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Variant: NM_000033.4:c.1024T>C

Version: 1.0

CA415101152

4710906 (ClinVar)

Gene: ABCD1 (HGNC:215)
Condition: adrenoleukodystrophy (MONDO:0018544)
Inheritance Mode: X-linked inheritance
UUID: 472c630c-6fa4-40e0-9bd6-a3a5ba108e43
Approved on: 2026/4/17
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HGVS expressions

NM_000033.4:c.1024T>C
NC_000023.11:g.153729355T>C
CM000685.2:g.153729355T>C
NC_000023.10:g.152994810T>C
CM000685.1:g.152994810T>C
NC_000023.9:g.152648004T>C
NG_009022.2:g.9488T>C
NG_023231.1:g.392A>G
ENST00000218104.6:c.1024T>C
ENST00000218104.5:c.1024T>C
ENST00000370129.4:c.469T>C
NM_000033.3:c.1024T>C

Likely Pathogenic

Met criteria codes 5

PP1 PP3 PP4_Moderate PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PS4 PM5

Evidence Links 0

Expert Panel

Peroxisomal Disorders VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Peroxisomal Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCD1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Peroxisomal Disorders VCEP

The NM_000033.4(ABCD1):c.1024T>C variant in ABCD1 is a missense variant predicted to cause the substitution of serine by proline at amino acid 342 (p.Ser342Pro). This missense variant occurs in exon 2 and is part of the transmembrane domain 6 of the ABCD1 protein. At least one individual with this variant meets phenotype criteria at the moderate strength, with evidence of adrenomyeloneuropathy, elevated VLCFAs, and a positive family history (PP4_Moderate, internal lab contribution). The variant has been reported to segregate with ABCD1 deficiency in 1 affected family member from 1 family (PP1; Internal lab contribution). Beta-oxidation assay with this variant in X-ALD fibroblasts showed absence of restoration of beta-oxidation activity, indicating that this variant impacts protein function even though

it was shown to localize to the peroxisome on immunofluorescence assay (PMID: 17542813; PS3_Supporting). This missense variant is completely absent from gnomAD v2.1.1, v3.1.2, and v4 (PM2_Supporting). It has a REVEL score of 0.853, which is above the PP3 threshold (>=0.85) for ABCD1 set by the Peroxisomal VCEP (PP3). In summary, this variant meets the criteria to be classified as likely pathogenic for X-linked ABCD1 deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Peroxisomal VCEP: PP4_Moderate, PP3, PP1, PS3_Supporting, PM2_Supporting. (ClinGen Peroxisomal Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCD1 Version 1.0.0)

Met criteria codes

PP1	✔	The variant has been reported to segregate with ABCD1 deficiency in 1 affected family member from 1 family (PP1; Internal lab contribution).
PP3	✔	p.Ser342Pro has a revel score of 0.853 which is above the specifications cut-off (0.85) supporting role of pathogenicity.
PP4_Moderate	✔	At least one patient with this variant displayed adrenomyeloneuropathy, elevated VLCFAs and positive family history, which is highly specific for ABCD1 deficiency (PP4_Moderate, Internal lab contribution).
PM2_Supporting	✔	p.Ser342Pro is absent in gnomAD v2.1, 3.1 and 4
PS3_Supporting	✔	In Takahashi et al., 2007 (PMID: 17542813) p.Ser342Pro His-ALDP was expressed at comparable levels to that of wild type His-ALDP by immunoblotting. Beta-oxidation activity was not restored by the transfection of each mutant cDNA. Subcellular localization of S342P exhibited a punctate staining pattern in the cells suggesting this mutant His ALDPs was correctly localized to peroxisomes. As G116R and S342P are located to TMDs, substitution of these amino acids seems to affect substrate binding or transport through ALDP. This variant was not studied in van de Stadt et al, 2021. In Jia Yutian 2022, transport activity and ATP hydrolysis of six mutants was investigated. All six mutants showed decreased transport toward three species of VLCFA-CoA but S342P, in contrast with the other five, did not show abrogated ATP hydrolysis. In Watkins PA 1995, fibroblast of patient 4 with S342P showed normal punctate ALDP immunofluorescence pattern. Protein is described as stable but not functioning. The S342P is described as possibly changing the hydrophobicity of the residue. The strength level is supporting based on the beta-oxidation activity findings, and moderate level is not applied due to the expression levels comparable to WT and the normal localization to peroxisomes.

Not Met criteria codes

PS4	✖	This variant has been reported in 1 proband meeting phenotype criteria for ABCD1 deficiency (PMID: 7668254). This is the same proband counted in PP4, with additional information obtained through personal communication. Therefore, PS4_Supporting not met.
PM5	✖	the variant c.1025C>T(p.Ser342Leu) has been identified 4x in ALD newborn screening (ref. 191, 200, 274 in the ALD database) but yet to be associated with disease

Curation History



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