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Variant: NM_000033.4(ABCD1):c.2037G>A (p.Trp679Ter)

Version: 1.0

CA415118457

449353 (ClinVar)

Gene: ABCD1 (HGNC:215)
Condition: adrenoleukodystrophy (MONDO:0018544)
Inheritance Mode: X-linked inheritance
UUID: d281773d-d5d8-4724-a03c-3fcfdd3448a2
Approved on: 2026/4/16
Published on: 2026/4/16

HGVS expressions

NM_000033.4(ABCD1):c.2037G>A (p.Trp679Ter)
NM_000033.4:c.2037G>A
NC_000023.11:g.153743534G>A
CM000685.2:g.153743534G>A
NC_000023.10:g.153008988G>A
CM000685.1:g.153008988G>A
NC_000023.9:g.152662182G>A
NG_009022.2:g.23667G>A
ENST00000218104.6:c.2037G>A
ENST00000218104.5:c.2037G>A
NM_000033.3:c.2037G>A

Likely Pathogenic

Met criteria codes 4

PVS1_Moderate | PS4_Moderate | PM2_Supporting | PP4

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.2037G>A (p.Trp679Ter)(NM_000033.4) variant in ABCD1 is a nonsense variant predicted to cause a premature stop codon in biologically-relevant-exon 10 that may cause loss of function of the protein, however it is predicted to escape nonsense mediated decay and remove <10% of the protein (PVS1_Moderate; PMID:30192042). At least one patient with this variant was positive for biochemical (C26 two tier measurement) and adrenal involvement, which is highly specific for adrenoleukodystrophy (PP4, PMID: 33920672). This variant has been reported in 2 heterozygote females with neurological impairments as measured by JOA and SSPROM scores meeting PP4_Supporting phenotype criteria (PS4_moderate; PMID: 24410807). This variant is absent from gnomAD v4.1 (PM2_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, PS4_moderate, PVS1_moderate, PM2_supporting. (ClinGen Peroxisomal Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCD1 Version 1.0.0)

Met criteria codes

PVS1_Moderate	✔	p.Trp679Ter creates a stop codon downstream of the last exon-junction as it is after nucleotide c.1942, leading to a loss of the last 67 aa of the total protein length which is 746 aa. 67/746 represents about 9% loss of the total protein. The transcript with this variant is not predicted to undergo NMD. Since this variant removes less than 10% of protein, a moderate strength is applied according to the PVS1 guidelines from Abou Tayoun et al., 2018 (PMID:30192042). Based on this criterion, PM4 will not be applied. Based on the ALD database the last (likely)pathogenic variant is located at position c.2078.
PS4_Moderate	✔	From PP4 description: 2 het females with age of symptoms 39/59 (Habekost CT et al., 2018, PMID: 24410807). In this study, 87% of het women were symptomatic, with neurological impairments as measured by JOA and SSPROM scores (B + E + F is considered for these het pts).
PM2_Supporting	✔	p.Trp679Ter is absent in gnomAD v2.1 and v3.1.
PP4	✔	1 male case from a newborn screening (Matteson J et al 2021, PMID: 33920672) was positive for biochemical (C26 two tier measurement) and adrenal involvement and had long-term follow up resolution (see supplementary table), thus meeting supporting strength (A+E+F from specification table).

Curation History

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