

Variant: NM_000527.5(LDLR):c.1285G>A (p.Val429Met)

Version: 1.0

CA023443 [↗](#)

3694 (ClinVar) [↗](#)

Gene: LDLR ([HGNC:3949](#))
Condition: hypercholesterolemia, familial ([MONDO:0007750](#))
Inheritance Mode: Semidominant inheritance
UUID: fc4ca2d1-7bd8-4eba-acb6-2a2b7805bad1
Approved on: 2023/3/27
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HGVS expressions

NM_000527.5:c.1285G>A
NM_000527.5(LDLR):c.1285G>A (p.Val429Met)
NC_000019.10:g.11113376G>A
CM000681.2:g.11113376G>A
NC_000019.9:g.11224052G>A
CM000681.1:g.11224052G>A
NC_000019.8:g.11085052G>A
NG_009060.1:g.28996G>A
ENST00000252444.10:c.1543G>A
ENST00000559340.2:c.1285G>A
ENST00000560467.2:c.1165G>A
ENST00000558518.6:c.1285G>A
ENST00000252444.9:c.1539G>A
ENST00000455727.6:c.781G>A
ENST00000535915.5:c.1162G>A
ENST00000545707.5:c.904G>A
ENST00000557933.5:c.1285G>A
ENST00000558013.5:c.1285G>A
ENST00000558518.5:c.1285G>A
ENST00000559340.1:c.6G>A
ENST00000560173.1:n.284G>A
ENST00000560467.1:c.765G>A
NM_000527.4:c.1285G>A
NM_001195798.1:c.1285G>A
NM_001195799.1:c.1162G>A
NM_001195800.1:c.781G>A
NM_001195803.1:c.904G>A
NM_001195798.2:c.1285G>A
NM_001195799.2:c.1162G>A
NM_001195800.2:c.781G>A
NM_001195803.2:c.904G>A

Pathogenic

Met criteria codes 6

PP1_Strong PS4 PS3_Moderate
PP3 PP4 PM2

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Not Met criteria codes 20

BP5BP7BP4BP3BP1BP2

PS1PS2PP2PM6PM1

PM3PM5PM4PVS1BA1

BS2BS1BS4BS3

Evidence Links 0

Criteria Specification Information

- [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.1285G>A (p.Val429Met) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS4, PM2, PS3_Moderate, PP3 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 27 March 2023. The supporting evidence is as follows: PM2: PopMax MAF = 0.00003266 (0.003%) in South Asian exomes (gnomAD v2.1.1). PP3: REVEL = 0.809. PS3_Moderate: Level 2 assay - PMID 2569482 (Leitersdorf et al., 1989) - Immunoprecipitation assay on heterozygous CHO cells where the receptor was degraded more rapidly. After 6 h, only 13% of the LDL receptor protein remained. Level 2 assay - PMID 3202825 (Fourie et al., 1988) - 125I-labelled LDL assay on homozygous patient's fibroblasts with overall LDL receptor activity of ~2% of wildtype. PS4, PP4: Variant meets PM2 and is identified in at least 55 unrelated index cases who fulfill criteria for FH - 1 case with DLCN score >=6 from Genomics Medicine Unit, Navarrabiomed - idiSNA, Spain; - 4 cases with DLCN score >=6 from Robarts Research Institute, Canada; - 9 cases with DLCN score >=6 from Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; - 2 cases with DLCN score >=6 and 1 case with possible FH by Simon Broome criteria from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, France; - 2 cases with possible FH by Simon Broome criteria from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czech Republic; - 36 cases fulfilling MEDPED criteria from PMID 8399083 (Kotze et al., 1993), South Africa. PP1_Strong: Variant segregates with FH phenotype in 27 informative meioses from at least 10 families from different labs (Genomics Medicine Unit, Navarrabiomed - idiSNA, Spain; Robarts Research Institute, Canada; Cardiovascular Genetics Laboratory, PathWest Laboratory Medicine WA, Australia; Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France; Molecular Genetics Laboratory, Centre for Cardiovascular Surgery and Transplantation, Czech Republic; Laboratory of Genetics and Molecular Cardiology, Brazil; PMID 26036859 (Brænne et al., 2016), Germany; PMID 21925660 (Versmissen et al., 2011), the Netherlands): 19 affected family members have the variant and 8 unaffected family members do not have the variant.

