

Variant: *NM_000527.5(LDLR):c.895G>T (p.Ala299Ser)*

Version: 1.0

CA10585180 [↗](#)

251508 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 2a2505bd-8b12-4619-8042-3a52401dd485

Approved on: 2022/2/10

Published on: 2022/4/25

HGVS expressions

NM_000527.5(LDLR):c.895G>T (p.Ala299Ser)

NM_000527.5:c.895G>T

NC_000019.10:g.11107469G>T

CM000681.2:g.11107469G>T

NC_000019.9:g.11218145G>T

CM000681.1:g.11218145G>T

NC_000019.8:g.11079145G>T

NG_009060.1:g.23089G>T

ENST00000252444.10:c.1153G>T

ENST00000559340.2:c.895G>T

ENST00000560467.2:c.895G>T

ENST00000558518.6:c.895G>T

ENST00000252444.9:c.1149G>T

ENST00000455727.6:c.391G>T

ENST00000535915.5:c.772G>T

ENST00000545707.5:c.514G>T

ENST00000557933.5:c.895G>T

ENST00000558013.5:c.895G>T

ENST00000558518.5:c.895G>T

ENST00000558528.1:n.410G>T

ENST00000560467.1:c.495G>T

NM_000527.4:c.895G>T

NM_001195798.1:c.895G>T

NM_001195799.1:c.772G>T

NM_001195800.1:c.391G>T

NM_001195803.1:c.514G>T

NM_001195798.2:c.895G>T

NM_001195799.2:c.772G>T

NM_001195800.2:c.391G>T

NM_001195803.2:c.514G>T

Uncertain Significance

Met criteria codes **2**

PP4

PM2

Not Met criteria codes **4**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information **!**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR): c.895G>T (p.Ala299Ser) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2, PP4) 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: PM2 Met: This variant is absent in gnomAD (gnomAD v2.1.1). PP4 Met: This variant meets PM2 and is identified in 1 index case who met clinical criteria for FH after alternative causes for high cholesterol were excluded (Lipid Clinic, Fundación Jiménez Díaz, Madrid, Spain, PMID 19318025). PP3 not Met: REVEL score = 0.519, which is below the threshold of 0.75. Functional data on splicing is not available, in silico splicing prediction is required. Variant is exonic and at least 50bp downstream from acceptor site and creates GT. MES scores: de novo donor = -2.99, authentic donor = 8.14. De novo score is negative and not used, therefore the variant is not predicted to alter splicing. BP4 not applicable: REVEL score is > 0.5, therefore BP4 is not applicable. PS3 not met: Functional data is not available. PM5 not met: There is one other variant in the same codon: LDLR: NM_000527:c.895G>A (p.Ala299Thr) is classified as Uncertain significance - insufficient evidence by these guidelines. Therefore PM5 is not met.

Met criteria codes

PP4			This variant meets PM2 and is identified in 1 index case who met clinical criteria for FH after alternative causes for high cholesterol were excluded (Lipid Clinic, Fundación Jiménez Díaz, Madrid, Spain, PMID 19318025).
PM2			This variant is absent in gnomAD (gnomAD v2.1.1).

Not Met criteria codes

BP4			REVEL score is > 0.5, therefore BP4 is not applicable.
PS3			Functional data is not available.
PP3			REVEL score = 0.519, which is below the threshold of 0.75. Functional data on splicing is not available, in silico splicing prediction is required. Variant is exonic and at least 50bp downstream from acceptor site and creates GT. MES scores: de novo donor = -2.99, authentic donor = 8.14. De novo score is negative and not used, therefore the variant is not predicted to alter splicing.
PM5			There is one other variant in the same codon: LDLR: NM_000527:c.895G>A (p.Ala299Thr) is classified as Uncertain significance - insufficient evidence by these guidelines. Therefore PM5 is not met.

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