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.1367T>C (p.Leu456Pro)

Version: 1.0

CA305300092

440637 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: f2e59569-194f-47a1-b281-2579bacb1f7e
Approved on: 2024/6/23
Published on: 2024/10/2

HGVS expressions

NM_000527.5(LDLR):c.1367T>C (p.Leu456Pro)
NM_000527.5:c.1367T>C
NC_000019.10:g.11113543T>C
CM000681.2:g.11113543T>C
NC_000019.9:g.11224219T>C
CM000681.1:g.11224219T>C
NC_000019.8:g.11085219T>C
NG_009060.1:g.29163T>C
ENST00000252444.10:c.1625T>C
ENST00000559340.2:c.1367T>C
ENST00000560467.2:c.1247T>C
ENST00000558518.6:c.1367T>C
ENST00000252444.9:c.1621T>C
ENST00000455727.6:c.863T>C
ENST00000535915.5:c.1244T>C
ENST00000545707.5:c.986T>C
ENST00000557933.5:c.1367T>C
ENST00000558013.5:c.1367T>C
ENST00000558518.5:c.1367T>C
ENST00000559340.1:c.88T>C
ENST00000560467.1:c.847T>C
NM_000527.4:c.1367T>C
NM_001195798.1:c.1367T>C
NM_001195799.1:c.1244T>C
NM_001195800.1:c.863T>C
NM_001195803.1:c.986T>C
NM_001195798.2:c.1367T>C
NM_001195799.2:c.1244T>C
NM_001195800.2:c.863T>C
NM_001195803.2:c.986T>C

Uncertain Significance

Met criteria codes 4

PS4_Supporting PP3 PP4 PM2

Not Met criteria codes 3

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

PM3 PM5 PS3

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5 (LDLR):c.1367T>C (p.Leu456Pro) variant is classified as Uncertain significance - insufficient evidence for Familial Hypercholesterolemia by applying ACMG/AMP evidence codes PM2, PP3, PP4 and PS4_Supporting 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=0.00006 in African population in gnomAD (gnomAD 2.1.1). PP3: REVEL=0.862. PS4_Supporting, PP4: Variant meets PM2 and is identified in at least 2 unrelated index cases who fulfill criteria for FH (1 case meeting Simon Broome criteria from UT Southwestern Medical Center, US, in PMID 23064986 (Ahmad et al., 2012); 1 case from University of Pennsylvania, US, in PMID 19026292 (Kolansky et al., 2008) with total cholesterol of 836 mg/dl at age of 8 yrs and pathogenic LDLR variant c.1846-1G>A.

Met criteria codes

PS4_Supporting	✔	Variant meets PM2 and is identified in 2 unrelated index cases reported in PubMed. PMID 23064986: one case met Simon Broome criteria reported by Ahmad et al, 2012, from UT Southwestern, US. PMID 19026292: one HoFH case with TC of 836 mg/dl at age of 8 yrs carries this variant and pathogenic LDLR: c.1846-1G>A, reported by Kolansky et al, 2008 from University of Pennsylvania, US.
PP3	✔	REVEL=0.862, it is above the impact threshold of 0.75.
PP4	✔	Variant meets PM2 and is identified in ˃1 index cases who fulfil criteria for FH after alternative causes of high cholesterol were excluded.
PM2	✔	PopMax MAF=0.00006 in African population in gnomAD (gnomAD 2.1.1).

Not Met criteria codes

PM3	✖	PMID 19026292 by Kolansky et al, 2008: variant identified in heterozygous state in one HoFH case who had TC of 836 mg/dl at age of 8 yrs old, and also carries heterozygous pathogenic LDLR:c.1846-1G>A. Variants were presented as 1st/2nd alleles in Table 2. However, two variants for this patient were not confirmed in trans by family or experimental data, although both variants were reported independently in unrelated heterozygous FH cases previously. This case is counted towards PS4.
PM5	✖	Two other variants at same codon: LDLR:c.1366C>T(p.Leu456Phe) classified as VUS; LDLR:c.1367T>A(p.Leu456His) classified as VUS by these guidelines, therefore PM5 is not met.
PS3	✖	Functional data is not available.

Curation History

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