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.898A>G (p.Arg300Gly)

Version: 1.0

CA030068

251510 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 1d588148-2877-4c5e-aad7-bcdee6f58936
Approved on: 2022/10/28
Published on: 2022/12/24

HGVS expressions

NM_000527.5(LDLR):c.898A>G (p.Arg300Gly)
NM_000527.5:c.898A>G
NC_000019.10:g.11107472A>G
CM000681.2:g.11107472A>G
NC_000019.9:g.11218148A>G
CM000681.1:g.11218148A>G
NC_000019.8:g.11079148A>G
NG_009060.1:g.23092A>G
ENST00000252444.10:c.1156A>G
ENST00000559340.2:c.898A>G
ENST00000560467.2:c.898A>G
ENST00000558518.6:c.898A>G
ENST00000252444.9:c.1152A>G
ENST00000455727.6:c.394A>G
ENST00000535915.5:c.775A>G
ENST00000545707.5:c.517A>G
ENST00000557933.5:c.898A>G
ENST00000558013.5:c.898A>G
ENST00000558518.5:c.898A>G
ENST00000558528.1:n.413A>G
ENST00000560467.1:c.498A>G
NM_000527.4:c.898A>G
NM_001195798.1:c.898A>G
NM_001195799.1:c.775A>G
NM_001195800.1:c.394A>G
NM_001195803.1:c.517A>G
NM_001195798.2:c.898A>G
NM_001195799.2:c.775A>G
NM_001195800.2:c.394A>G
NM_001195803.2:c.517A>G

Likely Pathogenic

Met criteria codes 2

PS3 PM2

Not Met criteria codes 6

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

BP4 PS4 PM1 PM5 PP3 PP4

Criteria Specifications for this VCEP

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.898A>G (p.Arg300Gly) variant is classified as likely Pathogenic variant for Familial Hypercholesterolemia by applying evidence code PM2, PS3 and PS4 supporting 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_Met : PopMax MAF = 0.00003 in European (Non-Finnish) exomes (gnomAD v2.1.1) PS3_Met : Level 1 assay: Study of the whole LDLR cycle in Heterologous cells (CHO-ldlA7 cells), WB+FACS+CLSM. LDLR expression was not statistically different as compared to control. Conversely, LDL binding (<60%) and uptake (<60%) were significantly decreased (P<0.001). Interestingly, although the variant affects LDL binding and uptake, do not affect VLDL uptake. This reveals that the conformational change occurring in the module does not propagate to the whole ligand binding domain. (from PMID:25545329)

Met criteria codes

PS3	✔	Level 1 assay: Study of the whole LDLR cycle in Heterologous cells (CHO-ldlA7 cells), WB+FACS+CLSM. LDLR expression was not statistically different as compared to control. Conversely, LDL binding (<60%) and uptake (<60%) were significantly decreased (P<0.001). Interestingly, although the variant affects LDL binding and uptake, do not affect VLDL uptake. This reveals that the conformational change occurring in the module does not propagate to the whole ligand binding domain. (from PMID:25545329)
PM2	✔	PopMax MAF = 0.00003 in European (Non-Finnish) exomes (gnomAD v2.1.1)

Not Met criteria codes

BP4	✖	REVEL = 0.556. It is not below 0.50.BP4 is not met
PS4	✖	No clear data are reported.
PM1	✖	Variant is not located in a mutational hot spot and/or critical and well-established functional domain (exon 6).
PM5	✖	There is 1 missense variant in the same codon (c.899G>A (p.Arg300Lys) not classified as pathogenic by these guidelines.
PP3	✖	REVEL = 0.556. It is not above 0.75. Splicing evaluation is required Functional data on splicing not available: A) not on limits B) does not create GT C) nearby GT MES scores: variant cryptic site=-14.9, wt cryptic site=-15.9, canonical donor site=10.4 Ratio variant cryptic site/wt criptic site= 0.93 ----it is not above 1.1 Ratio variant cryptic site/canonical donor site = - 1.43---- it is not above 0.95 PP3 is Not Met
PP4	✖	

variant met PM2 and was reported in 5 FH patients with DLCN>6 (PMID: 28965616 - LIPIGEN study- and PMID: 19318025). However 4 out 5 patients were compound heterozygotes. Therefore, we cannot exclude alternative causes of high LDL-C

Curation History

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