCN≥6 published in PMID: 11810272, Netherlands; 1 case with DLCN criteria ≥6 from Robarts Research Institute, Canada; 1 case with Simon-Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czechia. PP4 - Variant meets PM2 and is identified in at least one case who fufills clinical criteria for FH (see PS4 for details), after alternative causes of high cholesterol were excluded.

Met criteria codes

PS4_Moderate		✓	Variant meets PM2 and is identified in 8 unrelated index cases (5 cases with Simon-Broome criteria of definite/possible FH published in PMID: 16542394, Denmark; at least 1 case with DLCN≥6 published in PMID: 11810272, Netherlands; 1 case with DLCN criteria ≥6 from Robarts Research Institute, Canada; 1 case with Simon-Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czechia.
PP4		✓	Variant meets PM2 and is identified in at least one case who fufills clinical criteria for FH (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2		✓	PopMax MAF = 0.0001782 (0.01782%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1).

Not Met criteria codes

BA1		✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✗	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			REVEL = 0.7. It is not above 0.75, splicing evaluation needed. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp downstream from the canonical donor site, but it does not create AG. C) there is a AG nearby. MES scores: variant cryptic = 4.78, wt cryptic = 2.69, canonical acceptor = 13.9. Ratio variant cryptic/wt cryptic: $4.78/2.69 = 1.78$ --- it is above 1.1 Ratio variant cryptic/canonical donor: $4.78/13.9 = 0.34$ -- it is not above 0.9 Variant is not predicted to alter splicing.
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 	
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