

Variant: *NM_000527.5(LDLR):c.1943C>T (p.Ser648Phe)*

Version: 1.0

CA404093077 [↗](#)

440670 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 3c403102-7e36-4477-9f15-7bedd7dc84fd

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HGVS expressions

NM_000527.5(LDLR):c.1943C>T (p.Ser648Phe)

NM_000527.5:c.1943C>T

NC_000019.10:g.11120189C>T

CM000681.2:g.11120189C>T

NC_000019.9:g.11230865C>T

CM000681.1:g.11230865C>T

NC_000019.8:g.11091865C>T

NG_009060.1:g.35809C>T

ENST00000252444.10:c.2201C>T

ENST00000559340.2:c.*12C>T

ENST00000560467.2:c.1823C>T

ENST00000558518.6:c.1943C>T

ENST00000252444.9:c.2197C>T

ENST00000455727.6:c.1439C>T

ENST00000535915.5:c.1820C>T

ENST00000545707.5:c.1562C>T

ENST00000557933.5:c.1943C>T

ENST00000558013.5:c.1943C>T

ENST00000558518.5:c.1943C>T

ENST00000559340.1:c.524C>T

NM_000527.4:c.1943C>T

NM_001195798.1:c.1943C>T

NM_001195799.1:c.1820C>T

NM_001195800.1:c.1439C>T

NM_001195803.1:c.1562C>T

NM_001195798.2:c.1943C>T

NM_001195799.2:c.1820C>T

NM_001195800.2:c.1439C>T

NM_001195803.2:c.1562C>T

Uncertain Significance

Met criteria codes **2**

PM2 BP4

Not Met criteria codes **20**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PS1

PS2

PS3

PS4

BA1

PP1

PP3

PP4

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

BS2

BP7

BP2

PVS1

Evidence Links 0

- [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.1943C>T (p.Ser648Phe) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PM2 and BP4) 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 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. BP4 - REVEL = 0.487, it is below 0.50, splicing evaluation required. Functional data on splicing not available. 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) variant is exonic and there is an GT nearby MES scores: variant cryptic = -20.85, wt cryptic = -15.66, canonical donor = 10.28. Ratio variant cryptic/wt cryptic: -20.85/-15.66 = 1,33 --- it is above 1.1 Ratio variant cryptic/canonical donor: -20.85/10.28 --- it is not above 0.9 Variant is not predicted to alter splicing --- BP4 is Met.

Met criteria codes

PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
BP4			REVEL = 0.379, it is below 0.50, splicing evaluation required. Functional data on splicing not available. 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) variant is exonic and there is an GT nearby MES scores: variant cryptic = -20.85, wt cryptic = -15.66, canonical donor = 10.28. Ratio variant cryptic/wt cryptic: -20.85/-15.66 = 1,33 --- it is above 1.1 Ratio variant cryptic/canonical donor: -20.85/10.28 --- it is not above 0.9 Variant is not predicted to alter splicing --- BP4 is Met.

Not Met criteria codes

PS1			No more missense variants that lead to the same amino acid change, so PS1 is Not Met.
PS2			de novo occurrence data not reported, so PS2 is Not Met.
PS3			There are no functional studies reported for this variant, so PS3 is not met.
PS4			Variant meets PM2, but case data not reported, so PS4 is Not Met.
BA1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 is Not Met.
PP1			Segregation data not reported, so PP1 is Not Met.

PP3			REVEL = 0.379, it is not above 0.75, so splicing evaluation is required. Functional data on splicing not available. 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) variant is exonic and there is an GT nearby MES scores: variant cryptic = -20.85, wt cryptic = -15.66, canonical donor = 10.28. Ratio variant cryptic/wt cryptic: -20.85/-15.66 = 1,33 --- it is above 1.1 Ratio variant cryptic/canonical donor: -20.85/10.28 = -2,03 --- it is not above 0.9 Variant is not predicted to alter splicing -- - PP3 is not met.
PP4			Variant meets PM2, but case data not reported, so PP4 is Not Met.
PM1			Variant meets PM2 but is not located in exon 4 or alters a cysteine residues, so PM1 is Not Met.
PM3			Not observed in trans with other LP/P variants, so PM3 is Not Met.
PM5			2 other missense variants in the same codon: - NM_000527.5(LDLR):c.1942T>G (p.Ser648Ala) (ClinVar ID 431538) - VUS by these guidelines - NM_000527.5(LDLR):c.1942T>C (p.Ser648Pro) (ClinVar ID 252120) - Likely Pathogenic by these guidelines No more missense variants at the same codon, classified as Pathogenic, so PM5 is Not Met.
PM4			Variant meets PM2 and is missense, so PM4 is Not Met.
PM6			de novo occurrence data not reported, so PM6 is Not Met.
BS1			No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BS1 is Not Met.
BS4			Lack of segregation data not reported, so BS4 is Not Met.
BS3			There are no functional studies reported for this variant, so BS3 is not met.
BS2			No control individuals tested, so BS2 is Not Met.
BP7			Variant is not synonymous, so BP7 is Not Met.
BP2			Not observed in trans with other LP/P variants, so BP2 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.

Curation History 

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