

Variant: NM_000527.5(LDLR):c.1474G>C (p.Asp492His)

Version: 1.0

CA10585474 [↗](#)

251864 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 407b6edd-ffe7-4abe-9722-8d4bfc2c0ea1

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HGVS expressions

NM_000527.5:c.1474G>C

NM_000527.5(LDLR):c.1474G>C (p.Asp492His)

NC_000019.10:g.11113650G>C

CM000681.2:g.11113650G>C

NC_000019.9:g.11224326G>C

CM000681.1:g.11224326G>C

NC_000019.8:g.11085326G>C

NG_009060.1:g.29270G>C

ENST00000252444.10:c.1732G>C

ENST00000559340.2:c.1474G>C

ENST00000560467.2:c.1354G>C

ENST00000558518.6:c.1474G>C

ENST00000252444.9:c.1728G>C

ENST00000455727.6:c.970G>C

ENST00000535915.5:c.1351G>C

ENST00000545707.5:c.1093G>C

ENST00000557933.5:c.1474G>C

ENST00000558013.5:c.1474G>C

ENST00000558518.5:c.1474G>C

ENST00000559340.1:c.195G>C

NM_000527.4:c.1474G>C

NM_001195798.1:c.1474G>C

NM_001195799.1:c.1351G>C

NM_001195800.1:c.970G>C

NM_001195803.1:c.1093G>C

NM_001195798.2:c.1474G>C

NM_001195799.2:c.1351G>C

NM_001195800.2:c.970G>C

NM_001195803.2:c.1093G>C

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM5 PM2

Not Met criteria codes 1

PS3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information 

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1474G>C (p.Asp492His) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PM5, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 7 November 2023. The supporting evidence is as follows: PM2: PopMax MAF=0.00002 in Non-Finnish European population in gnomAD (gnomAD v2.1.1). PP3: REVEL=0.993. PM5: Two other missense variants in the same codon: NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn), ClinVar 161285, classified as Pathogenic by these guidelines; NM_000527.5(LDLR):c.1475A>G (p.Asp492Gly), ClinVar 251865, classified as Likely Pathogenic by these guidelines. Therefore PM5 is met. PP4: Variant meets PM2 and is identified in 1 index case who fulfils Simon Broome criteria for FH diagnosis after alternative causes of high cholesterol were excluded, reported in PMID 10208479 (Heath et al., 1999), from University College London Medical School, UK.

Met criteria codes

PP3			REVEL=0.993.
PP4			Variant meets PM2 and is identified in 1 index case who fulfils Simon Broome criteria for FH diagnosis after alternative causes of high cholesterol were excluded, reported in PMID 10208479 by Heath et al, 1999, from University College London Medical School, UK.
PM5			Two other missense variants in the same codon: NM_000527.5(LDLR):c.1474G>A(p.Asp492Asn (ClinVarID 161285) classified as Pathogenic by these guidelines. NM_000527.5(LDLR):c.1475A>G(p.Asp492Gly) (ClinVarID 251865) classified as Likely Pathogenic by these guidelines. Therefore PM5 is met.
PM2			PopMax MAF=0.00002 in Non-Finnish European population in gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PS3			Functional data is not available.
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Curation History [↗](#)

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