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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: 2021/6/18
Published on: 2021/6/24

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 PP3 BS4

Not Met criteria codes 23

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

Expert Panel

Familial Hypercholesterolemia VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

BA1 PM1 PM3 PM5 PM4 PM6 PM2 BS2 PVS1 BS1 BS3

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.
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).

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
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.
PP2		✖	Not applicable.
PP4		✖	Variant does not meet PM2, so not applicable
BA1		✖	FAF = 0.00004981 (0.004981%) in African exomes (gnomAD v2.1.1). FAF is not above 0.5%
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%
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.
PVS1		✖	Missense variant. Not applicable.
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.

Curation History

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ee Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View	NM_000527.5(LDLR):c.2096C>T (p.Pro...	Uncertain Significance	Hypercholesterolemia, Familial	2021-06-24	1.0	-	LDLR

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