

Variant: *NM_000527.5(LDLR):c.1927G>C (p.Ala643Pro)*

Version: 1.2

CA10585682 [↗](#)

252114 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 67ec196b-6313-43ac-a7da-0017f218f6af

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HGVS expressions

NM_000527.5(LDLR):c.1927G>C (p.Ala643Pro)

NM_000527.5:c.1927G>C

NC_000019.10:g.11120173G>C

CM000681.2:g.11120173G>C

NC_000019.9:g.11230849G>C

CM000681.1:g.11230849G>C

NC_000019.8:g.11091849G>C

NG_009060.1:g.35793G>C

ENST00000252444.10:c.2185G>C

ENST00000559340.2:c.1787G>C

ENST00000560467.2:c.1807G>C

ENST00000558518.6:c.1927G>C

ENST00000252444.9:c.2181G>C

ENST00000455727.6:c.1423G>C

ENST00000535915.5:c.1804G>C

ENST00000545707.5:c.1546G>C

ENST00000557933.5:c.1927G>C

ENST00000558013.5:c.1927G>C

ENST00000558518.5:c.1927G>C

ENST00000559340.1:c.508G>C

NM_000527.4:c.1927G>C

NM_001195798.1:c.1927G>C

NM_001195799.1:c.1804G>C

NM_001195800.1:c.1423G>C

NM_001195803.1:c.1546G>C

NM_001195798.2:c.1927G>C

NM_001195799.2:c.1804G>C

NM_001195800.2:c.1423G>C

NM_001195803.2:c.1546G>C

Uncertain Significance

Met criteria codes **2**

PP4

PM2

Not Met criteria codes **2**

PP3

PM5

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1927G>C (p.Ala643Pro) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 2 July 2024. The supporting evidence is as follows: PM2: This variant is absent from gnomAD (gnomAD v2.1.1). PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills Simon Broome criteria for FH (PMID 17539906) after alternative causes of high cholesterol were excluded.

Met criteria codes

PP4			Variant meets PM2 and is identified in at least 1 index case who fulfills SB possible or definite FH criteria (PMID: 17539906) after alternative causes of high cholesterol were excluded.
PM2			This variant is absent from gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PP3			REVEL = 0.686 Does not meet BP4 or PP3 criteria, splicing evaluation required A). Not on limits B). Does not create AG or GT C). There is a GT nearby MES Scores: >var cryptic CTTGTTGCC MAXENT: -25.74 >WT cryptic CTTGTTGGC MAXENT: -14.01 variant cryptic/wild-type cryptic score = -25.74/-14.01 = 1.84 --> it is above 1.1. However, PP3 is not met. When both splice sites have negative MES score, the resulting ratio (-25.74/-14.01=1.84) suggests that there is an increase in relative strengths between these two cryptic splice sites. However, this is misleading as donor with MES of -25.74 is weaker than -14.01 because the former has a smaller number value. Additionally, negative MES score generally suggests a splice site that is unlikely to be used as a bona fide splice site (though there might be some exceptions).
PM5			The NM_000527.5(LDLR):c.1928C>T (p.Ala643Val) is classified as VUS by the FH VCEP guidelines.

Curation History



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owing 1 to 3 of 3 rows

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