

Variant: *NM_000527.5(LDLR):c.343C>T (p.Arg115Cys)*

Version: 1.0

CA043225 [↗](#)

251162 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 6663dc62-0d62-4323-967d-4431216d3b1f

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HGVS expressions

NM_000527.5(LDLR):c.343C>T (p.Arg115Cys)

NM_000527.5:c.343C>T

NC_000019.10:g.11105249C>T

CM000681.2:g.11105249C>T

NC_000019.9:g.11215925C>T

CM000681.1:g.11215925C>T

NC_000019.8:g.11076925C>T

NG_009060.1:g.20869C>T

ENST00000252444.10:c.601C>T

ENST00000559340.2:c.343C>T

ENST00000560467.2:c.343C>T

ENST00000558518.6:c.343C>T

ENST00000252444.9:c.597C>T

ENST00000455727.6:c.314-2143C>T

ENST00000535915.5:c.220C>T

ENST00000545707.5:c.314-1316C>T

ENST00000557933.5:c.343C>T

ENST00000558013.5:c.343C>T

ENST00000558518.5:c.343C>T

NM_000527.4:c.343C>T

NM_001195798.1:c.343C>T

NM_001195799.1:c.220C>T

NM_001195800.1:c.314-2143C>T

NM_001195803.1:c.314-1316C>T

NM_001195798.2:c.343C>T

NM_001195799.2:c.220C>T

NM_001195800.2:c.314-2143C>T

NM_001195803.2:c.314-1316C>T

Likely Pathogenic

Met criteria codes 4

PP3 PP4 PM1 PM2

Not Met criteria codes 22

PS1 PS2 PS3 PS4 BP5 BP7
BP4 BP3 BP1 BP2 PP1 PP2

Expert Panel

[Familial Hypercholesterolemia VCEP](#) [↗](#)

Criteria Specification Information **!**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.343C>T (p.Arg115Cys) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes (PM1, PM2, PP3 and PP4) as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (<https://doi.org/10.1101/2021.03.17.21252755>). The supporting evidence is as follows: PM1 - Missense at codon 115. Variant meets PM2 and is in exon 4. PM2 - FAF = 0.0001446 (0.014%) in Latino/Admixed American exomes (gnomAD v2.1.1). PP3 - REVEL = 0.81. PP4 - Variant meets PM2. Identified in at least 1 FH case with clinical diagnosis of definite heterozygous hypercholesterolemia by DLCN score from PMID 16250003.

Met criteria codes

PP3			REVEL = 0.81. It is above 0.75, so PP3 is Met
PP4			Variant meets PM2. Identified in at least 1 FH case with clinical diagnosis of definite heterozygous hypercholesterolemia by DLCN score from PMID 16250003. --- PP4 is Met
PM1			Missense at codon 115. Variant meets PM2 and is in exon 4, so PM1 is Met
PM2			FAF = 0.0001446 (0.014%) in Latino/Admixed American exomes (gnomAD v2.1.1). FAF is under 0.02%, so PM2 is Met

Not Met criteria codes

PS1			Variant meets PM1, so PS1 is not applicable
PS2			no de novo cases were identified, so PS2 is Not Met
PS3			no functional assays performed, not applicable
PS4			Variant meets PM2. Identified in 1 index case with DLCN criteria for FH from PMID 16250003. Not enough evidence to meet PS4. --- PS4 is Not Met
BP5			Not applicable
BP7			Missense variant, so BP7 is not applicable
BP4			REVEL = 0.81. It is not below 0.15 and PP3 is Met, so BP4 is Not Met

BP3			Not applicable
BP1			Not applicable
BP2			Variant identified in an index case with heterozygous FH phenotype and NM_000527.5(LDLR):c.977C>G p.Ser326Cys (ClinVar ID 251581), classified as Likely pathogenic by these guidelines, in trans, from Laboratory of Genetics and Molecular Cardiology. so BP2 is not met
PP1			family members tested are compound heterozygotes for another variant. PP1 is Not Met
PP2			Not applicable
PM3			not identified in individuals with other variants and homozygous FH phenotype --- PM3 is Not Met
PM5			Variant meets PM1, so PM5 is not applicable
PM4			Missense variant, not applicable
BA1			FAF = 0.00005597 (0.006%) in Latino/Admixed American exomes (gnomAD v2.1.1). FAF is not above 0.5%, so BA1 is Not Met.
PM6			no de novo cases were identified, so PM6 is Not Met
BS1			FAF = 0.00005597 (0.006%) in Latino/Admixed American exomes (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met.
BS4			family members tested are compound heterozygotes for another variant. BS4 is Not Met
BS3			no functional assays performed, not applicable
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
PVS1			Missense variant, PVS1 Not Met

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