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Variant: NM_000018.4(ACADVL):c.1468G>C (p.Ala490Pro)

Version: 1.0

CA8338123

474888 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: d6773d57-2435-4518-9782-c156dc2c7aa8
Approved on: 2023/4/11
Published on: 2023/4/11

HGVS expressions

NM_000018.4:c.1468G>C
NM_000018.4(ACADVL):c.1468G>C (p.Ala490Pro)
NC_000017.11:g.7224179G>C
CM000679.2:g.7224179G>C
NC_000017.10:g.7127498G>C
CM000679.1:g.7127498G>C
NC_000017.9:g.7068222G>C
NG_007975.1:g.9346G>C
NG_008391.2:g.872C>G
NG_033038.1:g.15366C>G
ENST00000356839.10:c.1468G>C
ENST00000322910.9:c.*1423G>C
ENST00000350303.9:c.1402G>C
ENST00000356839.9:c.1468G>C
ENST00000542255.6:c.326G>C
ENST00000543245.6:c.1537G>C
ENST00000578711.1:n.675G>C
ENST00000579391.1:n.76G>C
ENST00000579425.5:n.584G>C
ENST00000579546.1:c.271+110G>C
ENST00000579894.5:n.255G>C
ENST00000583074.5:n.153+110G>C
ENST00000583850.5:n.243G>C
ENST00000583858.5:c.463+110G>C
ENST00000585203.6:n.659G>C
NM_000018.3:c.1468G>C
NM_001033859.2:c.1402G>C
NM_001270447.1:c.1537G>C
NM_001270448.1:c.1240G>C
NM_001033859.3:c.1402G>C
NM_001270447.2:c.1537G>C
NM_001270448.2:c.1240G>C

Likely Pathogenic

Met criteria codes 6

PM2_Supporting PP1 PP3 PM1 PP4_Moderate PM3_Supporting

Not Met criteria codes 1

PS3

Evidence Links 0

Expert Panel

ACADVL VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.1468G>C (NM_000018.4) variant in ACADVL is a missense variant predicted to cause substitution of alanine by proline at amino acid 490 (p.Ala490Pro), also known as Ala450Pro when numbered from the mature protein. This variant has been detected in at least 5 individuals with very long chain acyl-CoA dehydrogenase (VLCAD) deficiency. Of those individuals, 2 were compound heterozygous for the variant and distinct pathogenic or likely pathogenic variant, presumed to be in trans (PM3_Supporting, PMID: 26453363, 30194637). This variant has been described in at least 3 unrelated individuals who displayed VLCAD enzyme activity <20%, which is highly specific for VLCAD deficiency (PP4_Moderate, PMID:26453363, 14517516, 30194637). The variant has been reported to segregate with VLCAD deficiency in 2 affected siblings from 1 family (PP1, PMID: 14517516). This variant resides within a region, amino acids 481-516, of ACADVL that is defined as a critical functional domain by the ClinGen ACADVL Variant Curation Expert Panel (PM1, PMID: 18227065, 20060901). A substrate specificity assay showed this variant displays abnormal substrate specificity; however, this assay does not meet the requirements for use by the ClinGen ACADVL Variant Curation Expert Panel (PMID: 9839948). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004 in the African 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 0.794, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for autosomal recessive VLCAD deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen ACADVL Variant Curation Expert Panel: PM1, PM2_Supporting, PM3_Supporting, PP1, PP3, PP4_Moderate (ACADVL VCEP specifications version 1; approved November 9, 2021).

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00004 in the African population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP1	✔	Found in two affected siblings from one family
PP3	✔	The computational predictor REVEL gives a score of 0.794, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3).
PM1	✔	This variant resides in the membrane binding region defined for PM1
PP4_Moderate	✔	VLCAD enzyme activity <20%
PM3_Supporting	✔	0.5 presumed in trans to G441D

Not Met criteria codes

PS3		✖	PMID 9839948 does not meet VCEP's PS3 criteria

Curation History

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