The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
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HGVS expressions

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

PM3 PM5 PM2 PS4 PP3 PP4 PS3_Supporting

Not Met criteria codes 15

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PVS1 PM1 PM4 PM6 BA1
BS1 BS4 BS3 BS2 BP7 BP4
BP2 PS1 PS2 PP1

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

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.
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.
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

PVS1	✖	Variant is missense, so PVS1 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.
BA1	✖	FAF = 0.000002920 (0.0002920%) in European (non-Finnish) exomes+genomes (gnomAD v2.1.1), so BA1 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.

BS2		✖	Not observed in 100 normolipidemic individuals from the Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), so BS2 is Not Met.
BP7		✖	Variant is not synonymous, so BP7 is Not Met.
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.
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.

Curation History

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