

Variant: *NM_000527.5(LDLR):c.1784G>A (p.Arg595Gln)*

Version: 1.1

CA023585 [↗](#)

183126 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 812ea6ba-58f9-4dc4-b88d-13dc9626d34f

Approved on: 2022/2/2

Published on: 2022/7/11

HGVS expressions

NM_000527.5(LDLR):c.1784G>A (p.Arg595Gln)

NM_000527.5:c.1784G>A

NC_000019.10:g.11116937G>A

CM000681.2:g.11116937G>A

NC_000019.9:g.11227613G>A

CM000681.1:g.11227613G>A

NC_000019.8:g.11088613G>A

NG_009060.1:g.32557G>A

ENST00000252444.10:c.2042G>A

ENST00000559340.2:c.1705+725G>A

ENST00000560467.2:c.1664G>A

ENST00000558518.6:c.1784G>A

ENST00000252444.9:c.2038G>A

ENST00000455727.6:c.1280G>A

ENST00000535915.5:c.1661G>A

ENST00000545707.5:c.1403G>A

ENST00000557933.5:c.1784G>A

ENST00000558013.5:c.1784G>A

ENST00000558518.5:c.1784G>A

ENST00000559340.1:c.426+725G>A

NM_000527.4:c.1784G>A

NM_001195798.1:c.1784G>A

NM_001195799.1:c.1661G>A

NM_001195800.1:c.1280G>A

NM_001195803.1:c.1403G>A

NM_001195798.2:c.1784G>A

NM_001195799.2:c.1661G>A

NM_001195800.2:c.1280G>A

NM_001195803.2:c.1403G>A

Pathogenic

Met criteria codes **7**

PS4

PP3

PP4

PM3

PM5

PM2

PS3_Supporting

Not Met criteria codes **15**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BA1BS2BS1BS4BS3BP4

BP2PVS1BP7PS1PS2

PP1PM1PM4PM6

Evidence Links 0

- [Criteria Specification: ClinGen Familial Hypercholesterolemia Expert Panel Specifications to the ACMG/AMP Variant Classification Guidelines Version 1.1](#)
- [PDF](#)
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1784G>A (p.Arg595Gln) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM2, PP3, PM5, PS3_supporting, PS4, PP4, PM3) 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 = 0.0002389 (0.02389%) in European (Finnish) exomes+genomes (gnomAD v2.1.1), since this is a founder effect variant in Finnish population (PMID: 11585102) we can consider PopMax MAF = 0.00005012 (0.005012%) in East Asian exomes+genomes (gnomAD v2.1.1), so PM2 is Met. PP3 - REVEL = 0.956. It is above 0.75, so PP3 is Met. PM5 - 2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp) (ClinVar ID: 161290) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1784G>T (p.Arg595Leu) (ClinVar ID: 252029) - Likely pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is Met. PS3_supporting - Level 3 assay: PMID 11585102: Heterozygous patient cells, 125I-LDL assays - result - 70% LDL-LDLR binding, 54-49% LDL-LDLR uptake and degradation. ---- functional study is consistent with damaging effect, so PS3_Supporting is Met. PS4 - Variant meets PM2 and is identified in 11 unrelated index cases: 1 index case with Simon Broome definite criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 4 index cases with DLCN criteria for FH (LDL > 95th percentile and presence of tendon xanthomas) from Finland (PMID: 11585102), 1 index case with FH criteria suggested by the Japan Atherosclerosis Society (TC > 260 mg/dL with tendon xanthomas OR TC > 260 mg/dL and TC > 260 mg/dL with tendon xanthomas in first or second degree relatives) from Japan (PMID: 18718593), 1 index case with DLCN criteria for FH (score=8) from Sweden (PMID: 29974534), 1 index case with DLCN criteria for FH (score>=6) from Argentina (PMID: 30270055), 2 index cases with DLCN criteria for FH (score>=6) from Russia (PMID: 33418990), 1 index case with homozygous FH phenotype (LDL = 16 mmol/L) from The Netherlands (PMID: 24585268), so PS4 is Met. PP4 - Variant meets PM2 and is identified in 11 unrelated index cases as described before, so PP4 is Met. PM3 - Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL = 16 mmol/L) and LDLR variant c.(1705+1_1706-1)(*2514_?)del (described as 16kb deletion exon 12-18) (PMID: 24585268), classified as Pathogenic by these guidelines, in trans, so PM3 is Met.

