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Variant: NM_000018.4:c.265C>T

Version: 1.0

CA397722455

1707712 (ClinVar)

Gene: ACADVL (HGNC:37)
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0dd0d739-a540-4cbb-af0b-514f1c7a3f3c
Approved on: 2022/8/9
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HGVS expressions

NM_000018.4:c.265C>T
NC_000017.11:g.7220664C>T
CM000679.2:g.7220664C>T
NC_000017.10:g.7123983C>T
CM000679.1:g.7123983C>T
NC_000017.9:g.7064707C>T
NG_007975.1:g.5831C>T
NG_008391.2:g.4387G>A
ENST00000356839.10:c.265C>T
ENST00000322910.9:c.*220C>T
ENST00000350303.9:c.199C>T
ENST00000356839.9:c.265C>T
ENST00000543245.6:c.334C>T
ENST00000577191.5:n.342C>T
ENST00000577433.5:n.473C>T
ENST00000577857.5:n.229-102C>T
ENST00000578269.5:n.712C>T
ENST00000578421.1:n.473C>T
ENST00000579286.5:n.446C>T
ENST00000579886.2:c.201+138C>T
ENST00000580263.5:n.429C>T
ENST00000581562.5:n.312C>T
ENST00000582056.5:n.355C>T
ENST00000582166.1:n.153C>T
ENST00000582356.5:n.464C>T
ENST00000583312.5:c.265C>T
ENST00000584103.5:c.265C>T
NM_000018.3:c.265C>T
NM_001033859.2:c.199C>T
NM_001270447.1:c.334C>T
NM_001270448.1:c.37C>T
NM_001033859.3:c.199C>T
NM_001270447.2:c.334C>T
NM_001270448.2:c.37C>T

Likely Pathogenic

Met criteria codes 5

PS3_Supporting PP4_Moderate PM2_Supporting PM3 PP3

Not Met criteria codes 1

PM1

Evidence Links 0

Expert Panel

ACADVL VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.265C>T variant in ACADVL is a missense variant predicted to cause substitution of proline by serine at amino acid 89 (p.Pro89Ser). This variant has been reported in two individuals with very long chain acyl-CoA dehydrogenase (VLCAD) deficiency in the literature with either significantly reduced VLCAD activity or variably increased C14:1 acylcarnitine levels (PP4_moderate; PMIDs: 11914034, Russian Paper). In these same probands, the variant was detected once confirmed in-trans with a pathogenic variant (PM3; PMIDs: 11914034). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). Site-directed mutagenesis expression showed impaired VLCAD enzyme activity (PS3_supporting; PMIDs: 11914034). The computational predictor REVEL gives a score of 0.922, 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_Moderate, PM3, PM2_Supporting, PS3_Supporting, PP3 (ACADVL VCEP specifications version 1; approved November 8, 2021).

Met criteria codes

PS3_Supporting	✔	The Pro89Ser variant displays variable enzyme activity depending on temperature, ranging from 7% to 32% of wild-type. Given that an insufficent number of variant controls were used, the maximum evidence available is PS3_supporting.
PP4_Moderate	✔	One proband's fibroblasts show an ~83% VLCAD activity reduction ranging over multiple publications; another proband shows elevated C14:1 levels after taking l-carnitine.
PM2_Supporting	✔	Not in gnomAD or ExAC
PM3	✔	This variant has been seen confirmed in-trans with c.1606-3_1606-2del variant (confirmed Pathogenic, 1 point) and not confirmed with a missense VUS (0 points). 1.0 points, would meet PM3 if c.1606-3_1606-2del were approved pathogenic.
PP3	✔	REVEL score of 0.922

Not Met criteria codes

PM1	✖	PMID:17999356 and other publications assert little functional change in VLCAD structure when expressing the variant.

Curation History

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