

Variant: *NM_000527.5(LDLR):c.268G>A (p.Asp90Asn)*

Version: 1.0

CA042604 [↗](#)

251105 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 5eb6bd54-ae4e-4b33-9b7c-222467e9a8f8

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HGVS expressions

NM_000527.5(LDLR):c.268G>A (p.Asp90Asn)

NM_000527.5:c.268G>A

NC_000019.10:g.11102741G>A

CM000681.2:g.11102741G>A

NC_000019.9:g.11213417G>A

CM000681.1:g.11213417G>A

NC_000019.8:g.11074417G>A

NG_009060.1:g.18361G>A

ENST00000252444.10:c.526G>A

ENST00000559340.2:c.268G>A

ENST00000560467.2:c.268G>A

ENST00000558518.6:c.268G>A

ENST00000252444.9:c.522G>A

ENST00000455727.6:c.268G>A

ENST00000535915.5:c.190+2396G>A

ENST00000545707.5:c.268G>A

ENST00000557933.5:c.268G>A

ENST00000557958.1:n.354G>A

ENST00000558013.5:c.268G>A

ENST00000558518.5:c.268G>A

NM_000527.4:c.268G>A

NM_001195798.1:c.268G>A

NM_001195799.1:c.190+2396G>A

NM_001195800.1:c.268G>A

NM_001195803.1:c.268G>A

NM_001195798.2:c.268G>A

NM_001195799.2:c.190+2396G>A

NM_001195800.2:c.268G>A

NM_001195803.2:c.268G>A

Pathogenic

Met criteria codes **6**

PS3_Moderate

PS4_Moderate

PM5_Strong

PP4

PM2

PP1_Moderate

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 20 [Criteria Specifications for this VCEP](#)

BS2 BS1 BS4 BS3 BP4 BP3
BP1 BP2 PVS1 BP5 BP7
BA1 PS1 PS2 PP2 PP3
PM6 PM1 PM3 PM4

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.268G>A (p.Asp90Asn) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM5_Strong, PM2, PP1_Moderate, PS3_Moderate, PS4_Moderate 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: PM5_strong - there are 4 other missense variants is the same codon: - 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 - NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) - Pathogenic by these guidelines --- There are 2 variants classified as Pathogenic, so PM5_Strong is met. PP1_moderate - Variant segregates with phenotype in 4 informative meioses from different labs: - 1 unaffected family member does not have the variant, from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); - 3 informative meioses from 1 family from PMID 12837857 (Chang et al. 2003): 1 relative has the variant and phenotype (III:1), plus 2 relatives do not have the variant and do not have the phenotype (II:1 and III:2) 4 informative meioses, so PP1_Moderate is met. PM2 - PopMax MAF = 0.0008019 (0.08019%) in East Asian (gnomAD v2.1.1), but this is a founder variant in East Asian populations, so PM2 can be met in this instance. PS3_moderate - Level 2 FS: Chang et al., 2003 (PMID:12837857): Heterologous cells (COS-7), FACS assays - results: 55% LDLR cell surface and uptake. Binding is not studied, so not all cycle is studied (level 2 and not level 1) ---- functional study is consistent with damaging effect, activity is below 70% of wild-type, so PS3_Moderate is met. PS4_moderate - variant meets PM2 and was identified in: - 1 index case who fulfills Simon Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 3 unrelated index cases, all with Dutch lipid clinic network >=6, from Robarts Research Institute, Canada; - at least 1 index case with DLCN score of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583645.1 in ClinVar), France; - 1 index case who fulfills SB criteria of at least possible FH from PMID 9259195 (Day et al., 1997), UK; - 1 index case who fulfills SB criteria of at least possible FH from PMID 25962062 (Han et al., 2015), Korea; - 2 unrelated index cases who fulfill SB criteria of possible FH (TC>8mmol/L, plus CAD) from PMID 12837857 (Chang et al., 2003), Taiwan, China; 9 cases, so PS4_Moderate is met. PP4 - variant meets PM2 and was identified in 9 unrelated index cases from different labs (see PS4 for details), so PP4 is met.

