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.2096C>T (p.Pro699Leu)

Version: 1.0

CA038525

252219 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: ea33bc95-d102-418a-b019-83d258dcad77
Approved on: 2021-06-18
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HGVS expressions

NM_000527.5:c.2096C>T
NM_000527.5(LDLR):c.2096C>T (p.Pro699Leu)
NC_000019.10:g.11120478C>T
CM000681.2:g.11120478C>T
NC_000019.9:g.11231154C>T
CM000681.1:g.11231154C>T
NC_000019.8:g.11092154C>T
NG_009060.1:g.36098C>T
ENST00000252444.10:c.2354C>T
ENST00000559340.2:c.*165C>T
ENST00000560467.2:c.1976C>T
ENST00000558518.6:c.2096C>T
ENST00000252444.9:c.2350C>T
ENST00000455727.6:c.1592C>T
ENST00000535915.5:c.1973C>T
ENST00000545707.5:c.1606+245C>T
ENST00000557933.5:c.2096C>T
ENST00000558013.5:c.2096C>T
ENST00000558518.5:c.2096C>T
NM_000527.4:c.2096C>T
NM_001195798.1:c.2096C>T
NM_001195799.1:c.1973C>T
NM_001195800.1:c.1592C>T
NM_001195803.1:c.1606+245C>T
NM_001195798.2:c.2096C>T
NM_001195799.2:c.1973C>T
NM_001195800.2:c.1592C>T
NM_001195803.2:c.1606+245C>T

Uncertain Significance

Met criteria codes 3

PP3 **BS4** **PP1_Strong**

Not Met criteria codes 23

PS1 **PS2** **PS3** **PS4** **PVS1**
PP2 **PP4** **PM1** **PM3** **PM5**

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

PM4 PM6 PM2 BA1 BS2
BS1 BS3 BP4 BP3 BP1 BP2
BP5 BP7

Evidence Links 0

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

NM_000527.5(LDLR):c.2096C>T (p.Pro699Leu) variant is classified as Uncertain significance for Familial Hypercholesterolemia by applying evidence codes (BS4, PP1_Strong and PP3) 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: BS4 - Variant does not segregate with FH phenotype in 11 informative meioses in 6 families (Laboratory of Genetics and Molecular Cardiology). PP1_strong - Variant segregates with FH phenotype in 58 informative meioses in 9 families from Laboratory of Genetics and Molecular Cardiology. PP3 - REVEL: 0,92.

Met criteria codes

PP3	✓	REVEL: 0,92. Score is above 0,75.
BS4	✓	Variant does not segregate with FH phenotype in 11 informative meioses (nonsegregations) in 6 families (Laboratory of Genetics and Molecular Cardiology).
PP1_Strong	✓	Variant segregates with FH phenotype in 58 informative meioses (segregations) in 9 families from Laboratory of Genetics and Molecular Cardiology.

Not Met criteria codes

PS1	✗	No variant described that leads to the same amino acid change.
PS2	✗	No de novo cases were identified.
PS3	✗	No functional assays performed/found - not applicable.
PS4	✗	Variant does not meet PM2, not applicable
PVS1	✗	Missense variant. Not applicable.
PP2	✗	Not applicable.
PP4	✗	Variant does not meet PM2, so not applicable
PM1	✗	Missense at codon 699. PM2 is not Met, it is not exon 4 or any of the 60 Cys residues listed. Not applicable.

PM3	✖	Variant does not meet PM2, so not applicable.
PM5	✖	No other variant found in this codon in ClinVar database (assessed 4 June 2020).
PM4	✖	Missense variant. Not applicable.
PM6	✖	No de novo cases were identified.
PM2	✖	PopMax MAF = 0.0003606 (0.036%) in African exomes (gnomAD v2.1.1). FAF is not below 0.02%
BA1	✖	FAF = 0.00004981 (0.004981%) in African exomes (gnomAD v2.1.1). FAF is not above 0.5%
BS2	✖	Variant identified in two unaffected heterozygous carriers from Laboratory of Genetics and Molecular Cardiology. At least 3 htz unaffected carriers are needed for adding this point. BS2 not met.
BS1	✖	FAF = 0.00004981 (0.004981%) in African exomes (gnomAD v2.1.1). FAF is not above 0.2%
BS3	✖	No functional assays performed/found - not applicable.
BP4	✖	REVEL: 0,92. Score is not below 0,50.
BP3	✖	Not applicable.
BP1	✖	Not applicable.
BP2	✖	No proven pathogenic variants in double heterozygocity: - One carrier also htz for PCSK9 c.1976G>T, p.Arg659Leu (ClinVar ID 297705) (Uncertain significance in ClinVar) found by Ambry Genetics. - One carrier also htz for APOB p.Leu3436Val (VUS) and - other carrier htz for PCSK9 c.1069C>T, p.Arg357Cys (ClinVar ID 575758)(Conflicting classifications in ClinVar) found by Laboratory of Genetics and Molecular Cardiology.
BP5	✖	Not applicable.
BP7	✖	Missense variant. Not applicable.

Curation History

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