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.1366C>T (p.Leu456Phe)

Version: 1.0

CA034017

926526 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: 1d551fc0-d415-4840-99f9-66e331949130
Approved on: 2023/6/23
Published on: 2024/10/2

HGVS expressions

NM_000527.5:c.1366C>T
NM_000527.5(LDLR):c.1366C>T (p.Leu456Phe)
NC_000019.10:g.11113542C>T
CM000681.2:g.11113542C>T
NC_000019.9:g.11224218C>T
CM000681.1:g.11224218C>T
NC_000019.8:g.11085218C>T
NG_009060.1:g.29162C>T
ENST00000252444.10:c.1624C>T
ENST00000559340.2:c.1366C>T
ENST00000560467.2:c.1246C>T
ENST00000558518.6:c.1366C>T
ENST00000252444.9:c.1620C>T
ENST00000455727.6:c.862C>T
ENST00000535915.5:c.1243C>T
ENST00000545707.5:c.985C>T
ENST00000557933.5:c.1366C>T
ENST00000558013.5:c.1366C>T
ENST00000558518.5:c.1366C>T
ENST00000559340.1:c.87C>T
ENST00000560467.1:c.846C>T
NM_000527.4:c.1366C>T
NM_001195798.1:c.1366C>T
NM_001195799.1:c.1243C>T
NM_001195800.1:c.862C>T
NM_001195803.1:c.985C>T
NM_001195798.2:c.1366C>T
NM_001195799.2:c.1243C>T
NM_001195800.2:c.862C>T
NM_001195803.2:c.985C>T

Uncertain Significance

Met criteria codes 2

BP4 PM2

Not Met criteria codes 3

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PS4 PM5 PP4

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c. 1366C>T (p. Leu456Phe) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2 and BP4 as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (specification version 1.2) on 23 June 2023. The supporting evidence is as follows: PM2: PopMax MAF=0.00003 in South Asian population in gnomAD (gnomAD v2.1.1). BP4: REVEL=0.487, it is not above 0.75, splicing evaluation required. Functional data on splicing is not available. MES performed: A) Variant is not on limits. B) Variant is on limit but does not crate de novo AG. Variant created GT however is not on limit. C) Variant is on limit and nearby three intra-exonic AGs: cctcctgcctcagcacccAGc/ttt , Var/Wt cryptic score = 0.37/-0.2 = -0.15, it is <1.1; ctcagcacccagc/tttgacAGagc, Var/Wt cryptic score = -3.2/-2.9 = 1.103, it is = 1.1, however both scores are negative; and agcacccagc/tttgacagAGccc, Var/Wt cryptic score = -33.4/-34.48 = 0.97, it is <1.1. MES score for canonical intron 9 acceptor cttctctcctcctgcctcAGcac is 6.76, so none of the Var cryptic scores/Wt score is >0.9. Variant is not predicted to alter splicing and REVEL score is below 0.5, therefore BP4 is met.

Met criteria codes

BP4	✔	REVEL=0.487, it is not above 0.75, splicing evaluation required. Functional data on splicing is not available. MES performed: A) Variant is not on limits. B) Variant is on limit but does not crate de novo AG. Variant created GT however is not on limit. C) Variant is on limit and nearby three intra-exonic AGs: cctcctgcctcagcacccAGc/ttt , Var/Wt cryptic score = 0.37/-0.2 = -0.15, it is <1.1; ctcagcacccagc/tttgacAGagc, Var/Wt cryptic score = -3.2/-2.9 = 1.103, it is = 1.1, however both scores are negative; and agcacccagc/tttgacagAGccc, Var/Wt cryptic score = -33.4/-34.48 = 0.97, it is <1.1. MES score for canonical intron 9 acceptor cttctctcctcctgcctcAGcac is 6.76, so none of the Var cryptic scores/Wt score is >0.9. Variant is not predicted to alter splicing. REVEL score is below 0.5, therefore BP4 is met. SpliceAI confirmed same result.
PM2	✔	PopMax MAF=0.00003 in South Asian population in gnomAD (gnomAD v2.1.1).

Not Met criteria codes

PS4	✖	Clinical data is not available.
PM5	✖	Two other variants at same codon: LDLR:c.1367T>C (p.Leu456Pro) classified as VUS; LDLR:c.1367T>A(p.Leu456His) classified as VUS by these guidelines, therefore PM5 is not met.
PP4	✖	Clinical data is not available.

Curation History

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