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Variant: NM_000018.4(ACADVL):c.848T>C (p.Val283Ala)

Version: 1.0

CA285294

21025 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: 7d9f7051-1a9d-4a3d-970a-d2e863e8a7c2
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HGVS expressions

NM_000018.4:c.848T>C
NM_000018.4(ACADVL):c.848T>C (p.Val283Ala)
NC_000017.11:g.7222272T>C
CM000679.2:g.7222272T>C
NC_000017.10:g.7125591T>C
CM000679.1:g.7125591T>C
NC_000017.9:g.7066315T>C
NG_007975.1:g.7439T>C
NG_008391.2:g.2779A>G
ENST00000356839.10:c.848T>C
ENST00000322910.9:c.*803T>C
ENST00000350303.9:c.782T>C
ENST00000356839.9:c.848T>C
ENST00000543245.6:c.917T>C
ENST00000577191.5:n.1020T>C
ENST00000581378.5:c.566T>C
ENST00000582379.1:n.232T>C
NM_000018.3:c.848T>C
NM_001033859.2:c.782T>C
NM_001270447.1:c.917T>C
NM_001270448.1:c.620T>C
NM_001033859.3:c.782T>C
NM_001270447.2:c.917T>C
NM_001270448.2:c.620T>C

Pathogenic

Met criteria codes 5

PP4_Moderate PS3_Supporting PP3 PM1 PM3_Strong

Not Met criteria codes 1

PM2

Evidence Links 0

Expert Panel

ACADVL VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.848T>C variant in ACADVL is a missense variant predicted to cause substitution of valine by alanine at amino acid 283 (p.Val283Ala). This variant is also known as Val243Ala when numbered from the mature peptide. The variant accounts for up to 29% of individuals with very long chain acyl-CoA dehydrogenase (VLCAD) deficiency identified by newborn screen (PMID:20301763). This variant has been reported in at least 12 individuals with VLCAD in the literature with either significantly reduced VLCAD activity or increased C14:1 acylcarnitine levels, which is highly specific for VLCAD deficiency (PP4_moderate; PMID: 17999356, 26385305, 20107901, 14517516). The variant was detected at least 9 times in the homozygous state as well as at least 1 confirmed in-trans with another pathogenic variant (PM3_Strong; PMID: 20107901; 17999356, 17999356). In vitro expression showed 20-25% residual enzyme activity when expressed in COS7 cells (PS3_supporting; PMID: 9973285). The highest population minor allele frequency in gnomAD v2.1.1 is 0.002238 in the European (non-Finnish) population (PM2_Supporting, BS1, and BA1 are not met). The variant is located in a well-studied outer loop with structural importance with high homology to medium-chain acyl-CoA dehydrogenase (PM1; PMID: 14517516). The computational predictor REVEL gives a score of 0.905, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3). In summary, this variant meets 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: PP4_Moderate, PM3_Strong, PM1, PP3, PS3_supporting (ACADVL specifications version 1; approved November 8, 2021)

Met criteria codes

PP4_Moderate	✔	This variant was identified in 3 patients with fibroblast cell line enzyme <20% of control (PMID: 17999356), and 7 abnormal NBS with elevated C14:1 (0.74-2.89, NL<0.6) (PMID: 26385305). This variant was also identified in trans with a splice variant c.342+1G>C in a neonate died at 38 hours of life with a postmortem C14:1 of 1.35 µmol/L.
PS3_Supporting	✔	This variant has about 20-25% residual enzyme activity when expressed as a construct in COS7 cells.
PP3	✔	This variant has a REVEL score of 0.905
PM1	✔	This variant is conserved in region with structural importance (outer loops) within the structural model of human MCAD due to high homology.
PM3_Strong	✔	This variant was identified in trans with a splice variant c.342+1G>C (paternally inherited and classified as likely pathogenic by VECP) in a neonate died at 38 hours of life with a postmortem C14:1 of 1.35 µmol/L (PMID 20107901). Homozygous in 2 patients.

Not Met criteria codes

PM2	✖	gnomad has 346 alleles in total; the highest MAF=0.2% in the European (nonFinnish) population; total MAF= 0.01%.

Curation History

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