

Variant: NM_000033.4:c.649A>G

Version: 1.0

CA415099400 [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 443be01c-2b2e-4d13-aac0-25e3b3726250

Approved on: 2026/4/16

Published on: 2026/4/16

HGVS expressions

NM_000033.4:c.649A>G

NC_000023.11:g.153725915A>G

CM000685.2:g.153725915A>G

NC_000023.10:g.152991370A>G

CM000685.1:g.152991370A>G

NC_000023.9:g.152644564A>G

NG_009022.2:g.6048A>G

NG_023231.1:g.3832T>C

ENST00000218104.6:c.649A>G

ENST00000218104.5:c.649A>G

ENST00000370129.4:c.94A>G

NM_000033.3:c.649A>G

Likely Pathogenic

Met criteria codes **6**

PS4_Moderate

PP4_Moderate

PP1

PP3

PS3_Supporting

PM2_Supporting

Not Met criteria codes **1**

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 variant c.649A>G (p.Lys217Glu) (NM_000033.4) is a missense variant in exon 1. At least one patient with this variant displayed Addison's disease/adrenal insufficiency, with positive family history (similarly affected sibling), and elevated VLCFAs. These symptoms are highly specific for adrenoleukodystrophy (PP4_Moderate, PMID: 11438993). This variant has been reported in at least 2 other probands meeting PP4_Supporting phenotype criteria (PS4_moderate; PMID: 11748843, 21300044). The ALD database (<https://adrenoleukodystrophy.info/mutations-and-variants-in-abcd1>) currently reports a total of 7 patients. The variant has been reported to segregate with adrenoleukodystrophy in ≥2 affected meioses from 1 family (PP1; PMID: 11438993). The computational predictor REVEL

gives a score of 0.98, which is above the ClinGen Peroxisomal Disorders VCEP threshold of ≥ 0.85 , evidence that correlates with impact to ABCD1 function (PP3). This variant is absent from gnomAD v4.1 (PM2_Supporting). Beta-oxidation assay in ALD patient fibroblasts transfected with the variant showed activity $\leq 26\%$ of WT, indicating that this variant impacts protein function (PMID: 11438993) (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 VCEP: PP4_Moderate, PS4_moderate, PP1, PP3, 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_Moderate			There are at least 3 patients meeting PP4_supporting criteria counting towards PS4, in addition to the patient considered for PP4 and the two brothers included in PP1. The ALD db reports a total of 7 patients (likely include the fetus described in Lan F et al. 2011 and the unpublished in addition to 2 of PS4, 1 of PP4 and 2 of PP1)
PP4_Moderate			At least one patient with this variant displayed Addison's disease/adrenal insufficiency (C), with positive family history (similarly affected sibling)(D), and elevated VLCFAs (F), which is highly specific for adrenoleukodystrophy (PP4_Moderate), PMID: 11438993).
PP1			Two brothers are described in Dvorakova et al., (2001) with isolated adrenal insufficiency (Addison disease, ADO). All patients in this study had elevated concentration of VLCFA in serum or plasma.
PP3			Revel score is confirmed to be 0.98, thus well above the specification threshold of 0.85 for pathogenicity.
PS3_Supporting			Dvorakova et al, (2001) performed in vitro mutagenesis of plasmid of the wt human cDNA to obtain variants identified in the in the two brothers. When transfected into X-ALD fibroblast (25% of WT beta-oxidation of VLCFA) K217E was not able to restore defective beta-oxidation, while the other variant (N13T) was able to restore to WT levels.
PM2_Supporting			the variant is not present in gnomAD, v2.1, 3.1, 4.1

Not Met criteria codes			
PM5			c.649A>T p.Lys217* is listed as pathogenic, identified in a single ALD case (88).

Curation History [↗](#)

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