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Variant: NM_000033.4(ABCD1):c.1816T>C (p.Ser606Pro)

Version: 1.0

CA249048

218422 (ClinVar)

Gene: ABCD1 (HGNC:215)
Condition: adrenoleukodystrophy (MONDO:0018544)
Inheritance Mode: X-linked inheritance
UUID: 424ab2b0-fa30-4bae-8ce0-d24ce5cf9e90
Approved on: 2026/4/15
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HGVS expressions

NM_000033.4:c.1816T>C
NM_000033.4(ABCD1):c.1816T>C (p.Ser606Pro)
NC_000023.11:g.153743022T>C
CM000685.2:g.153743022T>C
NC_000023.10:g.153008476T>C
CM000685.1:g.153008476T>C
NC_000023.9:g.152661670T>C
NG_009022.2:g.23155T>C
ENST00000218104.6:c.1816T>C
ENST00000218104.5:c.1816T>C
NM_000033.3:c.1816T>C

Pathogenic

Met criteria codes 7

PS4 PP3 PP4 PM5 PM6_Supporting PM2_Supporting PS3_Supporting

Not Met criteria codes 1

BA1

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.1816T>C variant in ABCD1 is a missense variant predicted to cause substitution of serine by proline at amino acid 606 (p.Ser606Pro). This variant has been reported in 6 probands meeting ABCD1 phenotype criteria at the supporting strength (PP4, PS4; PMIDs: 21700483), with one of them reported to be de novo (PM6_Supporting, PMID: 21700483, 22479560, 21966424, 21889498, 8651290). The variant is absent from gnomAD v4.1 (PM2_Supporting). β-oxidation activity assay in ALD fibroblasts showed <50% of that of WT, although a substantial amount of mutant ALDP was expressed in the cells, indicating that this variant impacts protein function (PS3_Supporting, PMID: 17542813). This missense variant has a REVEL score of 0.877, which is above the PP3 threshold (>=0.85) for ABCD1 set by the Peroxisomal VCEP. Another missense variant (c.1817C>T, p.Ser606Leu, ClinVar ID: 11310) in the same codon has been

classified as pathogenic for X-linked adrenoleukodystrophy by the ClinGen Peroxisomal VCEP (PM5). In summary, this variant meets the criteria to be classified as Pathogenic for X-linked adrenoleukodystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen Peroxisomal VCEP: PS4, PM2_Supporting, PM5, PP4, PM6_Supporting, PP3, 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	✔	Based on at least 5 individuals reported in the literature who meet the phenotype criteria determined by the Peroxisomal VCEP, PS4 can be applied. The variant would meet the population code, BA1, based on frequency data in gnomAD v2.1.1; however, the Peroxisomal VCEP deemed that the code will not be applicable to this variant given that the gnomAD data (https://gnomad.broadinstitute.org/variant/X-153008476-T-C?dataset=gnomad_r2_1) is unreliable. The variant fails the RF filters for genomes, and it appears that the variant cosegregates with an additional variant (Gly608Asp) in the sequenced heterozygotes in gnomAD. The VCEP opines that this may be an issue related to the pseudogene amplification and therefore population data for this variant should not be considered. Cases were counted based on confirmation of sequencing methodology avoiding pseudogene amplification.
PP3	✔	This missense variant has a REVEL score of 0.877, which is above the PP3 threshold (>=0.85) for ABCD1 set by the Peroxisomal VCEP.
PP4	✔	At least one patient with this variant displayed childhood cerebral form of ALD and increased plasma VLCFA , which is highly specific for X-linked adrenoleukodystrophy. (PP4, PMID: 21700483).
PM5	✔	Three other amino acid changes at the same residue due to four different nucleotide changes have been reported in the ABCD1 database: Ser606Leu, Ser606Ala, Ser606= (c.1818G>A and c.1818G>C). Both Ser606= have not been reported in any individuals meeting phenotype criteria for ABCD1 deficiency, and they are likely benign. Ser606Leu is pathogenic and Ser606Ala is a VUS. PM5 is applied based on the classification of Ser606Leu, the benign variants are not considered as they are synonymous changes and not missense.
PM6_Supporting	✔	Patient 21 reported in PMID: 21700483 is a male with X-ALD and elevated VLCFA levels and is hemizygous for the Ser606Pro variant. Variant was identified to be de novo with no maternal mosaicism. Maternity is assumed. The proband meets phenotype criteria at the supporting strength, but 0.5 points are awarded for de novo occurrence with assumed maternity, meeting criteria for PM6_Supporting.
PM2_Supporting	✔	The variant is absent from gnomAD v4.1 (PM2_Supporting).
PS3_Supporting	✔	Authors in PMID: 17542813 introduced the c.1816T>C (p.Ser606Pro) 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). Ser606Pro 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.

Not Met criteria codes

BA1	✖	

The c.1816T>C (p.Ser606Pro) variant is reported at a POPMAX filtering allele frequency of 0.0003831 in African/American alleles in exomes, with no hemizygotes or homozygotes (however, it is noted that at least one of the heterozygous individuals may actually be homozygous), meeting the BA1 threshold of >=0.00017 set by the Peroxisomal VCEP. Note, the FAF is higher in East Asian alleles in genomes (0.005536); however, this is not considered as this analysis failed the random forest filters. Gly608Asp in cis with this variant in several hets in gnomAD v2.1.1. VCEP decided to not apply BA1 or PM2_Supporting as data are unreliable perhaps due to pseudogene overlap.

Curation History





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