The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000018.4(ACADVL):c.637G>C (p.Ala213Pro)

Version: 1.0

CA233431

166643 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: b99a999c-190c-492d-89b9-5e39b681ea2f
Approved on: 2024/4/15
Published on: 2024/4/15

HGVS expressions

NM_000018.4:c.637G>C
NM_000018.4(ACADVL):c.637G>C (p.Ala213Pro)
NC_000017.11:g.7221966G>C
CM000679.2:g.7221966G>C
NC_000017.10:g.7125285G>C
CM000679.1:g.7125285G>C
NC_000017.9:g.7066009G>C
NG_007975.1:g.7133G>C
NG_008391.2:g.3085C>G
ENST00000356839.10:c.637G>C
ENST00000322910.9:c.*592G>C
ENST00000350303.9:c.571G>C
ENST00000356839.9:c.637G>C
ENST00000543245.6:c.706G>C
ENST00000577191.5:n.714G>C
ENST00000577857.5:n.453G>C
ENST00000579286.5:n.818G>C
ENST00000580365.1:n.368G>C
ENST00000581378.5:c.355G>C
ENST00000581562.5:n.539G>C
ENST00000582379.1:n.21G>C
ENST00000583312.5:c.652G>C
ENST00000583760.1:n.419G>C
NM_000018.3:c.637G>C
NM_001033859.2:c.571G>C
NM_001270447.1:c.706G>C
NM_001270448.1:c.409G>C
NM_001033859.3:c.571G>C
NM_001270447.2:c.706G>C
NM_001270448.2:c.409G>C

Likely Pathogenic

Met criteria codes 5

PM2_Supporting | PP3 | PP4_Moderate | PM5_Supporting | PM3_Supporting

Expert Panel

ACADVL VCEP

Criteria Specification Information

Evidence Links 0

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The NM_000018.4 c.637G>C (p.Ala213Pro) in ACADVL is a missense variant predicted to cause substitution of alanine by proline at amino acid 213 (p.Ala213Pro). The highest population minor allele frequency in gnomAD V2.1.1 is 0.00018 in African/African American 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 has been detected in homozygous fashion in an individual affected with very long chain acyl CoA dehydrogenase (VLCAD) deficiency, who displayed markedly reduced enzyme mRNA levels and activity (< 10 % of wildtype), which is highly specific for VLCAD deficiency (PP4_Moderate, PM3 score = 0.5, PM3_Supporting, PMID: 10077518). Another missense variant c.637G>A (p.Ala213Thr) in the same codon has been classified as likely pathogenic for very long chain acyl CoA dehydrogenase (VLCAD) deficiency by the ClinGen ACADVL Variant Curation Expert Panel (PM5_Supporting). The computational predictor REVEL gives a score of 0.946, 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 very long chain acyl-CoA dehydrogenase (VLCAD) deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen ACADVL Variant Curation Expert Panel: PM3_Supporting, PM5_Supporting, PP4_Moderate, PM2_Supporting, PP3 (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 0.00018 in African/African American 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 0.946
PP4_Moderate	✔	This variant has been detected in homozygous fashion in an individual affected with very long chain acyl CoA dehydrogenase (VLCAD) deficiency, who displayed markedly reduced enzyme mRNA levels and activity (< 10 % of wildtype), which is highly specific for VLCAD deficiency (PP4_Moderate, PM3 score = 0.5, PM3_Supporting, PMID: 10077518).
PM5_Supporting	✔	Another missense variant c.637G>A (p.Ala213Thr) in the same codon has been classified as likely pathogenic for very long chain acyl CoA dehydrogenase (VLCAD) deficiency by the ClinGen ACADVL Variant Curation Expert Panel (PM5_Supporting).
PM3_Supporting	✔	This variant has been detected in homozygous fashion in an individual affected with very long chain acyl CoA dehydrogenase (VLCAD) deficiency, who displayed markedly reduced enzyme mRNA levels and activity (< 10 % of wildtype), which is highly specific for VLCAD deficiency (PP4_Moderate, PM3 score = 0.5, PM3_Supporting, PMID: 10077518).

Curation History

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