

Variant: *NM_000527.5(LDLR):c.1928C>T (p.Ala643Val)*

Version: 1.2

CA10585683 [↗](#)

252115 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 656f504a-4c79-4833-b888-b28a2118cd3d

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HGVS expressions

NM_000527.5(LDLR):c.1928C>T (p.Ala643Val)

NM_000527.5:c.1928C>T

NC_000019.10:g.11120174C>T

CM000681.2:g.11120174C>T

NC_000019.9:g.11230850C>T

CM000681.1:g.11230850C>T

NC_000019.8:g.11091850C>T

NG_009060.1:g.35794C>T

ENST00000252444.10:c.2186C>T

ENST00000559340.2:c.1788C>T

ENST00000560467.2:c.1808C>T

ENST00000558518.6:c.1928C>T

ENST00000252444.9:c.2182C>T

ENST00000455727.6:c.1424C>T

ENST00000535915.5:c.1805C>T

ENST00000545707.5:c.1547C>T

ENST00000557933.5:c.1928C>T

ENST00000558013.5:c.1928C>T

ENST00000558518.5:c.1928C>T

ENST00000559340.1:c.509C>T

NM_000527.4:c.1928C>T

NM_001195798.1:c.1928C>T

NM_001195799.1:c.1805C>T

NM_001195800.1:c.1424C>T

NM_001195803.1:c.1547C>T

NM_001195798.2:c.1928C>T

NM_001195799.2:c.1805C>T

NM_001195800.2:c.1424C>T

NM_001195803.2:c.1547C>T

Uncertain Significance

Met criteria codes **3**

PM2

BP4

PP4

Not Met criteria codes **2**

PM5

PP3

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1928C>T (p.Ala643Val) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, BP4 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). BP4: REVEL = 0.481; score is below 0.50, splicing evaluation required. A). Not on limits. B). it creates a GT. Variant is exonic and at least 50bp upstream/downstream from canonical donor/acceptor site and creates a de novo GT. MES scores: variant cryptic site = -9.79, WT cryptic site = -17.54, canonical donor site= 10.28. De novo score is negative, so it is not used. Variant is not predicted to alter splicing. PP4: Variant meets PM2 and is identified in at least 1 index case who fulfills Simon-Broome criteria for FH (PMID 20809525) after alternative causes of high cholesterol were excluded.

Met criteria codes

PM2			This variant is absent from gnomAD (gnomAD v2.1.1)
BP4			REVEL = 0.481; score is below BP4 threshold of 0.5 Splicing evaluation required A). Not on limits B). Variant does not create an AG but it does create a GT Variant is exonic and at least 50bp upstream/downstream from canonical donor/acceptor site and creates a de novo GT MES scores: variant cryptic site = -9.79, WT cryptic site = -17.54, canonical donor site= 10.28 Ratio de novo variant/canonical donor = -9.79/10.28 = -0.95 --- it is not above 0.9. It is below 0.8 --> Variant is not predicted to alter splicing and meets BP4.
PP4			Variant meets PM2 and is identified in at least 1 index case who fulfills SB definite FH (PMID: 20809525) after alternative causes of high cholesterol were excluded.

Not Met criteria codes

PM5			The NM_000527.5(LDLR):c.1927G>C (p.Ala643Pro) is classified as VUS by the FH VCEP guidelines.
PP3			REVEL = 0.481; score is below PP3 threshold of 0.75 Splicing evaluation required A). Not on limits B). Variant does not create an AG but it does create a GT Variant is exonic and at least 50bp upstream/downstream from canonical donor/acceptor site and creates a de novo GT MES scores: variant cryptic site = -9.79, WT cryptic site = -17.54, canonical donor site= 10.28 Ratio de novo variant/canonical donor = -9.79/10.28 = -0.95 --- it is not above 0.9. It is below 0.8, so meets BP4.

