

Variant: NM_000033.4:c.284C>A

Version: 1.0

CA415098539 [↗](#)

Gene: ABCD1 ([HGNC:215](#))

Condition: adrenoleukodystrophy ([MONDO:0018544](#))

Inheritance Mode: X-linked inheritance

UUID: 33aebe52-2cab-4078-98b3-0b2d71af13ee

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HGVS expressions

NM_000033.4:c.284C>A

NC_000023.11:g.153725550C>A

CM000685.2:g.153725550C>A

NC_000023.10:g.152991005C>A

CM000685.1:g.152991005C>A

NC_000023.9:g.152644199C>A

NG_009022.2:g.5683C>A

NG_023231.1:g.4197G>T

ENST00000218104.6:c.284C>A

ENST00000218104.5:c.284C>A

NM_000033.3:c.284C>A

Likely Pathogenic

Met criteria codes **5**

PS4_Supporting

PP1_Moderate

PM2_Supporting

PS3_Supporting

PP4

Not Met criteria codes **2**

BP4

PP3

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:c.284C>A variant in ABCD1 is a missense variant predicted to cause the substitution of alanine by asparagine at amino acid 95 (p.Ala95Asp). At least one patient with this variant was diagnosed with childhood cerebral form adrenoleukodystrophy (C) and elevated VLCFAs, which are specific for adrenoleukodystrophy (PP4, PMID 23651979). This variant has been reported in 1 additional family meeting PP4 phenotype criteria (PS4_Supporting; PMID 23430809). The variant has been reported to segregate with ABCD1 deficiency in 2 affected meioses in addition to the proband (the proband's sister and nephew) in one family (PP1_Moderate; PMID 23430809). This variant is absent from gnomAD v4.1 (PM2_Supporting). Beta-oxidation activity assays in CADDs fibroblasts lacking the ABCD1 gene were completed. They were transfected with the ABCD1 c.284C>A variant, resulting in scarce expression. The C24:0 Beta-oxidation activities

were not recovered, indicating that this variant impacts protein function (PMID: 23430809)(PS3_Supporting). In summary, this variant meets the criteria to be classified as likely pathogenic for X-linked adrenoleukodystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen Peroxisomal Disorders VCEP: PP4, PS4_Supporting, PP1_Moderate, PM2_Supporting, PS3_Supporting (ClinGen Peroxisomal Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCD1 Version 1.0.0)			
Met criteria codes			
PS4_Supporting			This variant has been reported in 1 additional family meeting PP4 phenotype criteria (PS4_Supporting; PMID 23430809).
PP1_Moderate			The variant has been reported to segregate with ABCD1 deficiency in 2 affected meioses in addition to the proband (the proband's sister and nephew) in one family (PP1_Moderate; PMID 23430809).
PM2_Supporting			This variant is absent from gnomAD v4.1 (PM2_Supporting).
PS3_Supporting			Beta-oxidation activity assays in CADD5 fibroblasts lacking the ABCD1 gene were completed. They were transfected with the ABCD1 c.284C>A variant, resulting in scarce expression. The C24:0 Beta-oxidation activities were not recovered, indicating that this variant impacts protein function (PMID: 23430809)(PS3_Supporting).
PP4			At least one patient with this variant was diagnosed with childhood cerebral form adrenoleukodystrophy (C) and elevated VLCFAs, which are specific for adrenoleukodystrophy (PP4, PMID 23651979).
Not Met criteria codes			
BP4			The results from 2 in silico predictors (REVEL and SpliceAI) do not agree, providing no evidence that correlates with a damaging or benign impact on ABCD1 function. SpliceAI gives a score of 0.03 for donor gain and 0.00 for acceptor loss, donor loss, and acceptor gain, which are below the threshold of ≤ 0.2 , suggesting that the variant has no impact on splicing. However, REVEL gives a score of 0.81, which is neither above (≥ 0.85) nor below (≤ 0.5) the thresholds set predicting a damaging or benign impact on ABCD1 function.
PP3			The computational predictor REVEL gives a score of 0.81, which is neither above (≥ 0.85) nor below (≤ 0.5) the thresholds set by the Peroxisomal Disorders VCEP predicting a damaging or benign impact on ABCD1 function.

Curation History [↗](#)

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