

Variant: *NM_000527.5(LDLR):c.2089G>C (p.Ala697Pro)*

Version: 1.0

CA10585767 [↗](#)

252213 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: b250a79d-b41f-4f83-8746-7aef43393c32

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HGVS expressions

NM_000527.5(LDLR):c.2089G>C (p.Ala697Pro)

NM_000527.5:c.2089G>C

NC_000019.10:g.11120471G>C

CM000681.2:g.11120471G>C

NC_000019.9:g.11231147G>C

CM000681.1:g.11231147G>C

NC_000019.8:g.11092147G>C

NG_009060.1:g.36091G>C

ENST00000252444.10:c.2347G>C

ENST00000559340.2:c.*158G>C

ENST00000560467.2:c.1969G>C

ENST00000558518.6:c.2089G>C

ENST00000252444.9:c.2343G>C

ENST00000455727.6:c.1585G>C

ENST00000535915.5:c.1966G>C

ENST00000545707.5:c.1606+238G>C

ENST00000557933.5:c.2089G>C

ENST00000558013.5:c.2089G>C

ENST00000558518.5:c.2089G>C

NM_000527.4:c.2089G>C

NM_001195798.1:c.2089G>C

NM_001195799.1:c.1966G>C

NM_001195800.1:c.1585G>C

NM_001195803.1:c.1606+238G>C

NM_001195798.2:c.2089G>C

NM_001195799.2:c.1966G>C

NM_001195800.2:c.1585G>C

NM_001195803.2:c.1606+238G>C

Likely Pathogenic

Met criteria codes **5**

PP1

PP3

PP4

PM2

PS4_Supporting

Not Met criteria codes **2**

PM5

PS3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

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.2089G>C (p.Ala697Pro) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP1, PP3, PP4 and PS4_Supporting as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 28 October 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v4.1.0). PP3: REVEL=0.78. PS4_Supporting, PP4: Variant meets PM2, and is identified in at least 5 unrelated index cases who fulfil FH criteria. One index case who fulfils Simon Broome definite FH criteria reported in PMID 23669246 (supplementary Table 2) by Futema et al, 2013 from University College London, UK. One index case who fulfils Simon Broome criteria for FH reported in PMID 17094996 (Table 2) by Tosi et al, 2007 from Imperial College London, UK. Three index cases fulfil DLCN ≥6 reported in PMID 33418990 (Appendix Table A1) by Meshkov et al, 2021 from National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia. PP1: Variant segregates with FH phenotype in at least 2 informative meiosis from 1 family, 2 affected relatives with definite FH by Simon Broome criteria and tested positive for the variant, reported in PMID 23669246 (supplementary Table 2) by Futema et al, 2013 from University College London, UK.

Met criteria codes

PP1			Variant segregates with FH phenotype in at least 2 informative meiosis from 1 family, 2 affected relatives with definite FH by Simon Broome criteria and tested positive for the variant, reported in PMID 23669246 (supplementary Table 2) by Futema et al, 2013 from University College London, UK.
PP3			REVEL=0.78, which is above the impact threshold.
PP4			Variant meets PM2, and is identified in >1 index case who fulfil criteria for FH after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v4.1.0).
PS4_Supporting			Variant meets PM2, and is identified in at least 5 unrelated index cases who fulfil FH criteria. One index case who fulfils Simon Broome definite FH criteria reported in PMID 23669246 (supplementary Table 2) by Futema et al, 2013 from University College London, UK. One index case who fulfils Simon Broome criteria for FH reported in PMID 17094996 (Table 2) by Tosi et al, 2007 from Imperial College London, UK. Three index cases fulfil DLCN ≥6 reported in PMID 33418990 (Appendix Table A1) by Meshkov et al, 2021 from National Medical Research Center for Therapy and Preventive Medicine, Moscow, Russia.

Not Met criteria codes

PM5		
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One other variant in the same codon: NM_000527.5 (LDLR):c. 2089G>A (p.Ala697Thr)(ClinVarID 440678) is classified as VUS by these guidelines. Therefore, PM5 is not met.

PS3



Functional data is not available.

Curation History



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