

Variant: *NM_000527.5(LDLR):c.344G>A (p.Arg115His)*

Version: 1.0

CA043240 [↗](#)

225402 (ClinVar) [↗](#)

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

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

Inheritance Mode: Semidominant inheritance

UUID: 42638e60-83a0-44a9-aefb-814182bee33a

Approved on: 2021/6/7

Published on: 2021/6/24

HGVS expressions

NM_000527.5(LDLR):c.344G>A (p.Arg115His)

NM_000527.5:c.344G>A

NC_000019.10:g.11105250G>A

CM000681.2:g.11105250G>A

NC_000019.9:g.11215926G>A

CM000681.1:g.11215926G>A

NC_000019.8:g.11076926G>A

NG_009060.1:g.20870G>A

ENST00000252444.10:c.602G>A

ENST00000559340.2:c.344G>A

ENST00000560467.2:c.344G>A

ENST00000558518.6:c.344G>A

ENST00000252444.9:c.598G>A

ENST00000455727.6:c.314-2142G>A

ENST00000535915.5:c.221G>A

ENST00000545707.5:c.314-1315G>A

ENST00000557933.5:c.344G>A

ENST00000558013.5:c.344G>A

ENST00000558518.5:c.344G>A

NM_000527.4:c.344G>A

NM_001195798.1:c.344G>A

NM_001195799.1:c.221G>A

NM_001195800.1:c.314-2142G>A

NM_001195803.1:c.314-1315G>A

NM_001195798.2:c.344G>A

NM_001195799.2:c.221G>A

NM_001195800.2:c.314-2142G>A

NM_001195803.2:c.314-1315G>A

Uncertain Significance

Met criteria codes **1**

PS3

Not Met criteria codes **25**

PS1

PS2

PS4

BP5

BP7

BP4

BP3

BP1

BP2

PP1

PP2

PP3

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.344G>A (p.Arg115His) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying evidence codes (PS3) 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: PS3 - Level 1 assays: PMID 12837857: Heterologous cells (COS-7), FACS assays - results - 64% LDLR expression and activity ---- results are below 70% of wild-type, so PS3 is Met.

Met criteria codes

PS3			Level 1 assays: PMID 12837857: Heterologous cells (COS-7), FACS assays - results - 64% LDLR expression and activity ---- results are below 70% of wild-type, so PS3 is Met (PMID 29874871 only refers to PMID 12837857 results)
-----	---	---	---

Not Met criteria codes

PS1			No variant described that leads to the same amino acid change, so PS1 is Not Met
PS2			no de novo cases were identified, so PS2 is Not Met
PS4			variant does not meet PM2, so PS4 is Not Met
BP5			Not applicable
BP7			Missense variant, so BP7 is not applicable
BP4			REVEL = 0.684. It is not below 0.15, so BP4 is Not Met
BP3			Not applicable
BP1			Not applicable
BP2			not identified in individuals with other variants, so BP2 is Not Met
PP1			no family members were tested, so PP1 is Not Met

PP2			Not applicable
PP3			REVEL = 0.684. It is not above 0.75, splicing evaluation is required. Functional data on splicing not available. A) variant not on limits. B) variant is exonic and at least 50bp upstream of canonical donor, but it does not create AG. C) there is AG nearby: MES scores: variant cryptic = -2.67, wt cryptic = -3.23, canonical acceptor = 8.16. scores are negative, which means they are not used, so PP3 is Not Met
PP4			Variant does not meet PM2, so PP4 is Not Met
PM1			Missense at codon 115. PM2 is Not Met, so even though it is exon 4, PM1 is Not Met
PM3			not identified in individuals with other variants, so PM3 is Not Met
PM5			One more missense variant described in same codon: (1)NM_000527.5(LDLR):c.344G>A (p.Arg115His) (ClinVar ID 225402) - classified as VUS by these guidelines, so PM5 is Not Met
PM4			Missense variant, not applicable
BA1			FAF = 0.001691 (0.169%) in East Asian 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
PM2			PopMax MAF = 0.002260 (0.23%) in East Asian exomes (gnomAD v2.1.1). MAF is not under 0.02%, so PM2 is Not Met
BS1			FAF = 0.001691 (0.169%) in East Asian exomes (gnomAD v2.1.1). FAF is not above 0.2%, so BS1 is Not Met
BS4			no family members were tested, so BS4 is Not Met
BS3			Level 1 assays: PMID 12837857: Heterologous cells (COS-7), FACS assays - results - 64% LDLR expression and activity ---- whole cycle is not above 90% of wild-type, so BS3 is Not Met (PMID 29874871 only refers to PMID 12837857 results)
BS2			no unaffected individuals identified with the variant, so BS2 is Not Met
PVS1			Missense variant, PVS1 Not Met

Showing 1 to 1 of 1 rows

--

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.