

Variant: *NM_000527.5(LDLR):c.912C>G (p.Asp304Glu)*

Version: 1.0

CA10576290 [↗](#)

226336 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: f3d3ae92-0a85-414d-b0ba-b872f7a9c1b3

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HGVS expressions

NM_000527.5(LDLR):c.912C>G (p.Asp304Glu)

NM_000527.5:c.912C>G

NC_000019.10:g.11107486C>G

CM000681.2:g.11107486C>G

NC_000019.9:g.11218162C>G

CM000681.1:g.11218162C>G

NC_000019.8:g.11079162C>G

NG_009060.1:g.23106C>G

ENST00000252444.10:c.1170C>G

ENST00000559340.2:c.912C>G

ENST00000560467.2:c.912C>G

ENST00000558518.6:c.912C>G

ENST00000252444.9:c.1166C>G

ENST00000455727.6:c.408C>G

ENST00000535915.5:c.789C>G

ENST00000545707.5:c.531C>G

ENST00000557933.5:c.912C>G

ENST00000558013.5:c.912C>G

ENST00000558518.5:c.912C>G

ENST00000558528.1:n.427C>G

ENST00000560467.1:c.512C>G

NM_000527.4:c.912C>G

NM_001195798.1:c.912C>G

NM_001195799.1:c.789C>G

NM_001195800.1:c.408C>G

NM_001195803.1:c.531C>G

NM_001195798.2:c.912C>G

NM_001195799.2:c.789C>G

NM_001195800.2:c.408C>G

NM_001195803.2:c.531C>G

Likely Pathogenic

Met criteria codes **5**

PS4_Supporting

PP3

PP4

PM5

PM2

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Not Met criteria codes **17**

BA1 BP7 BP4 BP2 BS2 BS1
BS4 BS3 PP1 PM1 PM3
PM4 PM6 PVS1 PS1 PS2
PS3

[Criteria Specifications for this VCEP](#)

Evidence Links **0**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.912C>G (p.Asp304Glu) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP3, PM5, PS4_supporting, 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 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. PP3 - REVEL = 0.871. It is above 0.75, so PP3 is Met. PM5 - 4 other missense variants in the same codon: - NNM_000527.5(LDLR):c.910G>A (p.Asp304Asn) (ClinVar ID 3692) - Pathogenic by these guidelines - 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.910G>T (p.Asp304Tyr) (ClinVar ID 251517) - Likely pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is Met. PS4_supporting - Variant meets PM2 and is identified in at least 2 unrelated index cases: 1 index case who fulfils DLCN>6 criteria for FH from Robarts Research Institute and 1 index case who fulfils Simon Broome criteria for FH from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996), so PS4_Supporting is Met. PP4 - Variant meets PM2 and is identified in at least 2 unrelated index cases as described in PS4, PP4 is Met.

Met criteria codes			
PS4_Supporting			Variant meets PM2 and is identified in at least 2 unrelated index cases: 1 index case who fulfils DLCN>6 criteria for FH from Robarts Research Institute and 1 index case who fulfils Simon Broome criteria for FH from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996), so PS4_Supporting is Met.
PP3			REVEL = 0.871. It is above 0.75, so PP3 is Met.
PP4			Variant meets PM2 and is identified in at least 2 unrelated index cases: 1 index case who fulfils DLCN>6 criteria for FH from Robarts Research Institute and 1 index case who fulfils Simon Broome criteria for FH from MRC Clinical Sciences Centre, London UK (Tosi et al, 2007)(PMID: 17094996), so PP4 is Met.
PM5			4 other missense variants in the same codon: - NNM_000527.5(LDLR):c.910G>A (p.Asp304Asn) (ClinVar ID 3692) - Pathogenic by these guidelines - 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.910G>T (p.Asp304Tyr) (ClinVar ID 251517) - Likely pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is Met.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
Not Met criteria codes			
BA1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.871. It is not below 0.50, so BP4 is Not Met.
BP2			not identified in index case with more than 1 variant, so BP2 is Not Met.

BS2			Not observed in controls (although the number of controls tested is not specified), so BS2 is Not Met.
BS1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BS1 is Not Met.
BS4			No family members were identified, so BS4 is Not Met.
BS3			There is no functional studies reported for this variant, so BS3 is Not Met.
PP1			No family members were identified, so PP1 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3			Not identified in index case with more than 1 variant, so PM3 is Not Met.
PM4			Variant meets PM2 but is missense, so PM4 is Not Met.
PM6			No evidence added, so PM6 is Not Met.
PVS1			Variant is missense, so PVS1 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.
PS3			There is no functional studies reported for this variant, so PS3 is Not Met.

Curation History 		
owing 1 to 1 of 1 rows		

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