

Variant: *NM_000527.5(LDLR):c.1836C>T (p.Ala612=)*

Version: 1.0

CA036837 [↗](#)

224618 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 7ca66b0a-7663-40c0-9d87-1cd640a32c28

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HGVS expressions

NM_000527.5(LDLR):c.1836C>T (p.Ala612=)

NM_000527.5:c.1836C>T

NC_000019.10:g.11116989C>T

CM000681.2:g.11116989C>T

NC_000019.9:g.11227665C>T

CM000681.1:g.11227665C>T

NC_000019.8:g.11088665C>T

NG_009060.1:g.32609C>T

ENST00000252444.10:c.2094C>T

ENST00000559340.2:c.1705+777C>T

ENST00000560467.2:c.1716C>T

ENST00000558518.6:c.1836C>T

ENST00000252444.9:c.2090C>T

ENST00000455727.6:c.1332C>T

ENST00000535915.5:c.1713C>T

ENST00000545707.5:c.1455C>T

ENST00000557933.5:c.1836C>T

ENST00000558013.5:c.1836C>T

ENST00000558518.5:c.1836C>T

ENST00000559340.1:c.426+777C>T

NM_000527.4:c.1836C>T

NM_001195798.1:c.1836C>T

NM_001195799.1:c.1713C>T

NM_001195800.1:c.1332C>T

NM_001195803.1:c.1455C>T

NM_001195798.2:c.1836C>T

NM_001195799.2:c.1713C>T

NM_001195800.2:c.1332C>T

NM_001195803.2:c.1455C>T

Likely Benign

Met criteria codes **2**

BP4 BP7

Not Met criteria codes **2**

BS1 BA1

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

- [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.1836C>T (p.Ala612=) variant is classified as likely benign for Familial Hypercholesterolemia by applying evidence code BP4 and BP7 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1016/j.gim.2021.09.012>). The supporting evidence is as follows: BP4 - No REVEL, splicing evaluation required. Functional data on splicing not available. - Variant is exonic and at least 50bp downstream from canonical acceptor site but it does not create GT. - There is a GT nearby. MES scores: variant cryptic = -16.82, wt cryptic = -12.61, canonical donor = 4.48. Ratio variant cryptic/wt cryptic: -16.82/-12.61 = 1.33 --- it is above 1.1 Ratio variant cryptic/canonical donor: -16.82/4.48 = -3.75 --- it is not above 0.9 Variant is not predicted to alter splicing. BP7 - Variant is synonymous and meets BP4.

Met criteria codes

BP4			No REVEL, splicing evaluation required. - Variant is exonic and at least 50bp downstream from canonical acceptor site but it does not create GT. - There is a GT nearby. MES scores: variant cryptic = -16.82, wt cryptic = -12.61, canonical donor = 4.48. Ratio variant cryptic/wt cryptic: -16.82/-12.61 = 1.33 --- it is above 1.1 Ratio variant cryptic/canonical donor: -16.82/4.48 = -3.75 --- it is not above 0.9 Variant is not predicted to alter splicing.
BP7			Variant is synonymous and meets BP4.

Not Met criteria codes

BS1			PopMax FAF = 0.0002341 (0.03%) in European (non -Finnish) exomes (gnomAD v2.1.1). It is between (0.0002 and 0.002)
BA1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History [↗](#)

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