

Variant: *NM_000527.5(LDLR):c.1618G>A (p.Ala540Thr)*

Version: 1.0

CA035437 [↗](#)

226363 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 10b60a8f-b6e6-40ce-bf9a-7a99e5b2a35b

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HGVS expressions

NM_000527.5(LDLR):c.1618G>A (p.Ala540Thr)

NM_000527.5:c.1618G>A

NC_000019.10:g.11116125G>A

CM000681.2:g.11116125G>A

NC_000019.9:g.11226801G>A

CM000681.1:g.11226801G>A

NC_000019.8:g.11087801G>A

NG_009060.1:g.31745G>A

ENST00000252444.10:c.1876G>A

ENST00000559340.2:c.1618G>A

ENST00000560467.2:c.1498G>A

ENST00000558518.6:c.1618G>A

ENST00000252444.9:c.1872G>A

ENST00000455727.6:c.1114G>A

ENST00000535915.5:c.1495G>A

ENST00000545707.5:c.1237G>A

ENST00000557933.5:c.1618G>A

ENST00000558013.5:c.1618G>A

ENST00000558518.5:c.1618G>A

ENST00000559340.1:c.339G>A

NM_000527.4:c.1618G>A

NM_001195798.1:c.1618G>A

NM_001195799.1:c.1495G>A

NM_001195800.1:c.1114G>A

NM_001195803.1:c.1237G>A

NM_001195798.2:c.1618G>A

NM_001195799.2:c.1495G>A

NM_001195800.2:c.1114G>A

NM_001195803.2:c.1237G>A

Pathogenic

Met criteria codes **7**

PS3_Supporting

PP3

PP4

PP1_Strong

PS4

PM3

PM2

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BP5BP7BP4BP3BP1BP2BS1BS4BS3BS2PP2PS1PS2BA1PM1PM5PM4PM6PVS1

Criteria Specifications for this VCEP

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1618G>A (p.Ala540Thr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS4, PP1_Strong, PM2, PM3, 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: PS4 - variant meets PM2 and was identified in: - at least 1 index case with DLCN at least 8 (TC =700mg/dl) from Ambry Genetics, USA; - 14 unrelated index cases, all with DLCN >=6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France; - at least 5 unrelated index cases (3 with Simon Broome definite FH, 2 with Simon Broome possible FH) from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 2 unrelated index cases who fulfill SB criteria of possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 4 unrelated index cases, all with DLCN >=6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; - 2 unrelated index cases, all with Dutch lipid clinic network >=6 from Robarts Research Institute, Canada; - at least 1 index case with DLCN>=6 from PMID 19318025 (Alonso et al., 2009), Spain; - at least 1 index case with SB criteria for FH from PMID 21376320 Chiou et al., 2011), Taiwan, --- 30 cases, so PS4 is met PP1_strong - variant segregates with the FH phenotype in 39 informative meiosis from at least 14 families: - 20 informative meiosis from 7 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo: 16 relatives with the variant have LDL-C >75th percentile, and 4 relatives without the variant have LDL-C <50th percentile; - 1 informative meiosis from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 1 relative positive for variant had LDL-C >75th percentile; - 8 informative meiosis from 3 families from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation): F1 with 2 relatives positive for variant and having LDL-C >75th percentile, and 2 relatives negative for variant and having LDL-C <50th percentile, F2: 1 relative who was positive for the variant and had LDL-C >75th percentile, F3: 2 relatives who were positive for variant with LDL-C >75th percentile, and 1 relative who was negative for the variant with LDL-C <50th percentile; - 2 informative meiosis from 2 families from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 1 relative positive for variant with LDL-C >75th percentile in each family; - 8 informative meiosis (unknown how many families) from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA): 5 relatives positive for variant with LDL-C >75th percentile, and 3 relatives were negative for variant with LDL-C <50th percentile. --- 39 segregations, so PP1_Strong is met PM2 - PopMax MAF = 0.00006533 (0.007%) in South Asian exomes (gnomAD v2.1.1). It is below than 0.02%, so PM2 is met. PM3 - variant meets PM2 and was identified in: - 1 index case homozygous for the variant with TC = 700mg/dl at 7 years old from Ambry Genetics. ---> individual is homozygous for variant and has an homozygous phenotype, so PM3 is met. - 2 unrelated index cases, both homozygous for the variant, with LDL-C 352mg/dL under statin treatment (352/0.7 = 503mg/dl) and LDL-C=409mg/dl under statin treatment (409/0.7 = 584mg/dl), respectively, both from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) ---> individuals are homozygous for variant and have an homozygous phenotype, so PM3 is met. PP3 - REVEL = 0.888. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in at least 30 unrelated index cases who fulfill clinical FH criteria (see PS4 for details), so PP4 is met. PS3_supporting - Level 3 FS: Sun et al., 1997 (PMID 9409298) - Htz patients' fibroblasts, immunoblot and 125I-LDL assays - results: 40-50% LDLR activity, cell surface LDLR 40-50% LDLR. --- Activity is below 85%, so PS3_Supporting is met.

