

Variant: *NM_000527.5(LDLR):c.1916T>A (p.Val639Asp)*

Version: 1.0

CA023607 [↗](#)

200922 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 76d64ef3-260a-4724-8567-92a57e6c92d3

Approved on: 2025/1/31

Published on: 2025/3/9

HGVS expressions

NM_000527.5:c.1916T>A

NM_000527.5(LDLR):c.1916T>A (p.Val639Asp)

NC_000019.10:g.11120162T>A

CM000681.2:g.11120162T>A

NC_000019.9:g.11230838T>A

CM000681.1:g.11230838T>A

NC_000019.8:g.11091838T>A

NG_009060.1:g.35782T>A

ENST00000252444.10:c.2174T>A

ENST00000559340.2:c.1776T>A

ENST00000560467.2:c.1796T>A

ENST00000558518.6:c.1916T>A

ENST00000252444.9:c.2170T>A

ENST00000455727.6:c.1412T>A

ENST00000535915.5:c.1793T>A

ENST00000545707.5:c.1535T>A

ENST00000557933.5:c.1916T>A

ENST00000558013.5:c.1916T>A

ENST00000558518.5:c.1916T>A

ENST00000559340.1:c.497T>A

NM_000527.4:c.1916T>A

NM_001195798.1:c.1916T>A

NM_001195799.1:c.1793T>A

NM_001195800.1:c.1412T>A

NM_001195803.1:c.1535T>A

NM_001195798.2:c.1916T>A

NM_001195799.2:c.1793T>A

NM_001195800.2:c.1412T>A

NM_001195803.2:c.1535T>A

Pathogenic

Met criteria codes **5**

PP1 PP4 PM3 PM2 PS4

Not Met criteria codes **17**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PP3

BA1

PM1

PM5

PM4

PM6

PVS1

BS2

BS1

BS4

BS3

PS1

PS2

PS3

BP7

BP4

BP2

Evidence Links 0

- [Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.2](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1916T>A (p.Val639Asp) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PM2, PM3, PP1 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on January 31, 2025. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.1.0). PS4, PP4: Variant meets PM2 and is identified in 10 unrelated index cases from different labs (2 cases with DLCN>=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, France; 1 case with DLCN>=6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case with DLCN>=6 from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; 1 case with DLCN=9 from Germany (PMID 11462246 - Nauck et al., 2001); at least 1 case with definite FH from The Netherlands (PMID 16250003 - Fouchier et al., 2005); 1 case with DLCN>=6 from Argentina (PMID 28502510 - Bañares et al., 2017); 1 case with Simon Broome criteria for FH from Poland (PMID 35741760 - Rutkowska et al. 2022); 1 true homozygous case with clinical diagnosis of HoFH from Spain (PMID 27784735); 1 case with homozygous FH phenotype (LDL-C= 13.52 mmol/L) from Germany (PMID 29502162). PP1: Variant segregates with FH phenotype in 2 informative meioses from 1 family from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic: 2 affected family members have the variant. PM3: Variant meets PM2 and is identified in 1 index case with homozygous FH phenotype (LDL-C=11.7 mmol/L) and LDLR c. 2043C>T/p.(Cys681*), classified as Pathogenic by these guidelines, in trans, from Germany (PMID 29502162 - Klaus et al., 2018).

Met criteria codes

PP1			Variant segregates with FH phenotype in 3 informative meioses from 2 families from different labs: 2 affected family members have the variant from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) and 1 affected family member has the variant (PMID: 35222550), so PP1 is met.
PP4			Variant meets PM2 and is identified in 10 unrelated index cases from different labs (2 cases with DLCN>=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies; 1 case with DLCN>=6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case with DLCN>=6 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with DLCN=9 from Germany (PMID: 11462246); at least 1 case with definite heterozygous hypercholesterolemia from The Netherlands (PMID: 16250003); 1 case with DLCN>=6 from Argentina (PMID: 28502510); 1 case with Simon Broome criteria for FH from Poland (PMID: 35741760); 1 true homozygous with clinical diagnosis of HoFH from Spain (PMID: 27784735); 1 index case with homozygous FH phenotype (LDL-C= 13.52 mmol/L) from Germany, after alternative causes of high cholesterol were excluded, so PP4 is met.
PM3			Variant meets PM2 and is identified in 1 index case with homozygous FH phenotype (LDL-C=11.7 mmol/L) and LDLR c. 2043C>T/p.(Cys681*), classified as Pathogenic by these guidelines, in trans, from Germany, so PM3 is met.
PM2			This variant is absent from gnomAD (gnomAD v4.1.0), so PM2 is Met.

PS4			Variant meets PM2 and is identified in 10 unrelated index cases from different labs (2 cases with DLCN>=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies; 1 case with DLCN>=6 from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; 1 case with DLCN>=6 from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); 1 case with DLCN=9 from Germany (PMID: 11462246); at least 1 case with definite heterozygous hypercholesterolemia from The Netherlands (PMID: 16250003); 1 case with DLCN>=6 from Argentina (PMID: 28502510); 1 case with Simon Broome criteria for FH from Poland (PMID: 35741760); 1 true homozygous with clinical diagnosis of HoFH from Spain (PMID: 27784735); 1 index case with homozygous FH phenotype (LDL-C= 13.52 mmol/L) from Germany, so PS4 is met.
Not Met criteria codes			
PP3			REVEL = 0.713, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. A) variant not on limits B) does not create AG or GT C) no AG/GT nearby Variant is not predicted to alter splicing, so PP3 is Not Met.
BA1			This variant is absent from gnomAD (gnomAD v4.1.0), so BA1 is not met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residue, so PM1 is Not Met.
PM5			1 other missense variant in the same codon: - NM_000527.5(LDLR):c.1916T>G (p.Val639Gly) (ClinVar ID 252112) - Likely pathogenic by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.
BS2			Not detected in 100 normolipidemic individuals, so BS2 is not met.
BS1			This variant is absent from gnomAD (gnomAD v4.1.0), so BS1 is not met.
BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			There are no functional studies reported for this variant, so BS3 is not met.
PS1			No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PS3			There are no functional studies reported for this variant, so PS3 is not met.

BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.713, it is not below 0.50, so BP4 is not met.
BP2			Variant meets PM2 and is identified in 1 index case with homozygous FH phenotype (LDL-C=11.7 mmol/L) and LDLR c. 2043C>T/p.(Cys681*), classified as Pathogenic by these guidelines, in trans, from Germany, so BP2 is Not Met.

Curation History 		
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