

Variant: *NM_000527.5(LDLR):c.1816G>T (p.Ala606Ser)*

Version: 1.0

CA023592 [↗](#)

161264 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 53a6114d-d0ac-4c36-b589-da6298a96154

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HGVS expressions

NM_000527.5(LDLR):c.1816G>T (p.Ala606Ser)

NM_000527.5:c.1816G>T

NC_000019.10:g.11116969G>T

CM000681.2:g.11116969G>T

NC_000019.9:g.11227645G>T

CM000681.1:g.11227645G>T

NC_000019.8:g.11088645G>T

NG_009060.1:g.32589G>T

ENST00000252444.10:c.2074G>T

ENST00000559340.2:c.1705+757G>T

ENST00000560467.2:c.1696G>T

ENST00000558518.6:c.1816G>T

ENST00000252444.9:c.2070G>T

ENST00000455727.6:c.1312G>T

ENST00000535915.5:c.1693G>T

ENST00000545707.5:c.1435G>T

ENST00000557933.5:c.1816G>T

ENST00000558013.5:c.1816G>T

ENST00000558518.5:c.1816G>T

ENST00000559340.1:c.426+757G>T

NM_000527.4:c.1816G>T

NM_001195798.1:c.1816G>T

NM_001195799.1:c.1693G>T

NM_001195800.1:c.1312G>T

NM_001195803.1:c.1435G>T

NM_001195798.2:c.1816G>T

NM_001195799.2:c.1693G>T

NM_001195800.2:c.1312G>T

NM_001195803.2:c.1435G>T

Uncertain Significance

Met criteria codes **1**

PP1

Not Met criteria codes **25**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

BA1

BP5

BP7

BP4

BP3

BP1

BP2

BS1

BS4

BS3

BS2

PP2

PP3

PP4

PM6

PM2

PM1

PM3

PM5

PM4

PS1

PS2

PS3

PS4

PVS1

Criteria Specifications for this VCEP

Evidence Links

0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1816G>T (p.Ala606Ser) variant is classified as variant of Uncertain significance for Familial Hypercholesterolemia by applying evidence codes (PP1) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PP1 - 2 informative meioses identified by Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge.

Met criteria codes

PP1	i	✓	2 informative meioses identified by Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge.
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Not Met criteria codes

BA1	i	✗	FAF = 0.0001156 (0.01156%) in European non-Finnish exomes (gnomAD v2.1.1). FAF is not above 0.5%.
BP5	i	✗	Not applicable.
BP7	i	✗	Missense variant. Not applicable.
BP4	i	✗	REVEL: 0,6. Score is not below 0,15.
BP3	i	✗	Not applicable.
BP1	i	✗	Not applicable.
BP2	i	✗	Insuficient information about cases.
BS1	i	✗	FAF = 0.0001156 (0.01156%) in European non-Finnish exomes (gnomAD v2.1.1). FAF is not above 0.2%.
BS4	i	✗	1 affected sibling without the variant from Cardiovascular Research Group,Instituto Nacional de Saude Doutor Ricardo Jorge. 2 cases in 2 families are needed for BS4. BS4 is not met.

BS3			No in vitro or in vivo functional studies showing non-damaging effect on protein function or splicing.
BS2			No unaffected individuals identified with the variant.
PP2			Not applicable.
PP3			REVEL: 0,6. Score is not above 0,75. Splicing predictors - negative.
PP4			Variant does not meet PM2.
PM6			No de novo cases were identified.
PM2			PopMax MAF = 0.0002323 (0.023%) in European non-Finnish exomes (gnomAD v2.1.1). MAF is not below 0.02%.
PM1			Missense at codon 606. PM2 is not Met, it is not exon 4 or any of the 60 Cys residues listed. Not applicable.
PM3			Variant does not meet PM2, not applicable
PM5			No other missense variants classified as Pathogenic in the same codon. Two other missense variants described in the same codon (accessed 19 August 2020): (1)NM_000527.5(LDLR):c.1816G>A (p.Ala606Thr) (ClinVar ID 252046) - classified as VUS by these guidelines. (2)NM_000527.4(LDLR):c.1817C>A (p.Ala606Asp) (ClinVar ID 440663) - classified as VUS by these guidelines.
PM4			Missense variant. Not applicable.
PS1			No variant described that leads to the same amino acid change.
PS2			No de novo cases were identified.
PS3			No in vitro or in vivo functional studies supportive of a damaging effect on the gene or gene product
PS4			Variant does not meet PM2.
PVS1			Missense variant. Not applicable.

Curation History

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