Met criteria codes

PS4			Variant meets PM2 and is identified in 11 unrelated index cases: 1 index case with Simon Broome definite criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 4 index cases with DLCN criteria for FH (LDL > 95th percentile and presence of tendon xanthomas) from Finland (PMID: 11585102), 1 index case with FH criteria suggested by the Japan Atherosclerosis Society (TC > 260 mg/dL with tendon xanthomas OR TC > 260 mg/dL and TC > 260 mg/dL with tendon xanthomas in first or second degree relatives) from Japan (PMID: 18718593), 1 index case with DLCN criteria for FH (score=8) from Sweden (PMID: 29974534), 1 index case with DLCN criteria for FH (score>=6) from Argentina (PMID: 30270055), 2 index cases with DLCN criteria for FH (score>=6) from Russia (PMID: 33418990), 1 index case with homozygous FH phenotype (LDL = 16 mmol/L) from The Netherlands (PMID: 24585268), so PS4 is Met.
PP3			REVEL = 0.956. It is above 0.75, so PP3 is Met.
PP4			Variant meets PM2 and is identified in 11 unrelated index cases: 1 index case with Simon Broome definite criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), 4 index cases with

DLCN criteria for FH (LDL > 95th percentile and presence of tendon xanthomas) from Finland (PMID: 11585102), 1 index case with FH criteria suggested by the Japan Atherosclerosis Society (TC > 260 mg/dL with tendon xanthomas OR TC > 260 mg/dL and TC > 260 mg/dL with tendon xanthomas in first or second degree relatives) from Japan (PMID: 18718593), 1 index case with DLCN criteria for FH (score=8) from Sweden (PMID: 29974534), 1 index case with DLCN criteria for FH (score>=6) from Argentina (PMID: 30270055), 2 index cases with DLCN criteria for FH (score>=6) from Russia (PMID: 33418990), 1 index case with homozygous FH phenotype (LDL = 16 mmol/L) from The Netherlands (PMID: 24585268), so PP4 is Met.

PM3			Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL = 16 mmol/L) and LDLR variant c.(1705+1_1706-1)_(*2514_?)del (described as 16kb deletion exon 12-18) (PMID: 24585268), classified as Pathogenic by these guidelines, in trans, so PM3 is Met.
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1783C>T (p.Arg595Trp) (ClinVar ID: 161290) - Pathogenic by these guidelines - NM_000527.5(LDLR):c.1784G>T (p.Arg595Leu) (ClinVar ID: 252029) - Likely pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines, so PM5 is Met.
PM2			PopMax MAF = 0.0002389 (0.02389%) in European (Finnish) exomes+genomes (gnomAD v2.1.1), since this is a founder effect variant in Finnish population (PMID: 11585102) we can consider PopMax MAF = 0.00005012 (0.005012%) in East Asian exomes+genomes (gnomAD v2.1.1), so PM2 is Met.
PS3_Supporting			Level 3 assay: PMID 11585102: Heterozygous patient cells, 125I-LDL assays - result - 70% LDL-LDLR binding, 54-49% LDL-LDLR uptake and degradation. ---- functional study is consistent with damaging effect, so PS3_Supporting is Met.

Not Met criteria codes

BA1			FAF = 0.000002920 (0.0002920%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so BA1 is not met.
BS2			Not observed in 100 normolipidemic individuals from the Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), so BS2 is Not Met.
BS1			FAF = 0.000002920 (0.0002920%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so BS1 is not met.
BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			Level 3 assays: PMID 25647241: HeLa-Kyoto cells and LDLR-GFP construct, laser-scanning confocal microscopy assays - result - assays only indicate expression of LDLR-GFP and uptake of DiI-LDL (not the whole LDLR cycle), so BS3_Supporting is not applicable.
BP4			REVEL = 0.956. It is not below 0.50, so BP4 is Not Met.
BP2			Variant meets PM2 and is identified in an index case with homozygous FH phenotype (LDL = 16 mmol/L) and LDLR variant c.(1705+1_1706-1)_(*2514_?)del (described as 16kb deletion exon 12-18) (PMID: 24585268), classified as Pathogenic by these guidelines, in trans, so BP2 is not met.

PVS1			Variant is missense, so PVS1 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
PS1			No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PP1			Segregation data not reported, so PP1 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.

Curation History 		
Showing 1 to 2 of 2 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.