

Variant: *NM_000527.5(LDLR):c.1291G>A (p.Ala431Thr)*

Version: 1.0

CA023445 [↗](#)

3695 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 77e0bdaf-bfa7-44ce-9ab5-62ba16365a7c

Approved on: 2022/8/28

Published on: 2022/8/28

HGVS expressions

NM_000527.5:c.1291G>A

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NC_000019.10:g.11113382G>A

CM000681.2:g.11113382G>A

NC_000019.9:g.11224058G>A

CM000681.1:g.11224058G>A

NC_000019.8:g.11085058G>A

NG_009060.1:g.29002G>A

ENST00000252444.10:c.1549G>A

ENST00000559340.2:c.1291G>A

ENST00000560467.2:c.1171G>A

ENST00000558518.6:c.1291G>A

ENST00000252444.9:c.1545G>A

ENST00000455727.6:c.787G>A

ENST00000535915.5:c.1168G>A

ENST00000545707.5:c.910G>A

ENST00000557933.5:c.1291G>A

ENST00000558013.5:c.1291G>A

ENST00000558518.5:c.1291G>A

ENST00000559340.1:c.12G>A

ENST00000560173.1:n.290G>A

ENST00000560467.1:c.771G>A

NM_000527.4:c.1291G>A

NM_001195798.1:c.1291G>A

NM_001195799.1:c.1168G>A

NM_001195800.1:c.787G>A

NM_001195803.1:c.910G>A

NM_001195798.2:c.1291G>A

NM_001195799.2:c.1168G>A

NM_001195800.2:c.787G>A

NM_001195803.2:c.910G>A

Pathogenic

Met criteria codes **7**

PP3

PP4

PP1_Strong

PS3

PS4

PM3

PM2

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Not Met criteria codes 19

BP5 BP7 BP4 BP3 BP1 BP2
BS1 BS4 BS3 BS2 PP2 PS1
PS2 BA1 PM1 PM5 PM4
PM6 PVS1

Criteria Specification Information ⓘ

Criteria Specifications for this VCEP

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1291G>A (p.Ala431Thr) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying evidence codes PS3, PS4, PP1_Strong, PM2, PM3, PP3, PP4 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: PS3 - Level 1 FS: Chang et al., 2003 (PMID 12837857): Heterologous cells (COS), FACS and WB assays - results: 22% LDLR expression, 20% LDL-LDLR binding and internalization, LDLR retained in endosomal/lysosomal regions. Activity is below 70% of wild-type, so PS3 is met. PS4 - variant meets PM2 and was identified in - 7 unrelated index cases (1 index case with Simon Broome possible FH and 6 index cases 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; - 1 index case with Simon Broome possible FH (high chol in child w/ family hx) from Ambry Genetics, USA; - 1 index case with Simon Broome possible FH (LDL-C high, family history of high cholesterol) from GeneDx Inc, USA; - 47 unrelated index cases w/ Simon Broome possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 1 index case with Simon Broome possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), reported in Tichy et al. 2012 PMID: 22698793, Czech Republic; at least 57 unrelated cases, so PS4 is met. PP1_strong - variant segregates with FH phenotype in 72 informative meiosis from 28 families: - 10 informative meiosis from 3 families from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): F1: 6 relatives with the variant have LDL >75th percentile, F2: 3 relatives with the variant have LDL >75th percentile, F3: 1 relative with the variant has LDL >75th percentile. - 28 informative meiosis from 14 families from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: in total, 21 relatives with the variant have LDL-C >75th percentile, and 7 relatives without the variant have LDL-C <50th percentile. The greatest # segregations occurring within a family is 5; - 34 informative meiosis from 11 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo: in total, 20 relatives with the variant have LDL-C >75th percentile, and 14 relatives without the variant have LDL-C <50th percentile. The greatest number of segregations occurring in a family was 9 (6 relatives positive for variant w/ phenotype, and 3 relatives negative for variant w/o phenotype). --- 72 informative meiosis support co-segregation, so PP1_Strong is met PM2 - PopMax MAF = 0.00005439 (0.005%) in East Asian exomes (gnomAD v2.1.1). It is below 0.02%, so PM2 is met. PM3 - Variant meets PM2 and was identified in - 1 index case homozygous for the variant under curation and untreated LDL = 512mg/dL from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. ----- it is an homozygous patient with an homozygous phenotype, so PM3 is met. PP3 - REVEL = 0.914. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in at least 57 unrelated cases (see PS4 for details), so PP4 is met.

Met criteria codes

PP3			REVEL = 0.914. It is above 0.75, so PP3 is met
PP4			variant meets PM2 and was identified in - 7 unrelated index cases (1 index case with Simon Broome possible FH and 6 index cases 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; - 1 index case with Simon Broome possible FH (PT4: high chol in child w/ family hx) from Ambry Genetics, USA; - 1 index case with Simon Broome possible FH (LDL-C 242, family history of high cholesterol) from GeneDx Inc, USA; - 47 unrelated index cases w/ Simon Broome possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor

