Variant: NM_000527.5(LDLR):c.148G>T (p.Ala50Ser)

Version: 1.0

CA023515

68099 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 7aea797c-2e2f-4ae1-a65b-1e4ca2e3f8e4
Approved on: 2024-10-28
Published on: 2025-01-20

HGVS expressions

NM_000527.5:c.148G>T
NM_000527.5(LDLR):c.148G>T (p.Ala50Ser)
NC_000019.10:g.11100303G>T
CM000681.2:g.11100303G>T
NC_000019.9:g.11210979G>T
CM000681.1:g.11210979G>T
NC_000019.8:g.11071979G>T
NG_009060.1:g.15923G>T
ENST00000252444.10:c.406G>T
ENST00000559340.2:c.148G>T
ENST00000560467.2:c.148G>T
ENST00000558518.6:c.148G>T
ENST00000252444.9:c.402G>T
ENST00000455727.6:c.148G>T
ENST00000535915.5:c.148G>T
ENST00000545707.5:c.148G>T
ENST00000557933.5:c.148G>T
ENST00000557958.1:n.234G>T
ENST00000558013.5:c.148G>T
ENST00000558518.5:c.148G>T
ENST00000560502.5:n.234G>T
NM_000527.4:c.148G>T
NM_001195798.1:c.148G>T
NM_001195799.1:c.148G>T
NM_001195800.1:c.148G>T
NM_001195803.1:c.148G>T
NM_001195798.2:c.148G>T
NM_001195799.2:c.148G>T
NM_001195800.2:c.148G>T
NM_001195803.2:c.148G>T

Uncertain Significance

Not Met criteria codes 21

PP1 PP3 PP4 BA1 PM6 PM2 PM1 PM3 PM5 PM4 BS2 BS1 BS4 BS3 BP4 BP3 BP2 PS1 PS2 PS3 PS4

Evidence Links 0

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.148G>T (p.Ala50Ser) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying no ACMG/AMP evidence codes as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on October 28th, 2024.

Not Met criteria codes

PP1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP3	✖	REVEL= 0.545. It is not above 0.75. Splicing evaluation required. A) variant not on limits. B) variant is exonic and at least 50bp downstream from the canonical acceptor site, but it does not create GT. C) No GT nearby. Variant is not predicted to alter splicing.
PP4	✖	Variant doesn't meet PM2.
BA1	✖	FAF= 0.0006315 (0.063%) in European (non-Finnish) exomes+genomes (gnomAD v4.1.0).
PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2	✖	PopMax MAF = 0.0007738 (0.077%) in European (non-Finnish) exomes+genomes (gnomAD v4.1.0).
PM1	✖	Not in exon 4. Not a cysteine residue.
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	1 other missense variants in the same codon: - NM_000527.5(LDLR):c.148G>A (p.Ala50Thr) (ClinVar ID 251037) - Unknown significance by these guidelines There is no variant in the same codon classified as Pathogenic by these guidelines.

PM4		✖	No in-frame deletions/insertions
BS2		✖	No data available
BS1		✖	FAF= 0.0006315 (0.063%) in European (non-Finnish) exomes+genomes (gnomAD v4.1.0).
BS4		✖	Variant does not segregate with FH phenotype in 1 informative meiosis from 1 family from Centre de Génétique Moléculaire et Chromosomique, Unité de génétique de l'Obésité et des Dyslipidémies
BS3		✖	No data available
BP4		✖	REVEL= 0.545. It is not below 0.5.
BP3		✖	No in-frame deletions/insertions
BP2		✖	Variant identified in an index case with heterozygous FH phenotype (maximum LDL-c= 308mg/dl) and APOB variant c.12460G>T (p.Glu4154Ter), classified as Likely Pathogenic from Genomics Medicine Unit, Navarrabiomed, but not for FH. Patient also has another LDLR variant, c.2282C>T (p.Thr761Met), classified as unknown significance by these guidelines.
PS1		✖	No other missense variant in the codon with the same amino acid change
PS2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No data available
PS4		✖	Variant doesn't meet PM2

Curation History

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