Met criteria codes

PS3_Moderate	 	Level 2 FS: Chang et al., 2003 (PMID:12837857): Heterologous cells (COS-7), FACS assays - results: 55% LDLR cell surface and uptake. Binding is not studied, so not all cycle is studied (level 2 and not level 1) ---- functional study is consistent with damaging effect, activity is below 70% of wild-type, so PS3_Moderate is met
PS4_Moderate	 	variant meets PM2 and was identified in: - 1 index case who fulfills Simon Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 3 unrelated index cases, all with Dutch lipid clinic network >=6, from Robarts Research Institute, Canada; - at least 1 index case with DLCN score of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583645.1 in ClinVar), France; - 1 index case who fulfills SB criteria of at least possible FH from PMID 9259195 (Day et al., 1997), UK; - 1 index case who fulfills SB criteria of at least possible FH from PMID 25962062 (Han et al., 2015), Korea; - 2 unrelated index cases who fulfill SB criteria of possible FH (TC>8mmol/L, plus CAD) from PMID 12837857 (Chang et al., 2003), Taiwan, China (- at least 1 index case with Simon-Broome criteria of at

least possible FH from PMID 21376320 (Chiou et al., 2011), Taiwan, China <-- do not consider to avoid double counting;) 9 cases, so PS4_Moderate is met

PM5_Strong			4 other missense variants is the same codon: - 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 - NM_000527.5(LDLR):c.270T>A (p.Asp90Glu) - Pathogenic by these guidelines There are 2 variants classified as Pathogenic, so PM5_Strong is met
PP4			variant meets PM2 and was identified in: - 1 index case who fulfills Simon Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 3 unrelated index cases, all with Dutch lipid clinic network >=6, from Robarts Research Institute, Canada; - at least 1 index case with DLCN score of definite FH from U4M - Lille University & CHRU Lille, Université de Lille - CHRU de Lille (SCV000583645.1 in ClinVar), France; - 1 index case who fulfills SB criteria of at least possible FH from PMID 9259195 (Day et al., 1997), UK; - 1 index case who fulfills SB criteria of at least possible FH from PMID 25962062 (Han et al., 2015), Korea; - 2 unrelated index cases who fulfill SB criteria of possible FH (TC>8mmol/L, plus CAD) from PMID 12837857 (Chang et al., 2003), Taiwan, China so PP4 is met
PM2			PopMax MAF = 0.0008019 (0.08019%) in East Asian (gnomAD v2.1.1), but this is a founder variant in East Asian populations, so PM2 can be met in this instance
PP1_Moderate			Variant segregates with phenotype in 4 informative meiosis from different labs: - 1 unaffected family member does not have the variant, from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); - 3 informative meiosis from 1 family from PMID 12837857 (Chang et al. 2003): 1 relative has the variant and phenotype (III:1), plus 2 relatives do not have the variant and do not have the phenotype (II:1 and III:2) 4 informative meiosis, so PP1_Moderate is met

Not Met criteria codes

BS2			not identified in normolipidemic individuals, so not met
BS1			FAF = 0.0004174 (0.04174%) in East Asian exomes (gnomAD v2.1.1). It is not above 0.2%, so not met
BS4			Variant does not segregate with phenotype in 1 informative meiosis: 1 affected family member does not have the variant from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) -- not enough, so BS4 is not met
BS3			no level FS: Chang et al., 2003 (PMID:12837857): Heterologous cells (COS-7), FACS assays - results: 55% LDLR cell surface and uptake. Binding is not studied, so not all cycle is studied so BS3 is not met
BP4			REVEL = 0.738. It is not below 0.50, so BP4 is not met
BP3			no applicable
BP1			not applicable

BP2		✖	variant not identified in index cases with more than 1 variant, so not met
PVS1		✖	variant is missense and not in initiation codon, so not met
BP5		✖	not applicable
BP7		✖	variant is missense, so not met
BA1		✖	FAF = 0.0004174 (0.04174%) in East Asian exomes (gnomAD v2.1.1). It is not above 0.5%, so not met
PS1		✖	no other missense variant leads to the same amino acid change in the same codon, so not met
PS2		✖	no de novo occurrence
PP2		✖	not applicable
PP3		✖	REVEL = 0.738. It is not above 0.75, so splicing evaluation is needed: Functional data on splicing not available. A) not on limits B) does not create GT C) variant is exonic, there is no AG nearby, but there is a GT nearby: MES scores: variant cryptic = -0.00, wt cryptic = 5.51, canonical donor = 9.90. Variant cryptic score is 0, so it is not used. PP3 is not met
PM6		✖	no de novo occurrence
PM1		✖	variant does not meet PM2, is not in exon 4 and does not alter Cys, so not met
PM3		✖	variant not identified in index cases with more than 1 variant, so not met
PM4		✖	variant is missense, so not met

Curation History 		
Showing 1 to 1 of 1 rows		

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