Ricardo Jorge, Portugal; - 1 index case with Simon Broome possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), reported in Tichy et al. 2012 PMID: 22698793, Czech Republic; at least 57 unrelated cases (no additional bibliographic search was done because number of cases is already over 10), so PP4 is met.			
PP1_Strong			variant segregates with FH phenotype in 72 informative meiosis from 28 families: - 10 informative meiosis from 3 families from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies (APHP.Sorbonne Université, Hôpital de la Pitié-Salpêtrière): F1: 6 relatives with the variant have LDL >75th percentile, F2: 3 relatives with the variant have LDL >75th percentile, F3: 1 relative with the variant has LDL >75th percentile. - 28 informative meiosis from 14 families from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge: in total, 21 relatives with the variant have LDL-C >75th percentile, and 7 relatives without the variant have LDL-C <50th percentile. The greatest # segregations occurring within a family is 5; - 34 informative meiosis from 11 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo: in total, 20 relatives with the variant have LDL-C >75th percentile, and 14 relatives without the variant have LDL-C <50th percentile. The greatest number of segregations occurring in a family was 9 (6 relatives positive for variant w/ phenotype, and 3 relatives negative for variant w/o phenotype). 72 informative meiosis support co-segregation, so PP1_Strong is met
PS3			Level 1 FS: Chang et al., 2003 (PMID 12837857): Heterologous cells (COS), FACS and WB assays - results: 22% LDLR expression, 20% LDL-LDLR binding and internalization, LDLR retained in endosomal/lysosomal regions. Activity is below 70% of wild-type, so PS3 is met. Level 2(Pathogenic) FS: Hobbs et al., 1990 (PMID 2088165): Hmz patient fibroblast, 125I-LDL assays - results: 5-15% LDLR activity. Activity is below 70%, so PS3_Moderate would be met, but PS3 is already met.
PS4			variant meets PM2 and was identified in - 7 unrelated index cases (1 index case with Simon Broome possible FH and 6 index cases 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; - 1 index case with Simon Broome possible FH (PT4: high chol in child w/ family hx) from Ambry Genetics, USA; - 1 index case with Simon Broome possible FH (LDL-C 242, family history of high cholesterol) from GeneDx Inc, USA; - 47 unrelated index cases w/ Simon Broome possible FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, Portugal; - 1 index case with Simon Broome possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), reported in Tichy et al. 2012 PMID: 22698793, Czech Republic; at least 57 unrelated cases (no additional bibliographic search was done because number of cases is already over 10), so PS4 is met.
PM3			Variant meets PM2 and was identified in - 1 index case with also NM_000527.5(LDLR):c.313+6T>C, confirmed to be in trans and LDL = 435mg/dL (unknown if on medications) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. --- 2nd variant is classified as VUS by these guidelines. But phenotype is not clearly heterozygous nor homozygous, so do not consider for PM3. - 1 index case homozygous for the variant under curation and untreated LDL = 512mg/dL from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. ----- it is an homozygous patient with an homozygous phenotype, so PM3 is met
PM2			PopMax MAF = 0.00005439 (0.005%) in East Asian exomes (gnomAD v2.1.1).. It is below 0.02%, so PM2 is met

Not Met criteria codes

BP5			not applicable
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BP7			variant is missense, not applicable
BP4			REVEL = 0.914. It is not below 0.50, so BP4 is not met
BP3			not applicable
BP1			not applicable
BP2			Variant was identified in - 1 index case with also NM_000527.5(LDLR):c.313+6T>C, confirmed to be in trans and LDL = 435mg/dL (unknown if on medications) from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge. --- 2nd variant is classified as VUS by these guidelines. But phenotype is not clearly heterozygous nor homozygous, so do not consider for BP2.
BS1			no FAF, just total MAF = 0.000003980 (0.0004%) in East Asian exomes (gnomAD v2.1.1). It is not above 0.2%, so BS1 is not met
BS4			variant does not segregate with FH phenotype in 4 informative meioses from 3 families: - 4 non-segregations from 3 families from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge - 4 relatives (2+1+1) with the phenotype do not have the variant. - 4 non-segregations from 4 families from Laboratory of Genetics and Molecular Cardiology, University of São Paulo - each family with 1 non-segregation: 2 relatives with variant and <50th percentile LDL and 2 relatives without the variant and >75th percentile LDL not one family with 2 non-segregations, so BS4 is not met
BS3			Level 1 FS: Chang et al., 2003 (PMID 12837857): Heterologous cells (COS), FACS and WB assays - results: 22% LDLR expression, 20% LDL-LDLR binding and internalization, LDLR retained in endosomal/lysosomal regions. Activity is not above 90% of wild-type, so BS3 is not met. Level 3(Benign) FS: Hobbs et al., 1990 (PMID 2088165): Hmz patient fibroblast, 125I-LDL assays - results: 5-15% LDLR activity. Activity is not above 90%, so BS3_Supporting is not met.
BS2			variant was - not identified in 0/190 non-FH alleles from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge; - not identified in 0/100 normolipidemic individuals from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation); - identified in 2 relatives, 1 from each family, with <50th percentile LDL from Laboratory of Genetics and Molecular Cardiology, University of São Paulo, Brazil, not enough, so not met.
PP2			not applicable
PS1			no other variant leads to the same amino acid change, so PS1 is not met
PS2			no de novo occurrence
BA1			no FAF, just total MAF = 0.000003980 (0.0004%) in East Asian exomes (gnomAD v2.1.1). It is not above 0.5%, so BA1 is not met
PM1			variant is not on exon 4 and does not alter Cys, so PM1 is not met

PM5			1 more missense variant in the same codon: - NM_000527.4(LDLR):c.1291G>C (p.Ala431Pro) - 1 star, Conflicting interpretations of pathogenicity: Likely pathogenic(1);Uncertain significance(1) in ClinVar - Likely pathogenic by these guidelines so PM5 is not met
PM4			variant is missense, 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.