Variant: NM_000018.4(ACADVL):c.1349G>A (p.Arg450His)

Version: 1.0

CA251910

1634 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: ab1b756a-f061-4e35-bdc2-4d326b69f79d
Approved on: 2022-12-14
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HGVS expressions

NM_000018.4:c.1349G>A
NM_000018.4(ACADVL):c.1349G>A (p.Arg450His)
NC_000017.11:g.7223984G>A
CM000679.2:g.7223984G>A
NC_000017.10:g.7127303G>A
CM000679.1:g.7127303G>A
NC_000017.9:g.7068027G>A
NG_007975.1:g.9151G>A
NG_008391.2:g.1067C>T
NG_033038.1:g.15561C>T
ENST00000356839.10:c.1349G>A
ENST00000322910.9:c.*1304G>A
ENST00000350303.9:c.1283G>A
ENST00000356839.9:c.1349G>A
ENST00000542255.6:c.207G>A
ENST00000543245.6:c.1418G>A
ENST00000578711.1:n.480G>A
ENST00000579425.5:n.465G>A
ENST00000579546.1:c.186G>A
ENST00000579894.5:n.60G>A
ENST00000583074.5:n.68G>A
ENST00000583850.5:n.124G>A
ENST00000583858.5:c.378G>A
ENST00000585203.6:n.540G>A
NM_000018.3:c.1349G>A
NM_001033859.2:c.1283G>A
NM_001270447.1:c.1418G>A
NM_001270448.1:c.1121G>A
NM_001033859.3:c.1283G>A
NM_001270447.2:c.1418G>A
NM_001270448.2:c.1121G>A

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PP3 PP4 PM3_Strong

Expert Panel

ACADVL VCEP

Not Met criteria codes 1

BP4

Evidence Links 0

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.1349G>A (p.Arg450His) variant in ACADVL is a missense variant predicted to cause substitution of arginine by histidine at amino acid 450. At least one individual with this variant displayed reduced VLCAD activity, which is specific for very long chain acyl CoA dehydrogenase (VLCAD) deficiency (PP4, PMID: 11158518). This variant has been confirmed in trans to at least one likely pathogenic variant, not confirmed in trans to distinct likely pathogenic variants, and has been identified in the homozygous state in 2 individuals (PM3_Strong, PMID: 29519241, 15210884, 11158518, 9546340). The highest population minor allele frequency in gnomAD v2.0 is 0.00025 in East Asian 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 0.92, 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: PP4, PM3_Strong, PM2_Supporting, PP3 (ACADVL specifications version 1; approved November 8, 2021)

Met criteria codes

PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.0 is 0.00025 in East Asian population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.92, which is above the threshold of 0.75, evidence that correlates with impact to ACADVL function (PP3).
PP4	✔	Patient in PMID 11158518 had assertion of reduced VLCAD activity without specific levels.
PM3_Strong	✔	Not confirmed in trans to A416T (LP), c.462_463del (not curated), D405H (not curated, but a VUS)=0.25 points Confirmed in trans to A416T (LP--not approved by VCEP), G441D (P-not approved by VCEP)=2 points if G441D approved path 2 individuals homozygous=1 point

Not Met criteria codes

BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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