

Variant: *NM_000018.4(ACADVL):c.1269G>A (p.Ser423=)*

Version: 2.0

CA8338048 [↗](#)

569548 (ClinVar) [↗](#)

Gene: ACADVL ([HGNC:37](#))

Condition: very long chain acyl-CoA dehydrogenase deficiency
([MONDO:0008723](#))

Inheritance Mode: Autosomal recessive inheritance

UUID: 142a9111-4aa0-4adc-bbfc-c69c7faa7696

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HGVS expressions

NM_000018.4(ACADVL):c.1269G>A (p.Ser423=)

NM_000018.4:c.1269G>A

NC_000017.11:g.7223730G>A

CM000679.2:g.7223730G>A

NC_000017.10:g.7127049G>A

CM000679.1:g.7127049G>A

NC_000017.9:g.7067773G>A

NG_007975.1:g.8897G>A

NG_008391.2:g.1321C>T

NG_033038.1:g.15815C>T

ENST00000356839.10:c.1269G>A

ENST00000322910.9:c.*1224G>A

ENST00000350303.9:c.1203G>A

ENST00000356839.9:c.1269G>A

ENST00000542255.6:c.127G>A

ENST00000543245.6:c.1338G>A

ENST00000578579.2:n.440G>A

ENST00000578711.1:n.226G>A

ENST00000578824.5:n.685G>A

ENST00000579425.5:n.293G>A

ENST00000579546.1:c.106G>A

ENST00000583850.5:n.44G>A

ENST00000583858.5:c.298G>A

ENST00000585203.6:n.477G>A

NM_000018.3:c.1269G>A

NM_001033859.2:c.1203G>A

NM_001270447.1:c.1338G>A

NM_001270448.1:c.1041G>A

NM_001033859.3:c.1203G>A

NM_001270447.2:c.1338G>A

NM_001270448.2:c.1041G>A

Pathogenic

Met criteria codes **4**

PM3_Supporting

PM2_Supporting

PP4_Moderate

PVS1

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.1269G>A (NM_000018.4) variant in ACADVL is a synonymous variant which occurs in the final nucleotide of exon 12, a position that is generally considered highly conserved. At least one patient with this variant displayed reduced very long chain acyl-CoA dehydrogenase (VLCAD) enzyme levels in lymphocytes, which is highly specific for VLCAD deficiency (PP4_moderate, PMID: 30194637). The highest population minor allele frequency in gnomAD v4.1.1 0.00001335 in African/African American 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 splicing predictor SpliceAI gives a score of 0.79 for donor loss, predicting that the variant disrupts the donor splice site of intron 12 of ACADVL (PP3). This variant has been detected in one individual with very long chain acyl CoA dehydrogenase (VLCAD) deficiency in a potential compound heterozygous state with a likely pathogenic variant, but this information is insufficient to use toward classification (PMID: 30194637). It has also been detected in one patient that was compound heterozygous for the variant and likely pathogenic variant (c.1055T>C (p.Met352Thr)) confirmed in trans by parental testing (PMID: 40678976), but this information is insufficient to use toward classification as no biochemical data for this patient is available (PM3 not applied). RT-PCR, ACADVL Minigene, Plasmid Construction and ACADVL expression analysis in 293T and HeLa cells showed skip of exon 12 and decreased mRNA expression indicating that this variant impacts protein function (PMID: 40678976) PVS1_RNA). In summary, this variant meets the criteria to be classified as pathogenic for autosomal recessive VLCAD deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen ACADVL Variant Curation Expert Panel: PVS1_RNA,PM2_supporting, PP4_Moderate (ACADVL VCEP specifications version 2.1.0; approved September 4, 2025).

Met criteria codes

PM3_Supporting			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2_Supporting			The highest population minor allele frequency in gnomAD v2.1.1 is 0.000046 (0.0046%) in European (non-Finnish) population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP4_Moderate			At least one patient with this variant displayed reduced very long chain acyl-CoA dehydrogenase (VLCAD) enzyme levels in lymphocytes, which is highly specific for VLCAD deficiency (PP4_moderate, PMID: 30194637).
PVS1			RT-PCR, ACADVL Minigene, Plasmid Construction and ACADVL expression analysis in 293T and HeLa cells showed skip of exon 12 and decreased mRNA expression indicating that this variant impacts protein function

Not Met criteria codes

PP3			PVS1_RNA applied
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Curation History 

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