

Variant: NM_000527.5(LDLR):c.1285G>C (p.Val429Leu)

Version: 1.2

CA10576303 [↗](#)

226353 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: b5d5eda5-5692-4db4-b70c-072b97df27b6

Approved on: 2023/3/27

Published on: 2024/10/4

HGVS expressions

NM_000527.5:c.1285G>C
NM_000527.5(LDLR):c.1285G>C (p.Val429Leu)
NC_000019.10:g.11113376G>C
CM000681.2:g.11113376G>C
NC_000019.9:g.11224052G>C
CM000681.1:g.11224052G>C
NC_000019.8:g.11085052G>C
NG_009060.1:g.28996G>C
ENST00000252444.10:c.1543G>C
ENST00000559340.2:c.1285G>C
ENST00000560467.2:c.1165G>C
ENST00000558518.6:c.1285G>C
ENST00000252444.9:c.1539G>C
ENST00000455727.6:c.781G>C
ENST00000535915.5:c.1162G>C
ENST00000545707.5:c.904G>C
ENST00000557933.5:c.1285G>C
ENST00000558013.5:c.1285G>C
ENST00000558518.5:c.1285G>C
ENST00000559340.1:c.6G>C
ENST00000560173.1:n.284G>C
ENST00000560467.1:c.765G>C
NM_000527.4:c.1285G>C
NM_001195798.1:c.1285G>C
NM_001195799.1:c.1162G>C
NM_001195800.1:c.781G>C
NM_001195803.1:c.904G>C
NM_001195798.2:c.1285G>C
NM_001195799.2:c.1162G>C
NM_001195800.2:c.781G>C
NM_001195803.2:c.904G>C

Pathogenic

Met criteria codes **6**

PS3

PP3

PP4

PM2

PM5

PS4_Supporting

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Not Met criteria codes 20

BP5 BP7 BP4 BP3 BP1 BP2
PS1 PS2 PP1 PP2 PM6
PM1 PM3 PM4 PVS1 BA1
BS2 BS1 BS4 BS3

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>C (p.Val429Leu) variant is classified as Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PM2, PM5, PP3, PP4 and PS4_Supporting, 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: This variant is absent from gnomAD (gnomAD v2.1.1). PP3: REVEL = 0.764. PM5: There is 1 variant in the same codon classified as Pathogenic by these guidelines, NM_000527.5(LDLR): c.1285G<A (p.Val429Met) (ClinVar ID: 3694). PS3: Level 1 assay: Heterologous cells (CHO), 125I-LDL and WB assays, 22% cell surface LDLR and binding and 10% uptake, PMID 25386756 (Etxebarria et al., 2014). Level 1 assay: Heterologous cells (CHO), 125I-LDL and WB assays, 15-30% LDLR activity, reduced mature protein, PMID 23021490 (Silva et al, 2012). ---- Overall, functional studies show an activity below 70% of wild-type, consistent with damaging effect. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 3 unrelated index cases (2 cases with DLCN score >=6 from PathWest Laboratory Medicine WA, Australia; 1 case with possible FH by Simon Broome criteria from Instituto Nacional de Saúde Dr. Ricardo Jorge, Portugal, PMID 17765246 (Bourbon et al., 2008)).

Met criteria codes

PS3			Level 1 assay: Heterologous cells (CHO), 125I-LDL and WB assays, 22% cell surface LDLR and binding and 10% uptake. PMID: 25386756 // Level 1 assay: Heterologous cells (CHO), 125I-LDL and WB assays, 15-30% LDLR activity, reduced mature protein. PMID: 23021490. ---- Overall, functional studies (PMID: 25386756 and 23021490) show an activity below 70% of wild-type, so functional study is consistent with damaging effect.
PP3			REVEL = 0.764. It is above 0.75.
PP4			Variant meets PM2 and is identified in 3 index cases who fulfill clinical criteria for FH from multiple labs (see PS4 for details), after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v20210610).
PM5			NM_000527.5(LDLR): c.1285G<A p.Val429Met (ClinVar ID: 3694) - Pathogenic by these guidelines There is 1 variant in the same codon classified as Pathogenic by these guidelines.
PS4_Supporting			Variant meets PM2 and is identified in at least 2 unrelated index cases (3 index cases total = 2 cases with DLCN criteria>=6 from PathWest Laboratory Medicine WA, Australia; 1 case with SB criteria of possible FH from Instituto Nacional de Saude Doutor, Portugal)/PMID:17765246 from lab Instituto Nacional de Saude Doutor, Portugal

Not Met criteria codes			
BP5			not applicable
BP7			Missense variant - not applicable.
BP4			REVEL: 0.764. Score is not below 0.50.
BP3			not applicable
BP1			Not applicable
BP2			Variant meets PM2 but is not identified in an index case with heterozygous or homozygous FH phenotype as well as LDLR variant, in trans, or APOB/PCSK9 variant classified as Pathogenic by these or general ACMG guidelines.
PS1			NM_000527.5(LDLR): c.1285G<T p.Val429Leu (ClinVar ID: 251767) - Pathogenic by these guidelines, but only after getting PM5 from variant NM_000527.5(LDLR): c.1285G<A p.Val429Met (ClinVar ID: 3694), so not met
PS2			No de novo cases were identified.
PP1			Familial segregation/testing info was not completed/available. PathWest Laboratory Medicine WA, Australia and PMID ID: 17765246.
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			Variant meets PM2 but is not identified in an index case with heterozygous or homozygous FH phenotype as well as LDLR variant, in trans, or APOB/PCSK9 variant classified as Pathogenic by these or general ACMG guidelines.
PM4			Missense variant - not applicable.
PVS1			Missense variant and not in exon 1- not applicable.
BA1			This variant is absent from gnomAD (gnomAD v20210610).
BS2			Variant not identified in at least 3 heterozygous/1 true homozygous well-phenotyped, normolipidemic, untreated, unrelated adults.
BS1			This variant is absent from gnomAD (gnomAD v20210610).

