The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2024/10/28
Published on: 2025/1/19

HGVS expressions

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

PS4_Supporting PM2 PP1 PP3 PP4

Not Met criteria codes 2

PS3 PM5

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Evidence Links 0

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

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.
PM2	✔	This variant is absent from gnomAD (gnomAD v4.1.0).
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.

Not Met criteria codes

PS3	✖	Functional data is not available.
PM5	✖	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.

Curation History

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