

Variant: NM_000527.5(LDLR):c.1414G>T (p.Asp472Tyr)

Version: 1.0

CA023492 [↗](#)

183116 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 6909d1ea-eaea-4522-82c1-9b4834556e06

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HGVS expressions

NM_000527.5(LDLR):c.1414G>T (p.Asp472Tyr)

NM_000527.5:c.1414G>T

NC_000019.10:g.11113590G>T

CM000681.2:g.11113590G>T

NC_000019.9:g.11224266G>T

CM000681.1:g.11224266G>T

NC_000019.8:g.11085266G>T

NG_009060.1:g.29210G>T

ENST00000252444.10:c.1672G>T

ENST00000559340.2:c.1414G>T

ENST00000560467.2:c.1294G>T

ENST00000558518.6:c.1414G>T

ENST00000252444.9:c.1668G>T

ENST00000455727.6:c.910G>T

ENST00000535915.5:c.1291G>T

ENST00000545707.5:c.1033G>T

ENST00000557933.5:c.1414G>T

ENST00000558013.5:c.1414G>T

ENST00000558518.5:c.1414G>T

ENST00000559340.1:c.135G>T

ENST00000560467.1:c.894G>T

NM_000527.4:c.1414G>T

NM_001195798.1:c.1414G>T

NM_001195799.1:c.1291G>T

NM_001195800.1:c.910G>T

NM_001195803.1:c.1033G>T

NM_001195798.2:c.1414G>T

NM_001195799.2:c.1291G>T

NM_001195800.2:c.910G>T

NM_001195803.2:c.1033G>T

Pathogenic

Met criteria codes 5

PP1_StrongPS4PP4PS3_SupportingPM2

Not Met criteria codes 4

PP3PM3PM5BP4

Evidence Links 0

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

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_000527.4(LDLR):c.1414G>T (p.Asp472Tyr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PP1_Strong, PM2, PP4 and PS3_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 31 January 2025. The supporting evidence is as follows: PM2: PopMax MAF = 0.0001098 (0.01098%) in South Asian exomes+genomes (gnomAD v4.1.0). PS3_Supporting: Level 3 assay - PMID:25647241 (Thormaehlen et al., 2015): In vitro microscopy assays in HeLa cells- LDLR expression in the ER was reduced by 36% compared to the wild-type, and reduction of free cholesterol, which indicated an impact on either LDLR biosynthesis or turnover. PS4, PP4: Variant meets PM2 and is identified in 13 unrelated index cases (1 case fulfilling DLCN criteria ≥ 6 from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France; 3 cases fulfilling DLCN criteria ≥ 6 from Research Lab of Molecular Genetics of Lipid Metabolism, Department of Translational and Precision Medicine, Italy; 4 cases with MedPed criteria from PMID:22698793 (Tichý et al., 2012), Czech Republic; 3 cases with MedPed criteria from PMID:27824480 (Gabčová et al., 2017), Slovakia; 1 case with MedPed criteria from PMID:29870584 (Saracoglu et al., 2018), Turkey; 1 case fulfilling Japanese Atherosclerosis Society criteria from PMID: 36229376 (Tada et al., 2022), Japan). PP1_Strong - Variant segregates with FH phenotype in at least 6 informative meioses from 3 families from Research Lab of Molecular Genetics of Lipid Metabolism, Department of Translational and Precision Medicine, Italy, PMID 17196209 and 27542166: 5 affected family members have the variant and 1 unaffected family member does not have the variant.

Met criteria codes

PP1_Strong	i ✓	Variant segregates with FH phenotype in at least 6 informative meioses from 3 families from Research Lab of Molecular Genetics of Lipid Metabolism, Department of Translational and Precision Medicine, Italy, PMID 17196209 and 27542166: 5 affected family members have the variant and 1 unaffected family member does not have the variant.
PS4	i ✓	Variant meets PM2 and is identified in 13 unrelated index cases (1 case fulfilling DLCN criteria ≥ 6 from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France; 3 cases fulfilling DLCN criteria ≥ 6 from Research Lab of Molecular Genetics of Lipid Metabolism, Department of Translational and Precision Medicine, Italy; 4 cases with MedPed criteria from PMID:22698793 (Tichý et al., 2012), Czech Republic; 3 cases with MedPed criteria from PMID:27824480 (Gabčová et al., 2017), Slovakia; 1 case with MedPed criteria from PMID:29870584 (Saracoglu et al., 2018), Turkey; 1 case fulfilling Japanese Atherosclerosis Society criteria from PMID: 36229376 (Tada et al., 2022), Japan)
PP4	i ✓	Variant meets PM2 and is identified in 13 index cases who fulfill DLCN criteria ≥ 6/MedPed/Japanese Atherosclerosis Society criteria from Service de Biochimie de Biologie Moléculaire, Hospices Civils de Lyon, France; Research Lab of

Molecular Genetics of Lipid Metabolism, Department of Translational and Precision Medicine, Italy; PMID: 22698793; 27824480; 29870584 and 36229376; after alternative causes of high cholesterol were excluded.

PS3_Supporting			Level 3 assay - PMID 25647241: In vitro microscopy assays in HeLa cells- LDLR expression in the ER was reduced by 36% compared to the wild-type, and reduction of free cholesterol, which indicated an impact on either LDLR biosynthesis or turnover.
PM2			PopMax MAF = 0.0001098 (0.01098%) in South Asian exomes+genomes (gnomAD v4.1.0)

Not Met criteria codes

PP3			REVEL = 0.649, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. A) variant is not on limits. B) variant does not create AG/GT. C) there is an AG nearby. MES scores: variant cryptic site = 3.87, wt cryptic site = 2.79, canonical acceptor = 6.76. Ratio variant cryptic/wt cryptic score: $3.87/2.79 = 1.38$ --- it is above 1.1 Ratio variant cryptic/canonical acceptor score: $3.87/6.76 = 0.57$ --- it is not above 0.9 ---PP3 is not met.
PM3			Variant meets PM2 and is identified in an index case with homozygous FH phenotype (15 yo on apheresis for past 5 years) and LDLR c.1729T>G, p.Trp577Gly), classified as Pathogenic by these guidelines, from PMID: 37129685. However, untreated LDL level and data about cis/trans not available, so cannot apply PM3.
PM5			Missense variant at the same codon predicting a different amino acid change (Asp472Asn), but variant classified as of uncertain significance by these guidelines, so PM5 not met.
BP4			REVEL = 0.649, it is not below 0.50.

Curation History

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