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Variant: NM_000018.4(ACADVL):c.753-2A>C

Version: 2.0

CA220220

92290 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: 6aa11fe3-6074-41da-ad5f-54746213c564
Approved on: 2023-05-09
Published on: 2023-05-09

HGVS expressions

NM_000018.4:c.753-2A>C
NM_000018.4(ACADVL):c.753-2A>C
NC_000017.11:g.7222175A>C
CM000679.2:g.7222175A>C
NC_000017.10:g.7125494A>C
CM000679.1:g.7125494A>C
NC_000017.9:g.7066218A>C
NG_007975.1:g.7342A>C
NG_008391.2:g.2876T>G
ENST00000356839.10:c.753-2A>C
ENST00000322910.9:c.*708-2A>C
ENST00000350303.9:c.687-2A>C
ENST00000356839.9:c.753-2A>C
ENST00000543245.6:c.822-2A>C
ENST00000577191.5:n.923A>C
ENST00000581378.5:c.471-2A>C
ENST00000582379.1:n.137-2A>C
NM_000018.3:c.753-2A>C
NM_001033859.2:c.687-2A>C
NM_001270447.1:c.822-2A>C
NM_001270448.1:c.525-2A>C
NM_001033859.3:c.687-2A>C
NM_001270447.2:c.822-2A>C
NM_001270448.2:c.525-2A>C

Likely Pathogenic

Met criteria codes 4

PVS1_Moderate **PM2_Supporting** **PM3** **PP4_Moderate**

Evidence Links 0

Expert Panel

ACADVL VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.753-2A>C variant in ACADVL occurs within the canonical splice acceptor site (+/- 1,2) of intron 8. It is predicted to cause skipping of biologically-relevant-exon 9/20, resulting in an in frame deletion (removes amino acids 252-293) that is predicted to escape nonsense mediated decay (PVS1_moderate). This variant has been identified by positive newborn screen in several individuals and in individuals presenting with very long-chain acyl-CoA dehydrogenase deficiency (PMID: 27246109, 26385305, 21378393, 17999356, 16488171, 10738914, 10077518, 9973285). This variant is reported in two individuals with a beta-oxidation flux less than 20% of normal which is highly specific for very long chain acyl-CoA dehydrogenase (VLCAD) deficiency. (PP4_Moderate, PMID: 21378393, 17999356, 20060901). At least three individuals were compound heterozygous for the variant and a distinct pathogenic or likely pathogenic variant, not confirmed in trans (PM3; PMID: 27246109, 16488171, 20060901, 21378393, 17999356). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 in the non-Finnish European population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting). 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: PVS1_Moderate, PM2_Supporting, PM3, PP4_Moderate (VCEP specifications v2.0, approved November 9, 2021).

Met criteria codes

PVS1_Moderate	✓	The c.753-2A>C variant in ACADVL occurs within the canonical splice acceptor site (+/- 1,2) of intron 8. It is predicted to cause skipping of biologically-relevant-exon 9/20, resulting in an in frame deletion (removes amino acids 252-293) that is predicted to escape nonsense mediated decay (PVS1_moderate).
PM2_Supporting	✓	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 in the non-Finnish European population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion.
PM3	✓	In at least three individuals, were compound heterozygous for the variant and a distinct pathogenic or likely pathogenic variant, not confirmed in trans (PM3; PMID: 27246109, 16488171, 20060901, 21378393, 17999356).
PP4_Moderate	✓	This variant has been identified by positive newborn screen in several individuals and in individuals presenting with very long-chain acyl-CoA dehydrogenase deficiency (PMID 27246109, 26385305, 21378393, 17999356, 16488171, 10738914, 10077518, 9973285). This variant is reported in two individuals with a beta-oxidation flux less than 20% of normal (PMID: 21378393, 17999356).

Curation History

Showing 1 to 2 of 2 rows
