Variant: NM_000018.4(ACADVL):c.1226C>T (p.Thr409Met)

Version: 1.0

CA312268

21013 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: d5898219-a2c1-4795-9e64-8372b2e0e1d2
Approved on: 2025-11-25
Published on: 2025-11-25

HGVS expressions

NM_000018.4:c.1226C>T
NM_000018.4(ACADVL):c.1226C>T (p.Thr409Met)
NC_000017.11:g.7223687C>T
CM000679.2:g.7223687C>T
NC_000017.10:g.7127006C>T
CM000679.1:g.7127006C>T
NC_000017.9:g.7067730C>T
NG_007975.1:g.8854C>T
NG_008391.2:g.1364G>A
NG_033038.1:g.15858G>A
ENST00000356839.10:c.1226C>T
ENST00000322910.9:c.*1181C>T
ENST00000350303.9:c.1160C>T
ENST00000356839.9:c.1226C>T
ENST00000542255.6:c.84C>T
ENST00000543245.6:c.1295C>T
ENST00000578579.2:n.397C>T
ENST00000578711.1:n.183C>T
ENST00000578824.5:n.642C>T
ENST00000579425.5:n.250C>T
ENST00000579546.1:c.63C>T
ENST00000583850.5:n.1C>T
ENST00000583858.5:c.255C>T
ENST00000585203.6:n.434C>T
NM_000018.3:c.1226C>T
NM_001033859.2:c.1160C>T
NM_001270447.1:c.1295C>T
NM_001270448.1:c.998C>T
NM_001033859.3:c.1160C>T
NM_001270447.2:c.1295C>T
NM_001270448.2:c.998C>T

Uncertain Significance

Met criteria codes 3

PP4_Moderate PM2_Supporting PM3

Expert Panel

ACADVL VCEP

Not Met criteria codes 1

PP3

Evidence Links 0

Criteria Specification Information

Criteria Specification: *ClinGen ACADVL Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ACADVL Version 2.1.0*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.1226C>T(NM_000018.4) variant in ACADVL is a missense variant predicted to cause substitution of threonine, by methionine, at amino acid 409 (p.Thr409Met). The highest population minor allele frequency in gnomAD v4.1 is 0.00076 in the East Asian population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.33, which is neither above nor below the thresholds predicting a damaging or benign impact on ACADVL function. This variant has been detected in numerous individuals with very long chain acyl CoA dehydrogenase (VLCAD) deficiency. Of those individuals, 1 was compound heterozygous for the variant and numerous were homozygous. (PM3 points: 1.5) (PMID: 31031081, 26743058) (PM3_Moderate). Five patients homozygous, and three patients compound heterozygous for the variant displayed increased C14:1 Levels (PMID: 31031081, 24503138),of which two compound heterozygotes displayed reduced enzyme levels (PMID: 31031081). One homozygote and one compound heterozygote displayed plasma acylcarnitine analysis consistent with VLCADD(PMID: 24503138), which is highly specific for VLCAD deficiency (PP4_Moderate) Due to limited evidence, this variant is classified as a variant of uncertain significance for autosomal recessive very long chain acyl-CoA dehydrogenase (VLCAD) deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen ACADVL Variant Curation Expert Panel: PM2_Supporting, PP4_Moderate, PM3_Moderate. (ACADVL VCEP Specifications Version 1; Approved November 8, 2021)

Met criteria codes

PP4_Moderate	✔	Rovelli V et al. Clinical and biochemical outcome of patients with very long-chain acyl-CoA dehydrogenase deficiency. Mol Genet Metab. 2019 May;127(1):64-73. PMID: 31031081. Case 15, 16: “Affected patients had mildly to moderately elevated C14:1-carnitine levels at birth (0.85 µmol/l and 2.20 µmol/l) with normal urine organic acids. Fibroblast testing was consistent with VLCAD deficiency in both cases, suggesting pathogenicity.” PP4_M: NBS C14:1 Levels ≥ 1.0 µM AND reduced VLCAD activity Merritt JL et al. Infants suspected to have very-long chain acyl-CoA dehydrogenase deficiency from newborn screening. Mol Genet Metab. 2014 Apr;111(4):484-92. PMID: 24503138. PP4_M: NBS C14:1 Levels ≥ 1.0 µM AND Plasma Acylcarnitine analysis “consistent with VLCADD” Five patients homozygous, and three patients compound heterozygous for the variant displayed increased C14:1 Levels (PMID: 31031081, 24503138),of which two compound heterozygotes displayed reduced enzyme levels (PMID: 31031081). One homozygote and one compound heterozygote displayed plasma acylcarnitine analysis consistent with VLCADD(PMID: 24503138), which is highly specific for VLCAD deficiency (PP4_Moderate)
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v4.1 is 0.00076 in the East Asian population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM3	✔	PMID: 31031081 (ACADVL):c.848T>C (p.Val283Ala) PP4_Moderate, PM3_Strong, PM1, PP3, PS3_supporting P not proven in trans: 0.5 points PMID: 26743058 NBS C14:1 levels >0.9 homoz. Heteroz : PP4 41 homoz. : 1 point This variant has been detected in numerous individuals with very long chain acyl CoA dehydrogenase (VLCAD) deficiency. Of those individuals, 1 was compound heterozygous for the variant and numerous were homozygous. (PM3 points: 1.5) (PMID: 31031081, 26743058) (PM3_Moderate).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.33, which is neither above nor below the thresholds predicting a damaging or benign impact on ACADVL function.

Curation History

ng 1 to 1 of 1 rows