

Variant: *NM_000527.5(LDLR):c.974G>A (p.Cys325Tyr)*

Version: 1.0

CA10585234 [↗](#)

251580 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: c2fbb3ac-387a-4133-aa27-c2ba47bb55a8

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HGVS expressions

NM_000527.5:c.974G>A

NM_000527.5(LDLR):c.974G>A (p.Cys325Tyr)

NC_000019.10:g.11110685G>A

CM000681.2:g.11110685G>A

NC_000019.9:g.11221361G>A

CM000681.1:g.11221361G>A

NC_000019.8:g.11082361G>A

NG_009060.1:g.26305G>A

ENST00000252444.10:c.1232G>A

ENST00000559340.2:c.974G>A

ENST00000560467.2:c.941-829G>A

ENST00000558518.6:c.974G>A

ENST00000252444.9:c.1228G>A

ENST00000455727.6:c.470G>A

ENST00000535915.5:c.851G>A

ENST00000545707.5:c.593G>A

ENST00000557933.5:c.974G>A

ENST00000558013.5:c.974G>A

ENST00000558518.5:c.974G>A

ENST00000560467.1:c.541-829G>A

NM_000527.4:c.974G>A

NM_001195798.1:c.974G>A

NM_001195799.1:c.851G>A

NM_001195800.1:c.470G>A

NM_001195803.1:c.593G>A

NM_001195798.2:c.974G>A

NM_001195799.2:c.851G>A

NM_001195800.2:c.470G>A

NM_001195803.2:c.593G>A

Likely Pathogenic

Met criteria codes **6**

PS4_Moderate

PS3_Supporting

PP3

PP4

PM2

PM1

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. 974G>A (p.Cys325Tyr) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PM1, PS4_Moderate, PP3, PP4, PS3_Supporting,) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows: PM2 Met: This variant is absent in gnomAD (gnomAD v2.1.1). PP3 Met: REVEL = 0.977, which is above the threshold of 0.75. PM1 Met: The variant meets PM2, and alters Cys325, which is located in EGF-like 1 domain and is one of 60 highly conserved cysteine residues. PS3_Supporting Met: FACS assay using heterozygous patients’ lymphocytes (level 3 functional assay) showed 50-60% LDLR activity compared to wild type, from one research lab (CEINGE-Biotecnologie Avanzate, Napoli, Italy, PMID21865347). PP4 Met: This variant meets PM2 and is identified >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded. PS4_Moderate Met: Variant meets PM2 and is identified in 8 unrelated index cases. Five of the index cases fulfil DLCN criteria for FH from 5 different laboratories (1 case from Mayo Clinic Atherosclerosis and Lipid genomics Laboratory, LabID500068; 1 case from University of Genova-University of Modena and Reggio Emilia, Italy, PMID32977124; 1 case from Lipid Clinic, Fundación Jiménez Díaz, Spain, PMID19318025; 1 case from Centre for Heart Lung Innovation, University of British Columbia, Canada, PMID31345425; and 1case from Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Diseases, China, PMID30526649). One index case fulfil FH diagnosis criteria established by the Societa Italiana per lo Studio della Arteriosclerosi, CEINGE-Biotecnologie Avanzate, Napoli, Italy, PMID21865347. Two index cases fulfil Japanese FH guidelines, from Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan, PMID31491741. There are three other variants in the same codon: LDLR: NM_000527: c.973T>C (p.Cys325Arg), LDLR: NM_000527: c.974G>C (p.Cys325Ser), LDLR: NM_000527: c.974G>T (p.Cys325Phe), which are classified as Uncertain significance by these guidelines. Therefore PM5 is not met.

Met criteria codes

PS4_Moderate			Variant meets PM2 and is identified in 8 unrelated index cases. Five of the index cases fulfil DLCN criteria for FH from 5 different laboratories (1 case from Mayo Clinic Atherosclerosis and Lipid genomics Laboratory, LabID500068; 1 case from University of Genova-University of Modena and Reggio Emilia, Italy, PMID32977124; 1 case from Lipid Clinic, Fundación Jiménez Díaz, Spain, PMID19318025; 1 case from Centre for Heart Lung Innovation, University of British Columbia, Canada, PMID31345425; and 1case from Division of Dyslipidemia, State Key Laboratory of Cardiovascular Disease, Fu Wai Hospital, National Center for Cardiovascular Diseases, China, PMID30526649). One index case fulfil FH diagnosis criteria established by the Societa Italiana per lo Studio della Arteriosclerosi, CEINGE-Biotecnologie Avanzate, Napoli, Italy, PMID21865347. Two index cases fulfil Japanese FH guidelines, from Department of Molecular Innovation in Lipidology, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan, PMID31491741.
PS3_Supporting			FACS assay using heterozygous patients’ lymphocytes (level 3 functional assay) showed 50-60% LDLR activity compared to wild type, from one research lab (CEINGE-Biotecnologie Avanzate, Napoli, Italy, PMID21865347).
PP3			REVEL = 0.977, which is above the threshold of 0.75.
PP4			This variant meets PM2 and is identified >1 index cases who met clinical criteria for FH after alternative causes for high cholesterol were excluded.

PM2			This variant is absent in gnomAD (gnomAD v2.1.1).
PM1			The variant meets PM2, and alters Cys325, which is located in EGF-like 1 domain and is one of 60 highly conserved cysteine residues.
Not Met criteria codes			
PM5			There are three other variants in the same codon: LDLR: NM_000527: c.973T>C (p.Cys325Arg), LDLR: NM_000527: c.974G>C (p.Cys325Ser), LDLR: NM_000527: c.974G>T (p.Cys325Phe), which are classified as Uncertain significance by these guidelines. Therefore PM5 is not met.

Curation History 			
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