

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(LDLR):c.1981C>G (p.Pro661Ala)

NM_000527.5:c.1981C>G

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

PP4

PM2

Not Met criteria codes **23**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

BA1

BS2

BS1

BS4

BS3

BP4

BP3

BP1

BP2

PVS1

BP5

BP7

PS1

PS2

PS4

PP1

PP2

PP3

PM1

PM3

PM5

PM4

PM6

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-IdIA7), 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-IdIA7), 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. 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.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

BA1			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
PVS1			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
PP1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3			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

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

Curation History



 

 

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