

Variant: *NM_000527.5(LDLR):c.241C>T (p.Arg81Cys)*

Version: 1.0

CA023666 [↗](#)

183083 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 91b21a4d-b55d-40a8-ab5f-5bacc76d8762

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HGVS expressions

NM_000527.5(LDLR):c.241C>T (p.Arg81Cys)

NM_000527.5:c.241C>T

NC_000019.10:g.11102714C>T

CM000681.2:g.11102714C>T

NC_000019.9:g.11213390C>T

CM000681.1:g.11213390C>T

NC_000019.8:g.11074390C>T

NG_009060.1:g.18334C>T

ENST00000252444.10:c.499C>T

ENST00000559340.2:c.241C>T

ENST00000560467.2:c.241C>T

ENST00000558518.6:c.241C>T

ENST00000252444.9:c.495C>T

ENST00000455727.6:c.241C>T

ENST00000535915.5:c.190+2369C>T

ENST00000545707.5:c.241C>T

ENST00000557933.5:c.241C>T

ENST00000557958.1:n.327C>T

ENST00000558013.5:c.241C>T

ENST00000558518.5:c.241C>T

NM_000527.4:c.241C>T

NM_001195798.1:c.241C>T

NM_001195799.1:c.190+2369C>T

NM_001195800.1:c.241C>T

NM_001195803.1:c.241C>T

NM_001195798.2:c.241C>T

NM_001195799.2:c.190+2369C>T

NM_001195800.2:c.241C>T

NM_001195803.2:c.241C>T

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PS3_Supporting PM2
PS4_Supporting

Not Met criteria codes 21

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PP1

PP2

BA1

PM6

BS1

BS4

BS3

PM1

PM3

PM5

PM4

BS2

BP5

BP7

BP4

BP3

BP1

BP2

PVS1

Evidence Links 0

- [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.241C>T (p.Arg81Cys) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PP4, PP3, PS4_supporting, and 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 - PopMax MAF = 0.00001758 (0.001758%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1). PP3 - REVEL = 0.817 PP4 - Variant meets PM2 and is identified 1 case with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge. PS3_supporting - Level 3 assay: PMID 25647241. HeLa cells, alternative microscopy assay, results - LDL-uptake 68%. PS4_supporting - Variant meets PM2 and is identified in 5 index cases (2 cases with DLCN criteria>=6 from in PMID: 33418990 (Meshkov et al., 2021); at least 1 case with DLCN definite in PMID: 11810272 (Fouchier et al., 2001); 1 case with DLCN definite in PMID: 9712531 (Nissen et al., 1998); 1 case with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge).

Met criteria codes

PP3			REVEL = 0.817
PP4			Variant meets PM2 and is identified 1 case with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge.
PS3_Supporting			Level 3 assay: PMID 25647241. HeLa cells, alternative microscopy assay, results - LDL-uptake 68%.
PM2			PopMax MAF = 0.00001758 (0.001758%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1)
PS4_Supporting			Variant meets PM2 and is identified in 5 index cases (2 cases with DLCN criteria>=6 from in PMID: 33418990 (Meshkov et al., 2021); at least 1 case with DLCN definite in PMID: 11810272 (Fouchier et al., 2001); 1 case with DLCN definite in PMID: 9712531 (Nissen et al., 1998); 1 case with Simon-Broome possible from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge).

Not Met criteria codes

PS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PP1			Only 1 documented case of segregation from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge.
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.242G>A (p.Arg81His)(ClinVar ID 924271) - Uncertain significance by these guidelines - NM_000527.5(LDLR):c.241C>A (p.Arg81Ser)(ClinVar ID 251088) - Uncertain significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4			

			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
Showing 1 to 1 of 1 rows		

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