The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

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
Approved on: 2023/4/28
Published on: 2023/5/1

HGVS expressions

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

PS3 PP4 PM2

Not Met criteria codes 19

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS1 PS2 PS4 PP1 PP3 PM6
PM1 PM3 PM5 PM4 BA1
BS2 PVS1 BS1 BS4 BS3
BP4 BP2 BP7

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.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

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.
PM2	✔	This variant is absent from gnomAD (gnomAD v2.1.1), so PM2 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.
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.
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.

PM6	✖	de novo occurrence data not reported, so PM6 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.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.
BA1	✖	No population data was found for this variant in gnomAD (gnomAD v2.1.1), so BA1 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.
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.
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.
BP7	✖	Variant is not synonymous, so BP7 is Not Met.

Curation History

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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.