

Variant: NM_000527.5(LDLR):c.81C>G (p.Cys27Trp)

Version: 1.4

CA041664 [↗](#)

226304 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 1b6349ea-5843-44ac-bd0b-6dbe58fb0da4

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HGVS expressions

NM_000527.5(LDLR):c.81C>G (p.Cys27Trp)

NM_000527.5:c.81C>G

NC_000019.10:g.11100236C>G

CM000681.2:g.11100236C>G

NC_000019.9:g.11210912C>G

CM000681.1:g.11210912C>G

NC_000019.8:g.11071912C>G

NG_009060.1:g.15856C>G

ENST00000252444.10:c.339C>G

ENST00000559340.2:c.81C>G

ENST00000560467.2:c.81C>G

ENST00000558518.6:c.81C>G

ENST00000252444.9:c.335C>G

ENST00000455727.6:c.81C>G

ENST00000535915.5:c.81C>G

ENST00000545707.5:c.81C>G

ENST00000557933.5:c.81C>G

ENST00000557958.1:n.167C>G

ENST00000558013.5:c.81C>G

ENST00000558518.5:c.81C>G

ENST00000560502.5:n.167C>G

NM_000527.4:c.81C>G

NM_001195798.1:c.81C>G

NM_001195799.1:c.81C>G

NM_001195800.1:c.81C>G

NM_001195803.1:c.81C>G

NM_001195798.2:c.81C>G

NM_001195799.2:c.81C>G

NM_001195800.2:c.81C>G

NM_001195803.2:c.81C>G

Pathogenic

Met criteria codes 7

PS3_Moderate

PP1

PP3

PP4

PS4

PM2

PM1

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_000527.5(LDLR):c.81C>G (p.Cys27Trp) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PM1, PM2, PS3_Moderate, PP1, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 25 February 2022. The supporting evidence is as follows: PM2: PopMax MAF = 0.00003518 (0.004%) in European (non-Finnish) exomes (gnomAD v2.1.1). PP3: REVEL = 0.759. PM1: Variant meets PM2 and alters Cys27, one of the cysteine residues listed. PS3_Moderate: PMID:1301956 - Level 2 assay. - study on hmz patient's fibroblast cell, LDLR activity value range: 15-30%. PS4, PP4: Variant meets PM2 and is identified in >15 unrelated index cases fulfilling FH clinical criteria (1 case with possible FH by Simon Broome criteria from Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; 1 case with DLCN score >=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; 2 cases with DLCN score >=6 from Robarts Research Institute, Canada; 2 cases with DLCN score >=6 from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca, Italy; >10 cases from PMID: 1301956, 9259195, 11317361, 11668627, 14974088, 16250003, 23375686, 25463123, 27497240, 27824480, 31345425). PP1: Variant segregates with FH phenotype in at least 2 informative meioses from 2 families from different labs (Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca, Italy; Laboratory of Genetics and Molecular Cardiology, Brazil): 2 affected family members have the variant.

Met criteria codes

PS3_Moderate			Study of at least one part of the whole LDLR cycle in homozygous patient cultured cells resulting in 15-30% LDLR activity (PMID: 1301956).
PP1			Variant segregates with FH phenotype in at least 2 informative meioses from 2 families from different labs (Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca, Italy; Laboratory of Genetics and Molecular Cardiology, Brazil): 2 affected family members have the variant.
PP3			REVEL = 0.759. It is above 0.75
PP4			Variant meets PM2 and is identified in several index cases who fulfil SB/DLCN>6/MedPed/other criteria for FH from different labs (see PS4), after alternative causes of high cholesterol were excluded.
PS4			Variant meets PM2 and is identified in at >15 unrelated index cases who fulfil clinical criteria for FH (1 case from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation) or DLCN > 6 (1 case from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA); 2 cases from Robarts Research Institute; 2 cases from Research Lab of Molecular Genetics of Lipid Metabolism - Prof. M.Arca) -as well as >10 cases from (PMID:

1301956, 9259195, 11317361, 11668627, 14974088, 16250003, 23375686, 25463123, 27497240, 27824480, 31345425)

PM2			PopMax MAF = 0.00004 (0.004%) in European non-Finnish exomes (gnomAD v2.1.1).
PM1			Variant meets PM2 and is located in highly conserved Cystein 27.

Curation History

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