

Variant: *NM_000527.5(LDLR):c.910G>A (p.Asp304Asn)*

Version: 1.0

CA023792 [↗](#)

3692 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 586da900-0f67-479c-89aa-50f096de6db6

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HGVS expressions

NM_000527.5:c.910G>A

NM_000527.5(LDLR):c.910G>A (p.Asp304Asn)

NC_000019.10:g.11107484G>A

CM000681.2:g.11107484G>A

NC_000019.9:g.11218160G>A

CM000681.1:g.11218160G>A

NC_000019.8:g.11079160G>A

NG_009060.1:g.23104G>A

ENST00000252444.10:c.1168G>A

ENST00000559340.2:c.910G>A

ENST00000560467.2:c.910G>A

ENST00000558518.6:c.910G>A

ENST00000252444.9:c.1164G>A

ENST00000455727.6:c.406G>A

ENST00000535915.5:c.787G>A

ENST00000545707.5:c.529G>A

ENST00000557933.5:c.910G>A

ENST00000558013.5:c.910G>A

ENST00000558518.5:c.910G>A

ENST00000558528.1:n.425G>A

ENST00000560467.1:c.510G>A

NM_000527.4:c.910G>A

NM_001195798.1:c.910G>A

NM_001195799.1:c.787G>A

NM_001195800.1:c.406G>A

NM_001195803.1:c.529G>A

NM_001195798.2:c.910G>A

NM_001195799.2:c.787G>A

NM_001195800.2:c.406G>A

NM_001195803.2:c.529G>A

Pathogenic

Met criteria codes **7**

PP1_Strong

PS4

PS3_Moderate

PP3

PP4

PM2

PM3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes 15

BP7 BP4 BP2 PS1 PS2
PM6 PM1 PM5 PM4 PVS1
BA1 BS2 BS1 BS4 BS3

Evidence Links 0

[Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.910G>A (p.Asp304Asn) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PS3_moderate, PS4, PP1_strong, PM3 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: PM2 - PopMax MAF = 0.0001203 (0.01203%) in African/African American genomes (gnomAD v2.1.1), so PM2 is Met. PP3 - REVEL = 0.883. It is above 0.75, so PP3 is Met. PS3_moderate - 2 Level 2 assays performed by different labs: PMID 2088165: Homozygous patient cells, 125I-LDL assays - result - 5-15% LDLR activity. PMID 6438436: Homozygous patient cells, 125I-LDL assays - result - 5-10% LDLR activity. 2 Level 3 assays performed by different labs: PMID 4061492: Heterozygous patient cells, 125I-LDL assays - result - 20-30% LDLR activity PMID 6438436: Heterozygous patient cells, 125I-LDL assays - result - 25-50% LDLR activity ---- all functional studies are consistent with damaging effect, so PS3_Moderate is Met. PS4 - Variant meets PM2 and is identified in at least 14 unrelated index cases: 4 index cases who fulfill Simon-Broome criteria for FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 7 unrelated index cases who fulfill Simon-Broome criteria for FH from Malaysia (Al-Khateeb et al, 2011) (PMID: 21418584); 1 index case who fulfills modified Simon-Broome criteria for FH (pretreatment LDL-C >95th percentile for age and sex, with (1) tendon xanthoma (proband or first-degree relative) or (2) either first-degree relative with premature CHD (<55 years of age in men or 65 years of age in women) or pretreatment LDL-C >95th percentile for age and sex) from Dallas, TX, USA (Ahmad et al, 2011) (PMID: 23064986); 1 index case who fulfils Simon-Broome criteria from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996); and 1 index case with clinical diagnosis of FH (based on (1) a plasma LDL cholesterol concentration above the 95th percentile for age and sex and (2) the presence of xanthoma or coronary heart disease in the proband or at least one first degree relative with type IIa hypercholesterolemia, xanthoma, or CVD) from France (Amsellem et al, 2002) (PMID: 12436241), so PS4 is Met. PP1_strong - Variant segregates with FH phenotype in at least 6 informative meioses from 3 families from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation): 6 affected family members have the variant, so PP1_Strong is Met. PM3 - Variant meets PM2 and is identified in an index case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with homozygous FH phenotype (14.9 mmol/L) and LDLR c.761A>C/p.(Gln254Pro), classified as Likely pathogenic by these guidelines, in trans, so PM3 is Met. PP4 - Variant meets PM2 and is identified in at least 14 unrelated index cases as described in PS4, PP4 is Met.

