

Variant: NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn)

Version: 1.0

CA023512 [↗](#)

161285 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 59719c7c-90ea-438f-bbc4-67a42598d0f2

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HGVS expressions

NM_000527.5(LDLR):c.1474G>A (p.Asp492Asn)

NM_000527.5:c.1474G>A

NC_000019.10:g.11113650G>A

CM000681.2:g.11113650G>A

NC_000019.9:g.11224326G>A

CM000681.1:g.11224326G>A

NC_000019.8:g.11085326G>A

NG_009060.1:g.29270G>A

ENST00000252444.10:c.1732G>A

ENST00000559340.2:c.1474G>A

ENST00000560467.2:c.1354G>A

ENST00000558518.6:c.1474G>A

ENST00000252444.9:c.1728G>A

ENST00000455727.6:c.970G>A

ENST00000535915.5:c.1351G>A

ENST00000545707.5:c.1093G>A

ENST00000557933.5:c.1474G>A

ENST00000558013.5:c.1474G>A

ENST00000558518.5:c.1474G>A

ENST00000559340.1:c.195G>A

NM_000527.4:c.1474G>A

NM_001195798.1:c.1474G>A

NM_001195799.1:c.1351G>A

NM_001195800.1:c.970G>A

NM_001195803.1:c.1093G>A

NM_001195798.2:c.1474G>A

NM_001195799.2:c.1351G>A

NM_001195800.2:c.970G>A

NM_001195803.2:c.1093G>A

Pathogenic

Met criteria codes **7**

PP1_Strong

PS3

PS4

PP3

PP4

PM2

PM3

Not Met criteria codes **1**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1474G>A (p.Asp492Asn) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PS4, PP1_Strong, PM2, PM3, 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=0.00011 in East Asian population in gnomAD (gnomAD v2.1.1). PP3: REVEL=0.918. PS3: Level 1 assays, heterologous cells (CHO) used for Western blot and flow cytometry, showing diminished LDLR expression, 70% LDL binding and 49% uptake, reported in PMID 32015373 (Galicia-Garcia et al., 2020), Universidad del Pais Vasco, Spain. PS4, PP4: Variant meets PM2 and is identified in at least 43 unrelated index cases fulfilling clinical criteria for FH reported in ClinGen VCI and PubMed: 1 case reported from Cardiovascular Research group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal; 1 case from PathWest Laboratory Medicine WA, Australia; 5 cases from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France; 2 cases from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory, USA; 2 cases from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca, Italy; 1 case from Robarts Research Institute, Canada; 6 cases from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies, APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière, France; 11 cases from University Hospital Brno, Czech Republic and PMID 22698793 (Tichý et al., 2012). There are at least 14 index cases fulfilling FH clinical criteria in PMID 9763532, 11737238, 12436241, 17094996, 17539906, 19318025, 19446849, 20538126, 26748104, 28965616, 29353225, 30592178, 32331935, 32977124. PP1_Strong: Variants segregates with FH phenotype in at least 28 informative meioses in 12 families from different labs (Cardiovascular Research group, Instituto Nacional de Saúde Doutor Ricardo Jorge, Portugal; University Hospital Brno, Czech Republic; PathWest Laboratory Medicine WA, Australia; Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France): 24 affected family members have the variant and 4 unaffected family members do not have the variant. PM3: 1 index case with HoFH phenotype (17 years female, LDL-C=12.44 mmol/L), also carries pathogenic LDLR p.Gly592Glu, confirmed in trans, reported from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic.

Met criteria codes

PP1_Strong	 	Variants segregates with FH phenotype in at least 28 informative meioses in 12 families, reported in ClinGen VCI. From Cardiovascular Research group, Instituto Nacional de Saude Doutor Ricardo Jorge, 1 affected relative tested positive for the variant. From University Hospital Brno, Czech Republic, 23 co-segregation in 8 families: 19 affected relatives tested posited and 4 unaffected tested negative for the variant. From PathWest Laboratory WA, 2 affected relatives tested positive in 1 family. From Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France, 2 affected relatives tested positive in 2 families.
PS3	 	PMID 32015373, level 1 assays, heterologous cells (CHO) used for western blot and flow cytometry, showing diminished LDLR expression, 70 % LDL binding and 49% uptake, reported by Galicia-Garcia et al, 2020, from Universidad del Pais Vasco, Spain.
PS4	 	Variant meets PM2 and is identified in at least 43 unrelated index cases reported in ClinGen VCI and PubMed. Fourteen cases fulfil DLCN criteria and four cases fulfil Simon Broome criteria for FH diagnosis reported in VCI. Of which, 1 case reported from Cardiovascular Research group, Instituto Nacional de Saude Doutor Ricardo Jorge; 1 case from PathWest Laboratory WA; 5 cases from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France; 2 cases from Mayo Clinic Atherosclerosis and Lipid Genomics Laboratory, USA; 2 cases from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca, Italy; 1 case from Robarts Research Institute, Canada; 6 cases from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des

Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France. In PMID 22698793 and in VCI, Tichy et al from University Hospital Brno, Czech Republic reported 11 unrelated HeFH cases fulfil DLCN≥6 and carry this variant. There are at least 14 additional index cases fulfil FH clinical criteria and carry this variant reported in PubMed. PMIDs for these publications are 9763532, 11737238, 12436241, 17094996, 17539906, 19318025, 19446849, 20538126, 26748104, 28965616, 29353225, 30592178, 32331935, 32977124.

PP3			REVEL=0.918.
PP4			Variant meets PM2 and is identified in >1 index cases who fulfil criteria for FH after alternative causes of high cholesterol were excluded.
PM2			PopMax MAF=0.00011 in East Asian population in gnomAD (gnomAD v2.1.1).
PM3			Reported in VCI from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation, Czech Republic, one index case with HoFH phenotype (17 years female, LDL-C=12.44 mmol/L) , also carries pathogenic LDLR: p.Gly592Glu, and two variants were confirmed in trans.

Not Met criteria codes

PM5			Two other missense variants in the same codon: NM_000527.5(LDLR):c.1474G>C(p.Asp492His (ClinVarID 251846) classified as Likely 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 not met.
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Curation History

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