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Variant: NM_000018.4(ACADVL):c.1837C>T (p.Arg613Trp)

Version: 1.0

CA251903

1623 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4945234d-6b48-4f46-9475-2f447ba44057
Approved on: 2023/6/13
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HGVS expressions

NM_000018.4:c.1837C>T
NM_000018.4(ACADVL):c.1837C>T (p.Arg613Trp)
NC_000017.11:g.7224966C>T
CM000679.2:g.7224966C>T
NC_000017.10:g.7128285C>T
CM000679.1:g.7128285C>T
NC_000017.9:g.7069009C>T
NG_007975.1:g.10133C>T
NG_008391.2:g.85G>A
NG_033038.1:g.14579G>A
ENST00000356839.10:c.1837C>T
ENST00000322910.9:c.*1792C>T
ENST00000350303.9:c.1771C>T
ENST00000356839.9:c.1837C>T
ENST00000542255.6:c.716C>T
ENST00000543245.6:c.1906C>T
ENST00000578033.1:n.262C>T
ENST00000578319.5:n.418C>T
ENST00000578711.1:n.1462C>T
ENST00000578809.5:n.409C>T
ENST00000579425.5:n.953C>T
ENST00000579546.1:c.572C>T
ENST00000583848.5:c.203C>T
ENST00000583850.5:n.608C>T
ENST00000583858.5:c.768C>T
NM_000018.3:c.1837C>T
NM_001033859.2:c.1771C>T
NM_001270447.1:c.1906C>T
NM_001270448.1:c.1609C>T
NM_001033859.3:c.1771C>T
NM_001270447.2:c.1906C>T
NM_001270448.2:c.1609C>T

Likely Pathogenic

Met criteria codes 5

PM3 PS3_Supporting PM2_Supporting PP3 PP4_Moderate

Not Met criteria codes 1

PM1

Evidence Links 0

Expert Panel

ACADVL VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.1837C>T variant in ACADVL is a missense variant predicted to cause substitution of arginine by tryptophan at amino acid 613 (p.Arg613Trp). This variant has been reported in ACADVL deficiency in numerous studies, including PMIDs:7479827, 8554073, 35281659, 17374501, 30194637. This variant is associated with increased C14:1 acylcarnitine levels in patients with ACADVL deficiency (PMID: 33986768, PP4_moderate). This variant was also detected in compound heterozygote with pathogenic variants from multiple patients (PM3, PMID: 7479827, 8554073, 30194637). This variant causes significantly reduced enzyme activity determined from lymphocytes, mammalian, and bacterial cell expression systems (PMID: 30194637, 8554073, 17374501, 33986768) and results in unstable protein product (PMID:8554073, PS3_supporting). This variant is also part of a C-terminal domain critical for mitochondiral membrane binding (PMID: 18227065). The highest population minor allele frequency in gnomAD is 0.0001 in the European non-Finnish population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) meeting this criterion (PM2_Supporting). The computational predictor REVEL gives a score of 0.77, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3). In summary the ACADVL Variant Curation Expert Panel VCEP classified the variant as likely pathogenic based on PS3_supporting+PM3+PP3+PP4_moderate+PM2_supporting.

Met criteria codes

PM3	✔	Trans hets with pathogenic c.343delG (PMID: 7479827) In trans with c.343_477del (PMID: 8554073) Homozygote with VLVADD 1.0 point
PS3_Supporting	✔	Mammalian and bacterial expression: reduced enzyme activity. Gel filtration: unstable protein
PM2_Supporting	✔	gnomAD European (Non-Finnish) = 0.00010 Panel threshold (<0.001)
PP3	✔	REVEL=0.77 (>0.75)
PP4_Moderate	✔	Reduced VLCAD activity from three patients (one homozygote) below studies.

Not Met criteria codes

PM1	✖	Part of the C-terminal domain membrane binding discussed by McAndrew et al. Sequence alignment also shows invariant arginine across the animal kingdom.

Curation History

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