

Variant: *NM_000033.4(ABCD1):c.2043C>G (p.Phe681Leu)*

Version: 1.0

CA10550392 [↗](#)

669027 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 0c07af21-2a6a-4805-b8d8-17f1b45fc8e3

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HGVS expressions

NM_000033.4(ABCD1):c.2043C>G (p.Phe681Leu)

NM_000033.4:c.2043C>G

NC_000023.11:g.153743540C>G

CM000685.2:g.153743540C>G

NC_000023.10:g.153008994C>G

CM000685.1:g.153008994C>G

NC_000023.9:g.152662188C>G

NG_009022.2:g.23673C>G

ENST00000218104.6:c.2043C>G

ENST00000218104.5:c.2043C>G

NM_000033.3:c.2043C>G

Benign

Met criteria codes **1**

BA1

Not Met criteria codes **3**

PP3

PM1

BP4

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

Evidence Summary: The c.2043C>G (NM_000033.4) variant in ABCD1 is a variant occurring in exon 10. The GrpMax filtering allele frequency in gnomAD v4.1 is 0.0003710 (19/33487 alleles) in the East Asian population with 6 hemizygotes, which is higher than the ClinGen Peroxisomal Disorders threshold ($\geq 0.017\%$ (0.00017)) for BA1. In summary, this variant meets the criteria to be classified as benign for adrenoleukodystrophy based on the ACMG/AMP criteria applied, as specified by the ClinGen Peroxisomal Disorders Variant Curation Expert Panel: BA1 (ClinGen Peroxisomal Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ABCD1 Version 1.0.0)

Met criteria codes

BA1			The GrpMax filtering allele frequency in gnomAD v4.1 is 0.0003710 (19/33487 alleles) in the East Asian population with 6 hemizygotes, which is higher than the ClinGen Peroxisomal Disorders threshold ($\geq 0.017\%$ (0.00017)) for BA1. The filtering allele frequency (the lower threshold of the 95% CI of 27/13704 (5 hemizygotes, 1 homozygote) of the c.2043C>G variant in ABCD1 is 0.001970 for East Asian chromosomes by gnomAD v21.1, which is higher than the ClinGen Peroxisomal Disorders threshold ($\geq 0.017\%$ (0.00017)) for BA1, and therefore meets this criterion (BA1). Variant not present in gnomAD v31.2.
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Not Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.638, which is above the BP4 threshold of 0.5., but below the PP3 threshold of 0.85. The SpliceAI score for acceptor loss was 0.01, while donor loss, acceptor gain, and donor gain was 0.00, which is less than the ClinGen Peroxisomal Disorders threshold of ≤ 0.2 for PP4. The results from 2 in silico predictors, REVEL and SpliceAI, do not agree, providing no evidence that correlates with a damaging or benign impact on ABCD1 function.
PM1			This variant does not reside within a region of ABCD1 that is defined as a mutational hotspot or critical functional domain by the ClinGen Peroxisomal Disorders.
BP4			The computational predictor REVEL gives a score of 0.638, which is above the BP4 threshold of 0.5., but below the PP3 threshold of 0.85. The SpliceAI score for acceptor loss was 0.01, while donor loss, acceptor gain, and donor gain was 0.00, which is less than the ClinGen Peroxisomal Disorders threshold of ≤ 0.2 for BP4. The results from 2 in silico predictors, REVEL and SpliceAI, do not agree, providing no evidence that correlates with a damaging or benign impact on ABCD1 function.

Curation History 

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