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# *Variant: NM_000018.4(ACADVL):c.1096C>T (p.Arg366Cys)*

Version: 1.0

*CA312264*

*203579 (ClinVar)*

**Gene**: ACADVL (HGNC:37)
**Condition**: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
**Inheritance Mode**: Autosomal recessive inheritance
**UUID:** 6b9acb5f-7ae6-4a8e-8190-ca116aec5881
**Approved on**: 2025/3/25
**Published on**: 2025/4/1

## *HGVS expressions*

**NM_000018.4(ACADVL):c.1096C>T (p.Arg366Cys)**
**NM_000018.4:c.1096C>T**
NC_000017.11:g.7223151C>T
CM000679.2:g.7223151C>T
NC_000017.10:g.7126470C>T
CM000679.1:g.7126470C>T
NC_000017.9:g.7067194C>T
NG_007975.1:g.8318C>T
NG_008391.2:g.1900G>A
ENST00000356839.10:c.1096C>T
ENST00000322910.9:c.*1051C>T
ENST00000350303.9:c.1030C>T
ENST00000356839.9:c.1096C>T
ENST00000543245.6:c.1165C>T
ENST00000578579.2:n.45C>T
ENST00000578824.5:n.512C>T
ENST00000579425.5:n.120C>T
ENST00000582379.1:n.747C>T
ENST00000583858.5:c.125C>T
ENST00000585203.6:n.304C>T
NM_000018.3:c.1096C>T
NM_001033859.2:c.1030C>T
NM_001270447.1:c.1165C>T
NM_001270448.1:c.868C>T
NM_001033859.3:c.1030C>T
NM_001270447.2:c.1165C>T
NM_001270448.2:c.868C>T

**Likely Pathogenic**

**Met criteria codes** 6

PP3 PM1 PM3 PP4_Moderate PM2_Supporting PM5_Supporting

**Not Met criteria codes** 1

PS3

## Expert Panel

ACADVL VCEP

## Criteria Specification Information

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

Evidence Links 0

*Guidelines Version 1*

**PDF**

**Criteria Specification Approval History**

**Criteria Specifications for this VCEP**

Evidence submitted by expert panel

***ACADVL VCEP***

**The NM_000018.4 c.1096C>T p.(Arg366Cys) in ACADVL is a missense variant predicted to cause substitution of arginine by cysteine at amino acid 366. It has also been reported in the literature as p.Arg326Cys. The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006152 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). It has been reported in patients with very long chain acyl-CoA dehydrogenase (VLCAD) deficiency or increased C14:1 acylcarnitine levels (PP4_Moderate; PMID: 32793418, 8845838). At least one individual with this variant was identified with VLCADD clinical phenotype, who also carried a pathogenic variant c.848T>C in trans, displaying reduced enzyme levels (PM3 score = 1.0, PM3, PMID: 8845838). The computational predictor REVEL gives a score of 0.955, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3). This variant resides within a region defined as a mutational hotspot by the ClinGen ACADVL Variant Curation Expert Panel (PMID: 9973285, PM1). A different aminoacid change in the same codon (p.Arg366His, ClinVar ID: 203580) has been classified as likely pathogenic for VLCAD deficiency by the ClinGen ACADVL Variant Curation Expert Panel (PM5_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic 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: PM3_Moderate, PP4_Moderate, PM2_Supporting, PP3_Supporting, PM5_supporting (ACADVL VCEP specifications version 1; approved November 9, 2021).**

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**Met criteria codes**

| | | |
|---|---|---|
| **PP3** | ✓ | Missense variant with REVEL 0.955 |
| **PM1** | ✓ | Located in a mutational hot spot CpG dinucleotides in the codon for arginine326 (legacy nomenclature for codon R366) (PMID 9973285). |
| **PM3** | ✓ | PMID: 8845838 - Patient 615 - reported as p.(Arg326Cys). In trans confirmed (cloning) with pathogenic variant c.848T>C (pathogenic by VCEP). - 1 point PMID: 32793418 - patient 3 - unconfirmed CH with c.604C>G p.(Leu202Val) (LP) - 0.25 points |
| **PP4_Moderate** | ✓ | In patient 615 (PMID: 8845838), plasma acyl-carnitine analysis indicated VLCAD and enzyme activity with 29% of activity (patient fibroblasts). In patient 3 (PMID: 32793418), identified by NBS (C14:1 0,94 uM in DBS and plasmatic follow up C14:1 0,42 uM) followed by enzyme activity measurement in lymphocytes with 18% of activity. |
| **PM2_Supporting** | ✓ | The highest population minor allele frequency in gnomAD v2.1.1 is 0.00006152 in African/African American population, which is lower than the ClinGen ACADVL Expert Panel threshold (<0.001 (0.1%)) for PM2_Supporting, meeting this criterion (PM2_Supporting). |
| **PM5_Supporting** | ✓ | A different aminoacid change at the same position (p.Arg366His) has been classified by the ACADVL VCEP group as likely pathogenic (ClinVar ID: 203580) |

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**Not Met criteria codes**

| | | | |
|---|---|---|---|
| **PS3** | ℹ | ✖ | Western blot analysis of patient fibroblasts showed that the identified variant results in severely reduced amounts of VLCAD protein (PMID: 8845838). |

Curation History

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