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Variant: NM_000033.4(ABCD1):c.346G>A (p.Gly116Arg)

Version: 1.0

CA278414

92325 (ClinVar)

Gene: ABCD1 (HGNC:215)
Condition: adrenoleukodystrophy (MONDO:0018544)
Inheritance Mode: X-linked inheritance
UUID: b3e35b5f-86ea-4be0-804a-8a98e4125fde
Approved on: 2026/4/15
Published on: 2026/4/15

HGVS expressions

NM_000033.4:c.346G>A
NM_000033.4(ABCD1):c.346G>A (p.Gly116Arg)
NC_000023.11:g.153725612G>A
CM000685.2:g.153725612G>A
NC_000023.10:g.152991067G>A
CM000685.1:g.152991067G>A
NC_000023.9:g.152644261G>A
NG_009022.2:g.5745G>A
NG_023231.1:g.4135C>T
ENST00000218104.6:c.346G>A
ENST00000218104.5:c.346G>A
NM_000033.3:c.346G>A

Likely Pathogenic

Met criteria codes 5

PS3_Supporting | PP4_Moderate | PP3 | PM2_Supporting | PS4

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.346G>A variant in ABCD1 is a missense variant predicted to cause the substitution of glycine by arginine at amino acid 116 (p.Gly116Arg). At least five individuals reported with this variant in the literature meet the phenotype criteria at the supporting strength (PMIDs: 31526374, 32101828, 34826210, 10737980, 8651290; PS4), while one female proband identified on newborn screening meets phenotype criteria at the moderate strength (PMID: 35466195), with evidence of elevated C26:0-lysoPC and VLCFAs and a positive family history (PP4_Moderate). Additional cases noted in the ABCD1 variant database could not be verified and were not included in this curation. 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 0.974, 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 adrenoleukodystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen Peroxisomal VCEP: PS4, PP4_Moderate, PP3, 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

PS3_Supporting	✔	Authors in PMID: 17542813 introduced the c.346G>A (p.Gly116Arg) variant into X-ALD fibroblasts as transiently expressed mutant His-ALDP as well as CHO-K1 cells stably expressing both wild type ALDP and mutant ALDP-green fluorescence proteins (GFPs). Gly116Arg is shown to be localized to the peroxisome with punctate staining on immunofluorescence assay in both ALD fibroblasts (and CHO cells with data not shown). However, β-oxidation activity was not restored by the transfection of the mutant cDNA (Fig 3A suggests activity was ~50% of that of WT), although a substantial amount of mutant ALDPs was expressed in the cells. PS3_Supporting is applied at this time, until more evidence to increase PS3 strength can be generated.
PP4_Moderate	✔	One female newborn proband is reported in PMID: 35466195 with the c.346G>A (p.Gly116Arg) variant detected by NGS (Table 1). Proband was studied based on elevated C26:0-lysoPC on repeat samples and increased VLCFA C26:0 on dried blood spots. Proband's mother is also noted to be heterozygous for the variant, and a positive family history is noted, wherein family members with confirmed, symptomatic X-ALD phenotype were present. Proband meets PP4_Moderate.
PP3	✔	This missense variant has a REVEL score of 0.974, which is above the PP3 threshold (>=0.85) for ABCD1 set by the Peroxisomal VCEP (PP3).
PM2_Supporting	✔	The c.346G>A (p.Gly116Arg) variant is completely absent from gnomAD v2.1.1, v3.1.2. and v4
PS4	✔	With 5 probands reported in the literature, each meeting at least supporting criteria for phenotype codes, PS4 is met at the strong level.

Curation History

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