

Variant: *NM_000018.4(ACADVL):c.104del (p.Pro35fs)*

Version: 1.2

CA624861220 [↗](#)

541718 (ClinVar) [↗](#)

Gene: ACADVL ([HGNC:37](#))
Condition: very long chain acyl-CoA dehydrogenase deficiency ([MONDO:0008723](#))
Inheritance Mode: Autosomal recessive inheritance
UUID: d4bf1068-23a1-499a-842b-683684db2c60
Approved on: 2022/4/6
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HGVS expressions

NM_000018.4(ACADVL):c.104del (p.Pro35fs)
NM_000018.4:c.104del
NC_000017.11:g.7220163del
CM000679.2:g.7220163del
NC_000017.10:g.7123482del
CM000679.1:g.7123482del
NC_000017.9:g.7064206del
NG_007975.1:g.5330del
NG_008391.2:g.4890del
ENST00000356839.10:c.104del
ENST00000322910.9:c.*59del
ENST00000350303.9:c.104del
ENST00000356839.9:c.104del
ENST00000543245.6:c.173del
ENST00000577191.5:n.181del
ENST00000577857.5:n.194del
ENST00000578269.5:n.211del
ENST00000578421.1:n.238del
ENST00000579286.5:n.211del
ENST00000579886.2:c.104del
ENST00000580263.5:n.194del
ENST00000581562.5:n.151del
ENST00000582056.5:n.194del
ENST00000582356.5:n.229del
ENST00000583312.5:c.104del
ENST00000584103.5:c.104del
NM_000018.3:c.104del
NM_001033859.2:c.104del
NM_001270447.1:c.173del
NM_001270448.1:c.-125del
NM_001033859.3:c.104del
NM_001270447.2:c.173del
NM_001270448.2:c.-125del

Pathogenic

PM3

PVS1

PP4_Moderate

PM2_Supporting

Not Met criteria codes

4

PM5

PM4

PS1

BP7

Evidence Links

0

ACADVL VCEP

Criteria Specification Information

Criteria Specification:

ClinGen ACADVL Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines Version 1

PDF

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.104del (p.(Pro35Leufs*26)) (NM_000018.4) variant in ACADVL is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 2/20 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMIDs: 9973285, 11590124). This variant has been detected in at least 4 individuals with VLCADD. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic or likely pathogenic variant and was not confirmed in trans (PM3 0.5 pt, PMID: 25834949). 3 individuals were homozygous for the variant (PM3 1.0 point max., PMIDs: 25834949, 32276429) (PM3). The highest population minor allele frequency in gnomAD v2.1.1 is 0.007886%(2/25360 alleles) in AMR population, which is lower than the ClinGen ACADVL VCEP threshold (<0.1%) for PM2_Supporting, meeting this criterion (PM2_Supporting). To our knowledge, functional assays have not been reported for this variant. To our knowledge, this variant has not been reported in the literature for segregation in family members affected with VLCADD. In summary, this variant has been classified as pathogenic for autosomal recessive very long chain acyl-CoA dehydrogenase deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen ACADVL Curation Expert Panel: PVS1, PM3, PP4_Moderate, PM2_Supporting (ACADVL VCEP specifications v2.0; Approved on 10/11/2021).

Met criteria codes

PM3

PM3 is met. This variant has been detected in at least 4 individuals with VLCADD. Of those individuals, 1 was compound heterozygous for the variant and a pathogenic or likely pathogenic variant and was not confirmed in trans (PM3 0.5 pt, PMID: 25834949). 3 individuals were homozygous for the variant (PM3 1 point max., PMIDs: 25834949, 32276429) (PM3_Strong).

PVS1

PVS1 met. The c.104del (p.(Pro35Leufs*26)) (NM_000018.4) variant in ACADVL is a frameshift variant predicted to cause a premature stop codon in biologically-relevant-exon 2/20 leading to nonsense mediated decay in a gene in which loss-of-function is an established disease mechanism (PVS1; PMIDs: 9973285, 11590124).

PP4_Moderate

At least 4 patients with this variant displayed <=20% ACADVL enzyme activity and/or > 1uM C14:1, which is highly specific for VLCADD (PP4_Moderate, PMIDs: 25834949, 32276429).

PM2_Supporting

PM2_Supporting (met). The highest population minor allele frequency in gnomAD v2.1.1 is 0.007886%(2/25360 alleles) in AMR population, which is lower than the ClinGen ACADVL VCEP threshold (<0.1%) for PM2_Supporting, meeting this criterion (PM2_Supporting).

Not Met criteria codes

PM5			Criterion not met because variant is a deletion predicted to result in a frameshift and premature termination codon.
PM4			Criterion not met because variant is a deletion predicted to result in a frameshift and premature termination codon.
PS1			Criterion not met because variant is a deletion predicted to result in a frameshift and premature termination codon.
BP7			Criterion not met because variant is a deletion predicted to result in a frameshift and premature termination codon.

Curation History 		
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