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
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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

PP1_Strong BS4 PP3

Not Met criteria codes 23

PM1 PM3 PM5 PM4 PM6
PM2 BA1 BS2 BS1 BS3

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

BP4 BP3 BP1 BP2 BP5 BP7
PVS1 PS1 PS2 PS3 PS4
PP2 PP4

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

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

Not Met criteria codes

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.
PVS1	✖	Missense variant. Not applicable.
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
PP2	✖	Not applicable.
PP4	✖	Variant does not meet PM2, so not applicable

Curation History

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