Met criteria codes

PS3_Supporting

Level 3 FS: Sun et al., 1997 (PMID 9409298) - Htz patients' fibroblasts, immunoblot and 125I-LDL assays - results: 40-50% LDLR activity, cell surface LDLR 40-50% LDLR. Activity is below 85%, so PS3_Supporting is met

PP3			REVEL = 0.888. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in: - at least 1 index case with DLCN at least 8 (TC =700mg/dl) from Ambry Genetics, USA; - 14 unrelated index cases, all with DLCN ≥ 6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France; - at least 5 unrelated index cases (3 with Simon Broome definite FH, 2 with Simon Broome possible FH) from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 2 unrelated index cases who fulfill SB criteria of possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 4 unrelated index cases, all with DLCN ≥ 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; - 2 unrelated index cases, all with Dutch lipid clinic network ≥ 6 from Robarts Research Institute, Canada; - at least 1 index case with DLCN ≥ 6 from PMID 19318025 (Alonso et al., 2009), Spain; - at least 1 index case with SB criteria for FH from PMID 21376320 Chiou et al., 2011), Taiwan, 30 cases, so PP4 is met
PP1_Strong			variant segregates with the FH phenotype in 39 informative meioses from at least 14 families: - 20 informative meioses from 7 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo: 16 relatives with the variant have LDL-C > 75 th percentile, and 4 relatives without the variant have LDL-C < 50 th percentile. The greatest # of segregations occurring in a family was 5; - 1 informative meiosis from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): 1 relative positive for variant had LDL-C > 75 th percentile; - 8 informative meiosis from 3 families from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation): F1 with 2 relatives positive for variant and having LDL-C > 75 th percentile, and 2 relatives negative for variant and having LDL-C < 50 th percentile, F2: 1 relative who was positive for the variant and had LDL-C > 75 th percentile, F3: 2 relatives who were positive for variant with LDL-C > 75 th percentile, and 1 relative who was negative for the variant with LDL-C < 50 th percentile; - 2 informative meiosis from 2 families from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: 1 relative positive for variant with LDL-C > 75 th percentile in each family; - 8 informative meiosis (unknown how many families) from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA): 5 relatives positive for variant with LDL-C > 75 th percentile, and 3 relatives were negative for variant with LDL-C < 50 th percentile. 39 segregations, so PP1_Strong is met
PS4			variant meets PM2 and was identified in: - at least 1 index case with DLCN at least 8 (TC =700mg/dl) from Ambry Genetics, USA; - 14 unrelated index cases, all with DLCN ≥ 6 from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière), France; - at least 5 unrelated index cases (3 with Simon Broome definite FH, 2 with Simon Broome possible FH) from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 2 unrelated index cases who fulfill SB criteria of possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 4 unrelated index cases, all with DLCN ≥ 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia; - 2 unrelated index cases, all with Dutch lipid clinic network ≥ 6 from Robarts Research Institute, Canada; - at least 1 index case with DLCN ≥ 6 from PMID 19318025 (Alonso et al., 2009), Spain; - at least 1 index case with SB criteria for FH from PMID 21376320 Chiou et al., 2011), Taiwan, 30 cases, so PS4 is met. (- 2 unrelated index cases who fulfill SB criteria (All subjects had untreated Friedewald-determined plasma low-density lipoprotein (LDL) cholesterol > 5.0 mmol/L (194 mg/dL), plus either a personal or family history of early cardiovascular disease (CVD), plus family history of hyperlipidemia.), from PMID 27765764 (Wang et al., 2016), Canada - do not consider to avoid double counting - 1 index case who fulfills SB criteria from PMID 31993549 (Garg et al., 2019), USA and Canada - do not consider to avoid double counting)
PM3			variant meets PM2 and was identified in: - 1 index case, heterozygous for the variant and also (phase unknown) for NM_000527.5(LDLR):c.81C>G (p.Cys27Trp), with LDL-C=519mg/dl from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la

