The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000033.4(ABCD1):c.1817C>T (p.Ser606Leu)

Version: 1.0

CA121420

11310 (ClinVar)

Gene: ABCD1 (HGNC:215)
Condition: adrenoleukodystrophy (MONDO:0018544)
Inheritance Mode: X-linked inheritance
UUID: a227d34e-93cb-4314-936d-5711bf74115f
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HGVS expressions

NM_000033.4:c.1817C>T
NM_000033.4(ABCD1):c.1817C>T (p.Ser606Leu)
NC_000023.11:g.153743023C>T
CM000685.2:g.153743023C>T
NC_000023.10:g.153008477C>T
CM000685.1:g.153008477C>T
NC_000023.9:g.152661671C>T
NG_009022.2:g.23156C>T
ENST00000218104.6:c.1817C>T
ENST00000218104.5:c.1817C>T
NM_000033.3:c.1817C>T

Pathogenic

Met criteria codes 6

PP1_Strong PP4_Moderate PS4 PP3 PM2_Supporting PS3_Supporting

Not Met criteria codes 2

PM1 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.1817C>T (p.Ser606Leu) (NM_000033.4) is a missense variant in exon 8 of the ABCD1 gene just upstream of the Walker B domain, which is a well-established mutational hot spot. At least one patient with this variant displayed adrenomyeloneuropathy and adrenal insufficiency, positive family history and elevated VLCFA levels, which is highly specific for adrenoleukodystrophy (PP4_Moderate, PMID: 31526374). The variant has been reported to segregate with adrenoleukodystrophy in ≥3 affected meioses from 1 or more families (PP1_strong; PMID: 8773611). This variant has been reported in 10 probands meeting PP4_Supporting phenotype criteria (PS4_strong; PMIDs: 34826210, 16087056, 15811009, 12624723, 11748843, 10190819, 7668254, 7581394, 8040304). This variant is absent from gnomAD v4.1 (PM2_Supporting). Beta-oxidation assay in ALD patient fibroblasts transfected with the variant showed reduced activity

indicating that this variant impact protein function although reduction did not reach ≤26% of WT(PMID: 21476988, 17542813), however it showed lower expression, and was degraded by proteasomes (PS3_Supporting). 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: PP1_strong, PS4, PP4_moderate, 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

PP1_Strong	✔	In Korenke GC et al. 1996 (PMID: 8773611), the twins' mother , maternal aunt, and grandmother all showed mild symptoms of AMN with disturbances of sensibility and reduced vibration sense. The same mutation of the probands (twin boys with AMN) was found at the heterozygous state. Additional co-segregations from other reports that count toward PP1: - In Coll MJ et al. 2005 (PMID: 15811009) two affected members of the same family have the same variant. - In Kok F et al. 1995 (PMID: 7581394) one kindred is reported with S606L and Addison's phenotype in addition to the index case (#21, see table 2).
PP4_Moderate	✔	p.Ser606Leu is currently identified in 43 ALD cases based on the ALD database. We select and apply PP4_Moderate to a case from Korenke et al. (1996). Based on the specification table we selected evidence A + D + F, thus PP4_Moderate.
PS4	✔	several cases reported meet PP4 criteria with at least supporting evidence level (A/B/C + F) as listed below.
PP3	✔	p.Ser606Leu has a REVEL score of 0.935 which is above the cut-off of 0.85 for pathogenicity at the supporting level, thus PP3_supporting.
PM2_Supporting	✔	p.Ser606Leu is absent in males in gnomad v2.1 and v3.1. One heterozygous female is present in EUR population in both gnomad versions. it is absent in v4
PS3_Supporting	✔	p.Ser606Leu showed significantly lower expression than wild type, was degraded by proteasomes after dimerization and beta-oxidation activity was not restored. Protein was correctly localized to peroxisomes. It is hypothesized that this variant affects the stability of the protein. Supporting level is selected as there is a reduction in expression in protein levels. Although B-oxidation activity was markedly reduced compared to mock, moderate strength cannot be selected as the reduction is not below <26% activity of WT (see Fig.3 in Takahashi N.) per specification.

Not Met criteria codes

PM1	✖	p.Ser606Leu is just upstream of the Walker B domain (starting at 617 aa) which is a well-established mutational hot spot. According to current specifications the C-sequence is not considered a hot spot, however variants in the Walker B domain show functional evidence similar to those of p.Ser606Leu, thus suggesting that the functional impact of variants in the C-sequence may be similar to those in the Walker A, B domains. * to be discussed if C-sequence will need to be added as hot spot together with Walker A and B domains.
PM5	✖	this code could potentially be applied due to pathogenicity of c.1816T>C (p.Ser606Pro), however since this code is not needed to reach pathogenic status for this variant, it will not be applied.

Curation History

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