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Variant: NM_000018.4:c.385GAG[1]

Version: 1.0

CA251904

1626 (ClinVar)

Gene: ACADVL
Condition: very long chain acyl-CoA dehydrogenase deficiency (MONDO:0008723)
Inheritance Mode: Autosomal recessive inheritance
UUID: 0e27fe91-6cf2-4326-97b0-f8b2923d9716
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HGVS expressions

NM_000018.4:c.385GAG[1]
NC_000017.11:g.7220969_7220971del
CM000679.2:g.7220969_7220971del
NC_000017.10:g.7124288_7124290del
CM000679.1:g.7124288_7124290del
NC_000017.9:g.7065012_7065014del
NG_007975.1:g.6136_6138del
NG_008391.2:g.4084_4086del
ENST00000356839.10:c.388_390del
ENST00000322910.9:c.*343_*345del
ENST00000350303.9:c.322_324del
ENST00000356839.9:c.388_390del
ENST00000543245.6:c.457_459del
ENST00000577191.5:n.465_467del
ENST00000577433.5:n.596_598del
ENST00000577857.5:n.293+139_293+141del
ENST00000579286.5:n.569_571del
ENST00000579886.2:c.226_228del
ENST00000580365.1:n.119_121del
ENST00000581378.5:c.87_89del
ENST00000581562.5:n.435_437del
ENST00000582056.5:n.571_573del
ENST00000582166.1:n.369_371del
ENST00000583312.5:c.388_390del
ENST00000584103.5:c.421_423del
NM_000018.3:c.388_390del
NM_001033859.2:c.322_324del
NM_001270447.1:c.457_459del
NM_001270448.1:c.160_162del
NM_000018.4:c.388_390del
NM_001033859.3:c.322_324del
NM_001270447.2:c.457_459del
NM_001270448.2:c.160_162del

Met criteria codes 5

Expert Panel

Pathogenic

PM4 PS3 PP4 PM2_Supporting PM3_Strong

Evidence Links 1

ACADVL VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

ACADVL VCEP

The c.385GAG[1] variant is predicted to cause a change in the length of the protein due to an in-frame deletion of one amino acid in a non-repeat region (p.Glu130del) (PM4). This variant has been detected in at least five individuals with very long chain acyl CoA dehydrogenase (VLCAD) deficiency (PMIDs 8554073, 10431122, 27209629,22847164). Of those individuals, four were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and one of those was confirmed in trans by parental testing (PM3_strong, PMID: 10431122). Several patients with this variant displayed VLCADD (PP4, PMIDs 8554073 , 10431122, 27209629, 22847164). Assays, including mRNA/protein expression (in CHO cells), and enzymatic activity demonstrate unstable protein products indicating that this variant impacts protein function (PMID: 8554073)(PS3). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 in European (Non-Finnish) 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 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: PM4, PM3_strong, PP4, PS3

Met criteria codes

PM4	✔	In-frame deletion of glutamic acid 130
PS3	✔	Lots of functional studies 8554073 (all abnormal): pulse chase transcript expression protein assembly palmitoyl-CoA dehydrogenase pulse chase transcript: Unstable protein product. (Figure 6) mRNA expression: 10% of WT. (Table 3) protein assembly from CHO cell: Abnormal based on gel filtration (Figure 7) Reduced palmitoyl-CoA dehydrogenase activity: less than 10% of WT (Table 4) PubMed:8554073
PP4	✔	VLCADD assertion and abnormal acyl carnitine during NBS
PM2_Supporting	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00002 in European (Non-Finnish) population, which is lower than the ClinGen ACADVL Variant Curation Expert Panel threshold (<0.001) for PM2_Supporting, meeting this criterion (PM2_Supporting).
PM3_Strong	✔	This variant has been detected in at least five individuals with very long chain acyl CoA dehydrogenase (VLCAD) deficiency (PMIDs 8554073, 10431122, 27209629,22847164). Of those individuals, four were compound heterozygous for the variant and a pathogenic or likely pathogenic variant and one of those were confirmed in trans by parental testing (PMID: 10431122 PM3_strong). Points = 0.25 (3) + 0.5 (1) + 1(1)= 2.25 --> PM3_Strong

Curation History

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