

Variant: *NM_000033.4(ABCD1):c.521A>G (p.Tyr174Cys)*

Version: 1.0

CA415099025 [↗](#)

458646 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 406a976d-39fc-4a01-9ee3-4217c8056e9a

Approved on: 2026/4/16

Published on: 2026/4/16

HGVS expressions

NM_000033.4(ABCD1):c.521A>G (p.Tyr174Cys)

NM_000033.4:c.521A>G

NC_000023.11:g.153725787A>G

CM000685.2:g.153725787A>G

NC_000023.10:g.152991242A>G

CM000685.1:g.152991242A>G

NC_000023.9:g.152644436A>G

NG_009022.2:g.5920A>G

NG_023231.1:g.3960T>C

ENST00000218104.6:c.521A>G

ENST00000218104.5:c.521A>G

NM_000033.3:c.521A>G

Pathogenic

Met criteria codes **7**

PM2_Supporting PS3_Supporting

PP1_Strong PS4 PP3

PP4_Moderate PM6_Supporting

Not Met criteria codes **2**

BS3 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 c.521A>G variant in ABCD1 is a missense variant predicted to cause substitution of tyrosine by cysteine at amino acid 174 (p.Tyr174Cys). At least one patient with this variant displayed rapid progression of inflammatory white matter demyelination in adolescence, had a X-linked pattern family history of disease including an affected male, and abnormal very long chain fatty acid testing, which is highly specific for adrenoleukodystrophy (PP4_Moderate, PMID:24722136). This variant has been reported in six more probands meeting a family history with an X-linked inheritance pattern where at least one family member is male or rapid progression of inflammatory white matter demyelination in childhood, and abnormal very long chain fatty acid testing (PS4; PMID:11336405, 28895702,

21068741, 26260157, 24722136). This variant has been assumed as a de novo occurrence with unconfirmed parental relationships in one individual with X-linked adrenoleukodystrophy (PM6_Supporting; PMID:11336405). The variant has been reported to segregate with X-linked adrenoleukodystrophy in eight affected family members from one family (PP1_Strong; PMID:11336405). This variant is absent from gnomAD v2.1.1, v3.1.2 and v4.1.0 (PM2_Supporting). Beta-oxidation assay in X-ALD fibroblasts (163T) showed that the beta-oxidation activity of the variant protein is approximately 5% of wild type ABCD1, indicating that this variant has an impact protein function (PMID:17542813)(PS3_Supporting). The computational predictor REVEL gives a score of 0.954, which is above the threshold of 0.85, evidence that correlates with impact to ABCD1 function (PP3). In summary, this variant meets the criteria to be classified as pathogenic for X-linked adrenoleukodystrophy based on ACMG/AMP criteria applied, as specified by the ClinGen Peroxisomal Disorders VCEP: PP1_Strong, PS4, PP3, PP4_Moderate, PM2_Supporting, PM6_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

PM2_Supporting			This variant is absent from gnomAD v2.1.1, v3.1.2 and v4.1.0 (PM2_Supporting)
PS3_Supporting			Beta-oxidation assay in X-ALD fibroblasts (163T) showed that the beta-oxidation activity of the variant protein is approximately 5% of wild type ABCD1, indicating that this variant has an impact protein function (PMID:17542813) (PS3_Supporting).
PP1_Strong			The variant has been reported to segregate with X-linked adrenoleukodystrophy in eight affected family members from one family (PP1_Strong; PMID:11336405).
PS4			This variant has been reported in six more probands meeting a family history with an X-linked inheritance pattern where at least one family member is male or rapid progression of inflammatory white matter demyelination in childhood, and abnormal very long chain fatty acid testing (PS4; PMID:11336405, 28895702, 21068741, 26260157, 24722136).
PP3			The computational predictor REVEL gives a score of 0.954, which is above the threshold of 0.85, evidence that correlates with impact to ABCD1 function (PP3).
PP4_Moderate			At least one patient with this variant displayed rapid progression of inflammatory white matter demyelination in adolescence, had a X-linked pattern family history of disease including an affected male, and abnormal very long chain fatty acid testing, which is highly specific for adrenoleukodystrophy (PP4_Moderate, PMID:24722136).
PM6_Supporting			This variant has been assumed as a de novo occurrence with unconfirmed parental relationships in one individual with X-linked adrenoleukodystrophy (PM6_Supporting; PMID:11336405).

Not Met criteria codes

BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5			PM5 is not applied here, as pathogenic can be reached without it, so that it may be applied to these variants using this classification. (Tyr174His - LP, Tyr174Asp - P, Tyr174Ser - P/LP, Tyr174Ter- P)

Curation History 		
Showing 1 to 1 of 1 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.