

Variant: *NM_000527.5(LDLR):c.269A>G (p.Asp90Gly)*

Version: 1.1

CA042622 [↗](#)

226313 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 243fe145-86fd-48f6-98dd-c946485388c0

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HGVS expressions

NM_000527.5:c.269A>G

NM_000527.5(LDLR):c.269A>G (p.Asp90Gly)

NC_000019.10:g.11102742A>G

CM000681.2:g.11102742A>G

NC_000019.9:g.11213418A>G

CM000681.1:g.11213418A>G

NC_000019.8:g.11074418A>G

NG_009060.1:g.18362A>G

ENST00000252444.10:c.527A>G

ENST00000559340.2:c.269A>G

ENST00000560467.2:c.269A>G

ENST00000558518.6:c.269A>G

ENST00000252444.9:c.523A>G

ENST00000455727.6:c.269A>G

ENST00000535915.5:c.190+2397A>G

ENST00000545707.5:c.269A>G

ENST00000557933.5:c.269A>G

ENST00000557958.1:n.355A>G

ENST00000558013.5:c.269A>G

ENST00000558518.5:c.269A>G

NM_000527.4:c.269A>G

NM_001195798.1:c.269A>G

NM_001195799.1:c.190+2397A>G

NM_001195800.1:c.269A>G

NM_001195803.1:c.269A>G

NM_001195798.2:c.269A>G

NM_001195799.2:c.190+2397A>G

NM_001195800.2:c.269A>G

NM_001195803.2:c.269A>G

Pathogenic

Met criteria codes **7**

PP1_Moderate

PS4

PP3

PP4

PM2

PM3

PM5

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

PP2

BA1

PM6

BS1

BS4

BS3

PM1

PM4

BS2

BP5

BP7

BP4

BP3

BP1

BP2

PVS1

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.269A>G (p.Asp90Gly) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4, PP1_Moderate, PM2, PM3, PM5, PP3 and PP4 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: PS4 - variant meets PM2 and was identified in at least 14 unrelated index cases with clinical criteria of FH: - 4 unrelated index cases with DLCN >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; - at least 1 index case with DLCN probable FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583646.1), France; - 8 unrelated index cases (7 with DLCN>=6 and 1 SB possible) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France; - at least 1 index case with SB criteria for FH (plasma cholesterol of >8.0 mmol/L and family histories of hypercholesterolemia and/or classical clinical stigmata of FH) from PMID 11857755 (Bunn et al., 2002), New Zeland; - 1 index case with SB criteria for FH (grossly increased plasma cholesterol concentration and the presence of xanthomata in childhood and cardiovascular involvement by puberty in the proband, together with hypercholesterolemia in both parents; this index case died at 31years, had cholesterol of 20.7mmol/L and CVD) from PMID 9026534 (Webb et al., 1996), UK so PS4 is met. PP1_moderate - Variant segregates with FH phenotype in 5 informative meiosis from 3 families: - 2 affected family members have the variant, from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); - 3 affected family members have the variant, from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), so PP1_Moderate is met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met. PM3 - variant meets PM2 and was identified in - 1 index case with phenotype of homozygous FH (cholesterol of 20.7mmol/L) and also NM_000527.5(LDLR):c.912C>G (p.Asp304Glu), Likely pathogenic by these guidelines, from PMID 9026534 (Webb et al., 1996), UK so PM3 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.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There is 1 variant classified as Pathogenic by these guidelines, so PM5 is met. PP3 - REVEL = 0.957. It is above 0.75, so PP3 is met PP4 - variant meets PM2 and was identified in at least 14 unrelated index cases with clinical criteria of FH (see PS4 for details), so PP4 is met

Met criteria codes

PP1_Moderate		Variant segregates with FH phenotype in 5 informative meiosis from 3 families: - 2 affected family members have the variant, from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA) - 3 affected family members have the variant, from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) so PP1_Moderate is met
PS4		variant meets PM2 and was identified in at least 14 unrelated index cases with clinical criteria of FH: - 4 unrelated index cases with DLCN >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; - at least 1 index case with DLCN probable FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583646.1), France; - 8 unrelated index cases (7 with DLCN>=6 and 1 SB possible) from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France - at least 1 index case with SB criteria for FH (plasma cholesterol of

>8.0 mmol/L and family histories of hypercholesterolemia and/or classical clinical stigmata of FH) from PMID 11857755 (Bunn et al., 2002), New Zeland; - 1 index case with SB criteria for FH (grossly increased plasma cholesterol concentration and the presence of xanthomata in childhood and cardiovascular involvement by puberty in the proband, together with hypercholesterolemia in both parents; this index case died at 31years, had cholesterol of 20.7mmol/L and CVD) from PMID 9026534 (Webb et al., 1996), UK so PS4 is met

PP3			REVEL = 0.957. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in at least 14 unrelated index cases with clinical criteria of FH (see PS4 for details) so PP4 is met
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is met.
PM3			variant meets PM2 and was identified in - 1 index case with phenotype of homozygous FH (cholesterol of 20.7mmol/L) and also NM_000527.5(LDLR):c.912C>G (p.Asp304Glu), Likely pathogenic by these guidelines, from PMID 9026534 (Webb et al., 1996), UK so PM3 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.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There is 1 variant classified as Pathogenic by these guidelines, so PM5 is met.

Not Met criteria codes

PS1			no other missense variant leads to the same amino acid change in the same codon, so not met
PS2			no de novo occurrence
PS3			only functional study on compound heterozygous individual, so not met
PP2			not applicable
BA1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
PM6			no de novo occurrence
BS1			This variant is absent from gnomAD (gnomAD v2.1.1), so not met
BS4			no lack of segregation was identified, so not met
BS3			only functional study on compound heterozygous individual, so not met

PM1			variant is not in exon 4 and does not alter Cys, so not met
PM4			variant is missense, so not met
BS2			not identified in normolipidemic individuals, so not met
BP5			not applicable
BP7			variant is missense, so not met
BP4			REVEL = 0.957. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			no index case with more than 1 variant and heterozygous phenotype was identified, so not met
PVS1			variant is missense and not in initiation codon, so not met

Curation History 

Showing 1 to 2 of 2 rows

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