

Variant: *NM_000527.5(LDLR):c.1942T>C (p.Ser648Pro)*

Version: 1.0

CA10585687 [↗](#)

252120 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 5486373f-4e03-4ac7-b53e-fce531d34ddf

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HGVS expressions

NM_000527.5:c.1942T>C

NM_000527.5(LDLR):c.1942T>C (p.Ser648Pro)

NC_000019.10:g.11120188T>C

CM000681.2:g.11120188T>C

NC_000019.9:g.11230864T>C

CM000681.1:g.11230864T>C

NC_000019.8:g.11091864T>C

NG_009060.1:g.35808T>C

ENST00000252444.10:c.2200T>C

ENST00000559340.2:c.*11T>C

ENST00000560467.2:c.1822T>C

ENST00000558518.6:c.1942T>C

ENST00000252444.9:c.2196T>C

ENST00000455727.6:c.1438T>C

ENST00000535915.5:c.1819T>C

ENST00000545707.5:c.1561T>C

ENST00000557933.5:c.1942T>C

ENST00000558013.5:c.1942T>C

ENST00000558518.5:c.1942T>C

ENST00000559340.1:c.523T>C

NM_000527.4:c.1942T>C

NM_001195798.1:c.1942T>C

NM_001195799.1:c.1819T>C

NM_001195800.1:c.1438T>C

NM_001195803.1:c.1561T>C

NM_001195798.2:c.1942T>C

NM_001195799.2:c.1819T>C

NM_001195800.2:c.1438T>C

NM_001195803.2:c.1561T>C

Likely Pathogenic

Met criteria codes **3**

PM2

PS3

PP4

Not Met criteria codes **19**

Expert Panel

Familial Hypercholesterolemia VCEP [↗](#)

Criteria Specification Information

PM1

PM3

PM5

PM4

PM6

BS1

BS4

BS3

BS2

PVS1

PS1

PS2

PS4

BP7

BP4

BP2

BA1

PP1

PP3

Evidence Links

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- 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.1942T>C (p.Ser648Pro) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PS3, PM2 and 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: PS3 - 2 Level 1 assays: PMID 25386756: Heterologous cells (CHO), FACS assays - result - 50% cell surface LDLR and binding and 26% uptake. PMID 23021490: Heterologous cells (CHO), 125I-LDL and WB assays - result - 30-50% LDLR activity; reduced mature protein. ---- activity is below 70% of wild-type, so functional studies are consistent with damaging effect and PS3 is Met. PM2 - This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met. PP4 - Variant meets PM2 and is identified in 1 index cases who fulfills SB possible criteria for FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so PP4 is met.

Met criteria codes

PM2			This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 is Met.
PS3			2 Level 1 assays: PMID 25386756: Heterologous cells (CHO), FACS assays - result - 50% cell surface LDLR and binding and 26% uptake. PMID 23021490: Heterologous cells (CHO), 125I-LDL and WB assays - result - 30-50% LDLR activity; reduced mature protein. ---- activity is below 70% of wild-type, so functional studies are consistent with damaging effect and PS3 is Met.
PP4			Variant meets PM2 and is identified in 1 index cases who fulfills SB possible criteria for FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so PP4 is met.

Not Met criteria codes

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.1943C>T (p.Ser648Phe) (ClinVar ID 440670) - VUS 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			2 Level 1 assays: PMID 25386756: Heterologous cells (CHO), FACS assays - result - 50% cell surface LDLR and binding and 26% uptake. PMID 23021490: Heterologous cells (CHO), 125I-LDL and WB assays - result - 30-50% LDLR activity; reduced mature protein. ---- activity is below 70% of wild-type, so functional studies are consistent with damaging effect and BS3 is not met.
BS2			Not observed in 100 normolipidemic individuals from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so BS2 is Not Met.
PVS1			Variant is missense, so PVS1 is Not Met.
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.
PS4			Variant meets PM2 and is identified in only 1 index cases who fulfills SB possible criteria for FH from Cardiovascular Research Group, Instituto Nacional de Saude Doutor Ricardo Jorge, so PS4 is not met.
BP7			Variant is not synonymous, so BP7 is Not Met.
BP4			REVEL = 0.604. It is not below 0.50, so BP4 is Not Met.
BP2			Not observed in trans with other LP/P variants, so BP2 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 = 0.604, 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 no GT nearby Variant is not predicted to alter splicing --- PP3 is not met.

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The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.