

Variant: NM_000527.5(LDLR):c.1175G>A (p.Cys392Tyr)

Version: 1.0

CA16616209 [↗](#)

406166 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 16240091-5fc4-42a0-ae12-4d806e89a8c8

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HGVS expressions

NM_000527.5:c.1175G>A

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NC_000019.10:g.11111628G>A

CM000681.2:g.11111628G>A

NC_000019.9:g.11222304G>A

CM000681.1:g.11222304G>A

NC_000019.8:g.11083304G>A

NG_009060.1:g.27248G>A

ENST00000252444.10:c.1433G>A

ENST00000559340.2:c.1175G>A

ENST00000560467.2:c.1055G>A

ENST00000558518.6:c.1175G>A

ENST00000252444.9:c.1429G>A

ENST00000455727.6:c.671G>A

ENST00000535915.5:c.1052G>A

ENST00000545707.5:c.794G>A

ENST00000557933.5:c.1175G>A

ENST00000558013.5:c.1175G>A

ENST00000558518.5:c.1175G>A

ENST00000560173.1:n.174G>A

ENST00000560467.1:c.655G>A

NM_000527.4:c.1175G>A

NM_001195798.1:c.1175G>A

NM_001195799.1:c.1052G>A

NM_001195800.1:c.671G>A

NM_001195803.1:c.794G>A

NM_001195798.2:c.1175G>A

NM_001195799.2:c.1052G>A

NM_001195800.2:c.671G>A

NM_001195803.2:c.794G>A

Likely Pathogenic

Met criteria codes6

PS4_SupportingPM2PM1PP1PP3PP4

Not Met criteria codes16

BP7BP4BP2PM6PVS1PM3PM5PM4BA1PS1PS2PS3BS1BS4BS3BS2

Evidence Links0

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_000527.5(LDLR):c.1175G>A (p.Cys392Tyr) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM1, PM2, PP1, PP3, PP4 and PS4_Supporting 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). PP3: REVEL = 0.966. It is above 0.75. PM1: Variant meets PM2 and is missense in exon 4 and alters Cys392, one of the cysteine residues listed. PS4_Supporting, PP4: Variant meets PM2 and is identified in 2 unrelated index cases from different labs (1 case 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 Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia), after alternative causes of high cholesterol were excluded. PP1: Variant segregates with FH phenotype in 2 informative meiosis from 1 family from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia: 2 affected family members have the variant.

Met criteria codes

PS4_Supporting		✓	Variant meets PM2 and is identified in 2 unrelated index cases from different labs (1 case 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 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)), after alternative causes of high cholesterol were excluded, so PS4_Supporting is met.
PM2		✓	This variant is absent from gnomAD (gnomAD v4.1.0), so PM2 is Met.
PM1		✓	Variant meets PM2 and is missense in exon 4 and alters Cys392, one of the cysteine residues listed, so PM1 is met.
PP1		✓	Variant segregates with FH phenotype in 2 informative meiosis from 1 family from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA): 2 affected family members have the variant, so PP1 is met.
PP3		✓	REVEL = 0.966. It is above 0.75, so PP3 is met.
PP4		✓	Variant meets PM2 and is identified in 2 unrelated index cases from different labs (1 case 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 Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA)), after alternative causes of high cholesterol were excluded, so PP4 is met.

Not Met criteria codes

BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.966. It is not below 0.50, so BP4 is Not Met.
BP2			Not observed in trans with other LP/P variants, so BP2 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.
PM3			Not observed in trans with other LP/P variants, so PM3 is Not Met.
PM5			Variant meets PM1, so PM5 is not applicable.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.
BA1			This variant is absent from gnomAD (gnomAD v4.1.0), so BA1 is not met.
PS1			Variant meets PM1, so PS1 is not applicable.
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.
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.
BS2			Case-control data not reported, so BS2 is Not Met.

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