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Variant: NM_000018.4(ACADVL):c.652G>A (p.Glu218Lys)

Version: 2.0

CA397723393

474901 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: 4eb52b3c-3d84-48d6-a3cb-9a64c6d1cb74
Approved on: 2023/11/28
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HGVS expressions

NM_000018.4(ACADVL):c.652G>A (p.Glu218Lys)
NM_000018.4:c.652G>A
NC_000017.11:g.7221981G>A
CM000679.2:g.7221981G>A
NC_000017.10:g.7125300G>A
CM000679.1:g.7125300G>A
NC_000017.9:g.7066024G>A
NG_007975.1:g.7148G>A
NG_008391.2:g.3070C>T
ENST00000356839.10:c.652G>A
ENST00000322910.9:c.*607G>A
ENST00000350303.9:c.586G>A
ENST00000356839.9:c.652G>A
ENST00000543245.6:c.721G>A
ENST00000577191.5:n.729G>A
ENST00000577857.5:n.468G>A
ENST00000579286.5:n.833G>A
ENST00000580365.1:n.383G>A
ENST00000581378.5:c.370G>A
ENST00000581562.5:n.554G>A
ENST00000582379.1:n.36G>A
ENST00000583312.5:c.667G>A
ENST00000583760.1:n.434G>A
NM_000018.3:c.652G>A
NM_001033859.2:c.586G>A
NM_001270447.1:c.721G>A
NM_001270448.1:c.424G>A
NM_001033859.3:c.586G>A
NM_001270447.2:c.721G>A
NM_001270448.2:c.424G>A

Likely Pathogenic

Met criteria codes 5

PM1 PM3 PP4_Moderate PP3 PM2_Supporting

Expert Panel

ACADVL VCEP

Criteria Specification Information

Not Met criteria codes 1

PS3

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.652G>A (NM_000018.4) variant in ACADVL is a missense variant predicted to cause substitution of glutamic acid by lysine at amino acid 218 (p.Glu218Lys, also known as Glu178Lys in traditional nomenclature). At least two patients with this variant displayed elevated C14:1 by newborn screen and/or reduced very long chain acyl CoA dehydrogenase (VLCAD) enzyme activity, which is highly specific for VLCAD deficiency (PP4_moderate; PMIDs: 34184355, 30194637). Of those individuals, one was homozygous for the variant, confirmed by parental testing, and one was presumed in trans to a pathogenic variant (PM3 1 point; PMIDs: 34184355, 30194637). Additionally, one patient carrying this variant displayed a reduced VLCAD protein level (PMID: 9973285). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000032 in South Asian population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). This variant resides within a region, amino acids 214–223, of ACADVL that is defined as a mutational hotspot and critical functional domain by the ClinGen ACADVL Variant Curation Expert Panel (PMIDs: 20060901, 9973285; PM1). The computational predictor REVEL gives a score of 0.957, 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, PP3, PP4_Moderate (ACADVL VCEP specifications version 1; approved November 9, 2021). This variant was originally curated December 15, 2022 and the recurated classification was approved by the expert panel on November 13, 2023.

Met criteria codes

PM1	✔	This variant resides within a region, amino acids 214–223, of ACADVL that is defined as a mutational hotspot and critical functional domain by the ClinGen ACADVL Variant Curation Expert Panel (PMIDs: 20060901, 9973285; PM1).
PM3	✔	Detected in homozygous state in affected individual, parents confirmed het (PM3 0.5 points; PMID: 34184355). Detected in presumed trans to c.848T>C, which is approved pathogenic by VCEP (PM3 0.5 points: PMID: 30194637).
PP4_Moderate	✔	Detected in abnormal newborn screen and reduced VLCAD activity (PMID: 34184355). Detected in individual with residual VLCAD activity of 6% (PMID: 30194637).
PP3	✔	The computational predictor REVEL gives a score of 0.957, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3).
PM2_Supporting	✔	). The highest population minor allele frequency in gnomAD v2.1.1 is 0.000032 in South Asian population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PS3	✖	

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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