

Variant: *NM_000527.5(LDLR):c.270T>A (p.Asp90Glu)*

Version: 1.1

CA10584821 [↗](#)

251107 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c59d43d0-b343-44d0-b9cb-f1b7f782876f

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HGVS expressions

NM_000527.5(LDLR):c.270T>A (p.Asp90Glu)

NM_000527.5:c.270T>A

NC_000019.10:g.11102743T>A

CM000681.2:g.11102743T>A

NC_000019.9:g.11213419T>A

CM000681.1:g.11213419T>A

NC_000019.8:g.11074419T>A

NG_009060.1:g.18363T>A

ENST00000252444.10:c.528T>A

ENST00000559340.2:c.270T>A

ENST00000560467.2:c.270T>A

ENST00000558518.6:c.270T>A

ENST00000252444.9:c.524T>A

ENST00000455727.6:c.270T>A

ENST00000535915.5:c.190+2398T>A

ENST00000545707.5:c.270T>A

ENST00000557933.5:c.270T>A

ENST00000557958.1:n.356T>A

ENST00000558013.5:c.270T>A

ENST00000558518.5:c.270T>A

NM_000527.4:c.270T>A

NM_001195798.1:c.270T>A

NM_001195799.1:c.190+2398T>A

NM_001195800.1:c.270T>A

NM_001195803.1:c.270T>A

NM_001195798.2:c.270T>A

NM_001195799.2:c.190+2398T>A

NM_001195800.2:c.270T>A

NM_001195803.2:c.270T>A

Pathogenic

Met criteria codes **6**

PM5

PM2

PP3

PP4

PS4_Supporting

PP1_Strong

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM1

PM3

PM4

PS1

PS2

PS3

BA1

PM6

PP2

PVS1

BS2

BS1

BS4

BS3

BP5

BP7

BP4

BP3

BP1

BP2

Evidence Links 0

- [Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence PP1_Strong, PM2, PM5, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PP1_strong - variant segregates with FH phenotype in 11 informative meioses from 2 families from PMID 20809525 (Marduel et al., 2010): F1: 4 affected relatives have the variant and 3 unaffected relatives do not have the variant; F2: 3 affected relatives have the variant and 1 unaffected relative does not have the variant, so PP1_Strong is met. PM2 - This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met. PM5 - 4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>C (p.Asp90Ala) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines There is 1 variant classified as Pathogenic by these guidelines, so PM5 is met. PP3 - REVEL = 0.833. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in 4 index cases with SB criteria of FH (total and LDL-cholesterol levels above the 95th percentile of a sex and age-matched French population and autosomal dominant transmission of hypercholesterolemia in the family) from PMID 20809525 (Marduel et al., 2010), so PP4 is met. PS4_supporting - variant meets PM2 and was identified in 4 index cases with SB criteria of FH from PMID 20809525 (Marduel et al., 2010), (see PP4 for details), so PS4_Supporting is met.

Met criteria codes

PM5			4 other missense variants is the same codon: - NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.268G>T (p.Asp90Tyr) - classified as Likely pathogenic by the FH VCEP, with these guidelines - NM_000527.5(LDLR):c.269A>C (p.Asp90Ala) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.269A>G (p.Asp90Gly) - Pathogenic by these guidelines There is 1 variant classified as Pathogenic by these guidelines, so PM5 is met.
PM2			This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met
PP3			REVEL = 0.833. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in 4 index cases with SB criteria of FH (total and LDL-cholesterol levels above the 95th percentile of a sex and age-matched French population and autosomal dominant transmission of hypercholesterolemia in the family) from PMID 20809525 (Marduel et al., 2010), so PP4 is met
PS4_Supporting			variant meets PM2 and was identified in: - at least 1 index case with DLCN score of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583647.1), France - 4 index cases with SB criteria of FH (total and LDL-cholesterol levels above the 95th percentile of a sex and age-matched French population and autosomal dominant transmission of hypercholesterolemia in the family) from PMID 20809525 (Marduel et al., 2010), France only count 4 cases to avoid double counting, so PS4_Supporting is met

PP1_Strong			variant segregates with FH phenotype in 11 informative meioses from 2 families from PMID 20809525 (Marduel et al., 2010): F1: 4 affected relatives have the variant and 3 unaffected relatives do not have the variant; F2: 3 affected relatives have the variant and 1 unaffected relative does not have the variant (4-3, 3-1 in paper), so PP1_Strong is met
Not Met criteria codes			
PM1			variant is not in exon 4 and does not alter Cys, so not met
PM3			no index cases with more than 1 variant were identified
PM4			variant is missense, so not met
PS1			no other missense variant leads to the same amino acid change, so not met
PS2			no de novo occurrence
PS3			no functional studies performed, so not met
BA1			This variant was not identified in gnomAD (gnomAD v2.1.1), so not met
PM6			no de novo occurrence
PP2			not applicable
PVS1			variant is missense and not in initiation codon, so not met
BS2			not identified in normolipidemic individuals, so not met
BS1			This variant was not identified in gnomAD (gnomAD v2.1.1), so not met
BS4			no lack of segregation was identified, so not met
BS3			no functional studies performed, so not met
BP5			not applicable
BP7			variant is missense, so not met
BP4			REVEL = 0.833. It is not below 0.50, so BP4 is not met



not applicable



not applicable



no index cases with more than 1 variant were identified

Curation History



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