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.1283A>G (p.Asn428Ser)

Version: 1.0

CA10585384

251765 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 33171974-9ced-41c5-8ab1-03a7f922799f
Approved on: 2024/4/17
Published on: 2024/10/2

HGVS expressions

NM_000527.5:c.1283A>G
NM_000527.5(LDLR):c.1283A>G (p.Asn428Ser)
NC_000019.10:g.11113374A>G
CM000681.2:g.11113374A>G
NC_000019.9:g.11224050A>G
CM000681.1:g.11224050A>G
NC_000019.8:g.11085050A>G
NG_009060.1:g.28994A>G
ENST00000252444.10:c.1541A>G
ENST00000559340.2:c.1283A>G
ENST00000560467.2:c.1163A>G
ENST00000558518.6:c.1283A>G
ENST00000252444.9:c.1537A>G
ENST00000455727.6:c.779A>G
ENST00000535915.5:c.1160A>G
ENST00000545707.5:c.902A>G
ENST00000557933.5:c.1283A>G
ENST00000558013.5:c.1283A>G
ENST00000558518.5:c.1283A>G
ENST00000559340.1:c.4A>G
ENST00000560173.1:n.282A>G
ENST00000560467.1:c.763A>G
NM_000527.4:c.1283A>G
NM_001195798.1:c.1283A>G
NM_001195799.1:c.1160A>G
NM_001195800.1:c.779A>G
NM_001195803.1:c.902A>G
NM_001195798.2:c.1283A>G
NM_001195799.2:c.1160A>G
NM_001195800.2:c.779A>G
NM_001195803.2:c.902A>G

Uncertain Significance

Met criteria codes 2

PM2 PP4

Expert Panel

Familial Hypercholesterolemia VCEP

Not Met criteria codes 4

BP4 PS3 PM5 PP3

Evidence Links 0

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1283A>G (p.Asn428Ser) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2 and PP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 17 April 2024. The supporting evidence is as follows: PM2: Variant is absent from gnomAD (gnomAD v2.1.1). PP4: Variant meets PM2 and is identified in 1 index case who fulfills MedPed criteria for FH after alternative causes of high cholesterol were excluded, reported in PMID 16627557 (Blesa et al., 2006), Spain.

Met criteria codes

PM2	✔	Variant is absent from gnomAD (gnomAD v2.1.1).
PP4	✔	Variant meets PM2 and is identified in 1 index case who fulfil MedPed criteria for FH after alternative causes of high cholesterol were excluded, reported in PMID 16627557 by Blesa et al, 2006, from Universitario de Valencia, Spain.

Not Met criteria codes

BP4	✖	REVEL=0.688, it is not above 0.75, splicing evaluation required. Functional data on splicing not available. MES performed: A) Variant is not on limits. B) Variant is on limits and creates AG. Var de novo/Wt score= -11.09/6.59= -1.68, it is <0.8. REVEL is not below 0.5, therefore PP3/BP4 is not met. C) Variant is on limits and nearby an AG (agcctcatccccaacctgAGgaa/g) and a GT (aa/gcGTGGTC). Var cryptic acceptor/Wt cryptic acceptor score= -2.74/-3.69=0.74, it is <1.1. Var cryptic acceptor/Wt acceptor score= -2.74/6.59= -0.42, it is <0.9; Var cryptic donor/Wt cryptic donor score= -13.97/-8.71=1.6, it is >1.1, however both scores were negative. Var cryptic donor/Wt donor score=-13.97/9.60= -1.46, it is <0.9. REVEL is not below 0.5, therefor PP3/BP4 is not met. Variant is not predicted to alter splicing. SpliceAI confirmed same result.
PS3	✖	Functional data is not available.
PM5	✖	One other variant at same codon: LDLR:c.1284C>G (p.Asn428Lys) is classified as VUS by these guidelines, therefore PM5 is not met.
PP3	✖	REVEL=0.688, it is not above 0.75, splicing evaluation required.

Curation History

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