Met criteria codes

PP1_Strong



Variant segregates with FH phenotype in 27 informative meioses from at least 10 families: - from 1 family: 2 family members positive for variant with LDL-C >75th percentile from Genomics Medicine Unit, Navarrabiomed - idiSNA, Spain - unclear how many families: 2 family members positive for variant and LDL>75th percentile from Robarts Research Institute, Canada - from 2 families: F1 has 3 relatives with the variant and LDL>75th percentile, F2 has 2 relatives with the variant and LDL>75th percentile from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia - from 1 family: 2 relatives are positive for variant and have LDL-C >75th percentile from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France - from 1 family: 1 relative with the phenotype and the variant from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czechia - from 2 families. Family 1: 1 relative positive for variant with LDL-C >75th percentile, 3 relatives negative for variant with LDL-C <50th percentile. Family 2: 1 relative positive for variant with LDL-C >75th percentile, 5 relatives negative for variant with LDL-C <50th percentile from Laboratory of Genetics and Molecular Cardiology, Brazil - from 1 family: 2 relatives with the variant and elevated LDLC levels (mean 341 mg/dl) from PMID: 26036859 (Brænne I et al. 2016), Germany - from 1 family: 3 relatives with the variant and cholesterol levels above the 95th percentile from PMID: 21925660 (Versmissen J et al. 2011), the Netherlands

PS4			Variant meets PM2 and is identified in over 10 unrelated index cases who fulfill SB possible/DLCN $\geq$ 6 from different labs: - 1 index case with Dutch lipid clinic network $\geq$ 6 from Genomics Medicine Unit, Navarrabiomed - idiSNA, Spain - 4 unrelated index cases, all with Dutch lipid clinic network $\geq$ 6 from Robarts Research Institute, Canada - 9 unrelated index cases, all with Dutch lipid clinic network $\geq$ 6 from Cardiovascular Genetics Laboratory (PathWest Laboratory Medicine WA), Australia - 3 unrelated index cases: 2 fulfill Dutch lipid clinic network $\geq$ 6 and 1 fulfills Simon Broome possible from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon, Lyon, France - 2 unrelated index cases with Simon-Broome criteria of possible FH from Molecular Genetics Laboratory (Centre for Cardiovascular Surgery and Transplantation), Czechia - 36 unrelated cases fulfilling MEDPED criteria from PMID: 8399083 (Kotze et al., 1993), South Africa.
PS3_Moderate			Level 2 assay - PMID:2569482 (Leitersdorf et al., 1989) - Immunoprecipitation assay on heterozygous CHO cells where LDLR protein was processed more slowly than normal and rapidly degraded. After 6 h, only - 13% of the LDL receptor protein remained. Level 2 assay - PMID:3202825 (Hobbs et al., 1992) - 125I-labelled LDL assay on homozygous patient's fibroblasts with overall LDL receptor activity of $\sim$ 2% of wildtype. ---- functional study is consistent with damaging effect.
PP3			REVEL = 0.809. Score is above 0.75.
PP4			Variant meets PM2 and is identified in identified in over 10 unrelated index cases who fulfill clinical criteria for FH from multiple labs (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2			PopMax MAF = 0.00003266 (0.003%) in South Asian exomes (gnomAD v2.1.1). MAF is below 0.02%.

Not Met criteria codes

BP5			not applicable
BP7			Missense variant - not applicable
BP4			REVEL: 0.809. Score is not below 0.50.
BP3			not applicable
BP1			not applicable
BP2			not identified in index cases with more than 1 variant
PS1			no other missense variant that leads to the same amino acid change in this codon
PS2			No de novo cases were identified
PP2			not applicable

PM6			No de novo cases were identified
PM1			Missense at codon 406. PM2 is Met, but it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3			not identified in index cases with more than 1 variant
PM5			NM_000527.5(LDLR):c.1285G>C (p.Val429Leu) - Pathogenic by these guidelines NM_000527.5(LDLR):c.1285G>T (p.Val429Leu) - Pathogenic by these guidelines Two other variants in the same codon classified as Pathogenic by these guidelines, but they both only get to Pathogenic with PM5 from this variant, so PM5 is not met here
PM4			Missense variant - not applicable
PVS1			Missense variant - not applicable
BA1			no FAF, just total MAF = 0.00001194 (0.002%) in South Asian exomes (gnomAD v2.1.1). MAF is not above 0.5%.
BS2			not identified in normolipidemic individuals
BS1			no FAF, just total MAF = 0.00001194 (0.002%) in South Asian exomes (gnomAD v2.1.1). MAF is not above 0.2%.
BS4			Variant does not co-segregate with phenotype in 1 informative meiosis: - 1 relative negative for variant with LDL-C >75 percentile from Laboratory of Genetics and Molecular Cardiology, Brazil not enough (only 1 family, only 1 informative meiosis, no relative positive for variant with LDL <50th percentile), so not met
BS3			Level 2 assay - PMID:2569482 (Leitersdorf et al., 1989) - Immunoprecipitation assay on heterozygous CHO cells where LDLR protein was processed more slowly than normal and rapidly degraded. After 6 h, only - 13% of the LDL receptor protein remained. Level 2 assay - PMID:3202825 (Hobbs et al., 1992) - 125I-labelled LDL assay on homozygous patient's fibroblasts with overall LDL receptor activity of ~2% of wildtype. ---- Overall, functional studies (PMID: 2569482 and 3202825) show an activity below 90% of wild-type, so functional study is consistent with damaging effect.

Curation History 		
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