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.1981C>G (p.Pro661Ala)

Version: 1.0

CA404093326

810849 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 0eee2ad7-300d-4df6-80b5-12ff2b1d6e7c
Approved on: 2023/6/23
Published on: 2025/9/15

HGVS expressions

NM_000527.5:c.1981C>G
NM_000527.5(LDLR):c.1981C>G (p.Pro661Ala)
NC_000019.10:g.11120227C>G
CM000681.2:g.11120227C>G
NC_000019.9:g.11230903C>G
CM000681.1:g.11230903C>G
NC_000019.8:g.11091903C>G
NG_009060.1:g.35847C>G
ENST00000252444.10:c.2239C>G
ENST00000559340.2:c.*50C>G
ENST00000560467.2:c.1861C>G
ENST00000558518.6:c.1981C>G
ENST00000252444.9:c.2235C>G
ENST00000455727.6:c.1477C>G
ENST00000535915.5:c.1858C>G
ENST00000545707.5:c.1600C>G
ENST00000557933.5:c.1981C>G
ENST00000558013.5:c.1981C>G
ENST00000558518.5:c.1981C>G
ENST00000559340.1:c.562C>G
NM_000527.4:c.1981C>G
NM_001195798.1:c.1981C>G
NM_001195799.1:c.1858C>G
NM_001195800.1:c.1477C>G
NM_001195803.1:c.1600C>G
NM_001195798.2:c.1981C>G
NM_001195799.2:c.1858C>G
NM_001195800.2:c.1477C>G
NM_001195803.2:c.1600C>G

Likely Pathogenic

Met criteria codes 3

PS3 PM2 PP4

Not Met criteria codes 23

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PVS1 BS2 BS1 BS4 BS3
BP4 BP3 BP1 BP2 BP5 BP7
PS1 PS2 PS4 BA1 PM1
PM3 PM5 PM4 PM6 PP1
PP2 PP3

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.1981C>G (p.Pro661Ala) variant is classified as Likely Pathogenic for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PS3, PM2 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PS3: Level 1 assays: PMID 31689621 (Gomez et al., 2019): Heterologous cells (CHO-ldlA7), RT qPCR and 125I-LDL assays - results – normal (100%) LDLR expression and 50% uptake and catabolism -> results are below 70% of wild-type, so functional study is consistent with damaging effect. PP4: Variant meets PM2 and is identified in 1 case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon (France) with DLCN score ≥ 6, after alternative causes of high cholesterol were excluded.

Met criteria codes

PS3	✔	Level 1 assays: PMID: 31689621: Heterologous cells (CHO-ldlA7), RT qPCR and 125I-LDL assays - results – normal (100%) LDLR expression and 50% uptake and catabolism ---- results are below 70% of wild-type, so functional study is consistent with damaging effect.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1).
PP4	✔	Variant meets PM2. Identified in 1 FH case from Service de Biochimie et de Biologie Moléculaire, Hospices Civils de Lyon (France) with clinical Dutch Lipid Clinic Network Criteria score ≥ 6, after alternative causes of high cholesterol were excluded.

Not Met criteria codes

PVS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1982C>T (p.Pro661Leu) (ClinVar ID 375827) - Uncertain significance - insufficient evidence by these guidelines - NM_000527.5(LDLR):c.1981C>A (p.Pro661Thr) (ClinVar ID 441225) - Uncertain significance - insufficient evidence by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.
PM4		✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

PM6	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP1	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2	ℹ	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	ℹ	✖	REVEL = 0.639, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. Scenario A, Acceptor site: The variant is NOT located at -20 to +3 bases of canonical acceptor splicing site of any exons. Scenario A, Donor site: The variant is NOT located at -3 to +6 bases of canonical splicing site of any exons. Scenario B, Acceptor site: The variant is NOT located within the range and DOES NOT create de novo AG site. Scenario B, Donor site: The variant is located within range and DOES NOT create de novo GT site. Scenario C, Acceptor site: The variant is NOT located at -20 to +3 bases of intraexonic AG. Scenario C, Donor site: The variant is NOT located at -3 to +6 bases of intraexonic GT. Interpretation: The variant DOES NOT affect splicing

Curation History

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