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Variant: NM_000527.5(LDLR):c.1291G>C (p.Ala431Pro)

Version: 1.0

CA023446

36454 (ClinVar)

Gene: LDLR (HGNC:3949)
Condition: hypercholesterolemia, familial (MONDO:0007750)
Inheritance Mode: Semidominant inheritance
UUID: e84a20c0-138d-4529-b5ae-386ecfbc2a26
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HGVS expressions

NM_000527.5(LDLR):c.1291G>C (p.Ala431Pro)
NM_000527.5:c.1291G>C
NC_000019.10:g.11113382G>C
CM000681.2:g.11113382G>C
NC_000019.9:g.11224058G>C
CM000681.1:g.11224058G>C
NC_000019.8:g.11085058G>C
NG_009060.1:g.29002G>C
ENST00000252444.10:c.1549G>C
ENST00000559340.2:c.1291G>C
ENST00000560467.2:c.1171G>C
ENST00000558518.6:c.1291G>C
ENST00000252444.9:c.1545G>C
ENST00000455727.6:c.787G>C
ENST00000535915.5:c.1168G>C
ENST00000545707.5:c.910G>C
ENST00000557933.5:c.1291G>C
ENST00000558013.5:c.1291G>C
ENST00000558518.5:c.1291G>C
ENST00000559340.1:c.12G>C
ENST00000560173.1:n.290G>C
ENST00000560467.1:c.771G>C
NM_000527.4:c.1291G>C
NM_001195798.1:c.1291G>C
NM_001195799.1:c.1168G>C
NM_001195800.1:c.787G>C
NM_001195803.1:c.910G>C
NM_001195798.2:c.1291G>C
NM_001195799.2:c.1168G>C
NM_001195800.2:c.787G>C
NM_001195803.2:c.910G>C

Likely Pathogenic

Met criteria codes 5

PP3 PP4 PM3 PM5 PM2

Expert Panel

Familial Hypercholesterolemia VCEP

Not Met criteria codes 21

PP1 PP2 BA1 PM1 PM4 PM6 PVS1 BS2 BS1 BS4 BS3 PS1 PS2 PS3 PS4 BP5 BP7 BP4 BP3 BP1 BP2

Evidence Links 0

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Familial Hypercholesterolemia VCEP

The NM_000527.5(LDLR):c.1291G>C (p.Ala431Pro) variant is classified as Likely pathogenic for Familial Hypercholesterolemia by applying evidence codes PM2, PM3, PM5, PP3 and PP4, as defined by the ClinGen Familial Hypercholesterolemia Expert Panel LDLR-specific variant curation guidelines (https://doi.org/10.1016/j.gim.2021.09.012). The supporting evidence is as follows: PM2 - This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met. PM3 - variant meets PM2 and was identified in: - index case who is homozygous for the variant and has LDL at least 550mg/dl (figure 2A in the paper) from PMID 29502162 (Klaus et al. 2018), Germany. --- individual is homozygous for variant and has an homozygous phenotype, so PM3 is met. PM5 - one other missense variant in the same codon: - NM_000527.5(LDLR):c.1291G>A (p.Ala431Thr) - 2 stars, Pathogenic/Likely pathogenic in ClinVar - Pathogenic by these guidelines, so PM5 is met. PP3 - REVEL = 0.939. It is above 0.75, so PP3 is met. PP4 - variant meets PM2 and was identified in 1 index case with DLCN at least 8 (untreated LDL at least 550mg/dl) from PMID 29502162 (Klaus et al., 2018), Germany, so PP4 is met.

Met criteria codes

PP3	✔	REVEL = 0.939. It is above 0.75, so PP3 is met
PP4	✔	variant meets PM2 and was identified in: - 1 index case with DLCN at least 8 (untreated LDL at least 550mg/dl) from PMID 29502162 (Klaus et al., 2018), Germany. so PP4 is met
PM3	✔	variant meets PM2 and was identified in: - index case who is homozygous for the variant and has LDL at least 550mg/dl (figure 2A in the paper) from PMID 29502162 (Klaus et al. 2018), Germany. --- individual is homozygous for variant and has an homozygous phenotype, so PM3 is met
PM5	✔	one other missense variant in the same codon: - NM_000527.5(LDLR):c.1291G>A (p.Ala431Thr) - 2 stars, Pathogenic/Likely pathogenic in ClinVar - Pathogenic by these guidelines, so PM5 is met
PM2	✔	This variant was not identified in gnomAD (gnomAD v2.1.1), so PM2 is met

Not Met criteria codes

PP1	✖	no segregation data
PP2	✖	not applicable

BA1		✖	This variant was not identified in gnomAD (gnomAD v2.1.1), so BA1 is not met
PM1		✖	variant is missense and PM2 is met, but it is not in exon 4 and does not alter Cys, so not met
PM4		✖	variant is missense, so not applicable
PM6		✖	no de novo occurrence
PVS1		✖	variant is missense and not in initiation codon, so not applicable
BS2		✖	no data in normolipidemic individuals, so not met
BS1		✖	This variant was not identified in gnomAD (gnomAD v2.1.1), so BS1 is not met
BS4		✖	no segregation data
BS3		✖	no functional study on this variant
PS1		✖	no other variant leads to the same amino acid change, so not met
PS2		✖	no de novo occurrence
PS3		✖	no functional study on this variant
PS4		✖	variant meets PM2 and was identified in: - 1 index case with DLCN at least 8 (untreated LDL at least 550mg/dl) from PMID 29502162 (Klaus et al., 2018), Germany. not enough, so PS4 is not met
BP5		✖	not applicable
BP7		✖	variant is missense, so not applicable
BP4		✖	REVEL = 0.939. It is not below 0.50, so BP4 is not met
BP3		✖	not applicable
BP1		✖	not applicable
BP2		✖	variant was not identified in index cases with other variants

Curation History

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