Pitié-Salpêtrière) ---> 2nd variant is classified as 1 star, Conflicting interpretations of pathogenicity: Likely benign(1);Likely pathogenic(9);Pathogenic(8) in ClinVar, Pathogenic by these guidelines, but phase in unknown, so not consider. - 1 index case homozygous for the variant with TC = 700mg/dl at 7 years old from Ambry Genetics. ---> individual is homozygous for variant and has an homozygous phenotype, so PM3 is met. - 2 unrelated index cases, both homozygous for the variant, with LDL-C 352mg/dL under statin treatment (352/0.7 = 503mg/dl) and LDL-C=409mg/dl under statin treatment (409/0.7 = 584mg/dl), respectively, both from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière) ---> individuals are homozygous for variant and have an homozygous phenotype, so PM3 is met.

PM2			PopMax MAF = 0.00006533 (0.007%) in South Asian exomes (gnomAD v2.1.1). It is below than 0.02%, so PM2 is met
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Not Met criteria codes

BP5			not applicable
BP7			variant is missense, not applicable
BP4			REVEL = 0.888. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			no other variants identified in index cases with heterozygous phenotype, so not met
BS1			FAF = 0.00001082 (0.001%) in South Asian exomes (gnomAD v2.1.1). It is not above 0.2%, so BS1 is not met
BS4			there is evidence of lack of segregation in 5 informative meiosis from 3 families: - 5 non-segregation from 3 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo: F1: 3 relatives positive for variant have LDL-C <50th percentile, F2: 1 relative negative for variant has LDL>75th percentile, F3: 1 relative negative for variant has LDL>75th percentile. --- there is only 1 family with more than 2 non-segregations, not enough, so not met
BS3			Level 3 FS: Sun et al., 1997 (PMID 9409298) - Htz patients' fibroblasts, immunoblot and 125I-LDL assays - results: 40-50% LDLR activity, cell surface LDLR 40-50% LDLR. Activity is not above 95%, so BS3_Supporting is not met
BS2			normolipidemic data: - 0/190 non-FH alleles from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge - 0/100 normolipidemic individuals from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); - 0/1000 normolipidemic individuals from Robarts Research Institute; - 3 relatives from the same family are positive for variant and have LDL-C <50th percentile from Laboratory of Genetics and Molecular Cardiology, University of São Paulo. --> related only sure of 1 unrelated individual with LDL <50th percentile with the variant, not enough to meet BS2
PP2			not applicable

PS1			no other missense variant that leads to the same amino acid change, so PS1 is not met
PS2			no de novo occurrence
BA1			FAF = 0.00001082 (0.001%) in South Asian exomes (gnomAD v2.1.1). It is not above 0.5%, so BA1 is not met
PM1			variant is not in exon 4 and does not alter Cys, so PM1 is not met
PM5			1 more missense variant in the same codon: - NM_000527.5(LDLR):c.1618G>T (p.Ala540Ser) - 1 star, Uncertain significance - Likely pathogenic by these guidelines so PM5 is not met
PM4			variant is missense, so not applicable
PM6			no de novo occurrence
PVS1			variant is missense and not on initiation codon, so PVS1 is not met

Curation History 		
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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.