Met criteria codes

PP1_Strong			Variant segregates with FH phenotype in at least 6 informative meioses from 3 families from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation): 6 affected family members have the variant, so PP1_Strong is Met.
PS4			Variant meets PM2 and is identified in at least 14 unrelated index cases: 4 index cases who fulfill Simon-Broome criteria for FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 7 unrelated index cases who fulfill Simon-Broome criteria for FH from Malaysia (Al-Khateeb et al, 2011) (PMID: 21418584); 1 index case who fulfills modified Simon-Broome criteria for FH (pretreatment LDL-C >95th percentile for age and sex, with (1) tendon xanthoma (proband or first-degree relative) or (2) either first-degree relative with premature CHD (<55 years of age in men or 65 years of age in women) or pretreatment LDL-C >95th percentile for age and sex) from Dallas, TX, USA (Ahmad et al, 2011) (PMID: 23064986); 1 index case who fulfils Simon-Broome criteria from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996); and 1 index case with

clinical diagnosis of FH (based on (1) a plasma LDL cholesterol concentration above the 95th percentile for age and sex and (2) the presence of xanthoma or coronary heart disease in the proband or at least one first degree relative with type IIa hypercholesterolemia, xanthoma, or CVD) from France (Amsellem et al, 2002) (PMID: 12436241), so PS4 is Met.			
PS3_Moderate			2 Level 2 assays performed by different labs: PMID 2088165: Homozygous patient cells, 125I-LDL assays - result - 5-15% LDLR activity. PMID 6438436: Homozygous patient cells, 125I-LDL assays - result - 5-10% LDLR activity. 2 Level 3 assays performed by different labs: PMID 4061492: Heterozygous patient cells, 125I-LDL assays - result - 20-30% LDLR activity PMID 6438436: Heterozygous patient cells, 125I-LDL assays - result - 25-50% LDLR activity ---- all functional studies are consistent with damaging effect, so PS3_Moderate is Met.
PP3			REVEL = 0.883. It is above 0.75, so PP3 is Met.
PP4			Variant meets PM2 and is identified in at least 14 unrelated index cases: 4 index cases who fulfill Simon-Broome criteria for FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 7 unrelated index case who fulfill Simon-Broome criteria for FH from Malaysia (Al-Khateeb et al, 2011) (PMID: 21418584); 1 index case who fulfills modified Simon-Broome criteria for FH (pretreatment LDL-C >95th percentile for age and sex, with (1) tendon xanthoma (proband or first-degree relative) or (2) either first-degree relative with premature CHD (<55 years of age in men or 65 years of age in women) or pretreatment LDL-C >95th percentile for age and sex) from Dallas, TX, USA (Ahmad et al, 2011) (PMID: 23064986); 1 index case who fulfils Simon-Broome criteria from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996); and 1 index case with clinical diagnosis of FH (based on (1) a plasma LDL cholesterol concentration above the 95th percentile for age and sex and (2) the presence of xanthoma or coronary heart disease in the proband or at least one first degree relative with type IIa hypercholesterolemia, xanthoma, or CVD) from France (Amsellem et al, 2002) (PMID: 12436241), so PP4 is Met.
PM2			PopMax MAF = 0.0001203 (0.01203%) in African/African American genomes (gnomAD v2.1.1), so PM2 is Met.
PM3			Variant meets PM2 and is identified in an index case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) with homozygous FH phenotype (14.9 mmol/L) and LDLR c.761A>C/p.(Gln254Pro), classified as Likely pathogenic by these guidelines, in trans, so PM3 is Met.

Not Met criteria codes

BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.883. It is not below 0.50, so BP4 is Not Met.
BP2			The index case has homozygous FH phenotype (14.9 mmol/L), so BP2 is Not Met.
PS1			There is no other missense variants in the same codon, so PS1 is Not Met.
PS2			No evidence added, so PS2 is Not Met.
PM6			No evidence added, so PM6 is Not Met.

PM1		✖	Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM5		✖	4 other missense variants in the same codon: - NM_000527.5(LDLR):c.910G>C (p.Asp304His) (ClinVar ID 440612) - VUS by these guidelines - NM_000527.5(LDLR):c.911A>T (p.Asp304Val) (ClinVar ID 440613) - VUS by these guidelines - NM_000527.5(LDLR):c.912C>G (p.Asp304Glu) (ClinVar ID 226336) - Likely pathogenic by these guidelines - NM_000527.5(LDLR):c.910G>T (p.Asp304Tyr) (ClinVar ID 251517) - Likely pathogenic by these guidelines There is no variants in the same codon classified as Pathogenic by these guidelines, so PM5 is Not Met.
PM4		✖	Variant meets PM2 but is missense, so PM4 is Not Met.
PVS1		✖	Variant is missense, so PVS1 is Not Met.
BA1		✖	FAF = 0.00004089 (0.004089%) in African/African American genomes (gnomAD v2.1.1), so BA1 is Not Met.
BS2		✖	Not observed in 100 normolipidemic individuals from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), so BS2 is Not Met.
BS1		✖	FAF = 0.00004089 (0.004089%) in African/African American genomes (gnomAD v2.1.1), so BS1 is Not Met.
BS4		✖	None non-segregations reported, so BS4 is Not Met.
BS3		✖	2 Level 2 assays performed by different labs: PMID 2088165: Homozygous patient cells, 125I-LDL assays - result - 5-15% LDLR activity. PMID 6438436: Homozygous patient cells, 125I-LDL assays - result - 5-10% LDLR activity. 2 Level 3 assays performed by different labs: PMID 4061492: Heterozygous patient cells, 125I-LDL assays - result - 20-30% LDLR activity PMID 6438436: Heterozygous patient cells, 125I-LDL assays - result - 25-50% LDLR activity ---- all functional studies are consistent with damaging effect, so BS3 is Not Met.

Curation History 		
Showing 1 to 1 of 1 rows		

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