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Variant: NM_005629.4(SLC6A8):c.544G>A (p.Val182Met)

Version: 1.0

CA10549204

465147 (ClinVar)

Gene: SLC6A8 (HGNC:6535)
Condition: creatine transporter deficiency (MONDO:0010305)
Inheritance Mode: X-linked inheritance
UUID: 91859ceb-d576-431c-b9fe-8e45c136f694
Approved on: 2022-06-06
Published on: 2022-10-08

HGVS expressions

NM_005629.4:c.544G>A
NM_005629.4(SLC6A8):c.544G>A (p.Val182Met)
NC_000023.11:g.153691453G>A
CM000685.2:g.153691453G>A
NC_000023.10:g.152956908G>A
CM000685.1:g.152956908G>A
NC_000023.9:g.152610102G>A
NG_012016.1:g.8157G>A
NG_012016.2:g.8157G>A
ENST00000253122.10:c.544G>A
ENST00000675713.1:n.298G>A
ENST00000253122.9:c.544G>A
ENST00000430077.6:c.199G>A
ENST00000466243.1:n.336G>A
ENST00000467402.1:n.91G>A
NM_001142805.1:c.544G>A
NM_001142806.1:c.199G>A
NM_005629.3:c.544G>A
NM_001142805.2:c.544G>A

Benign

Met criteria codes 3

BS2 BS1 BP4

Evidence Links 0

Expert Panel

Cerebral Creatine Deficiency Syndromes VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Cerebral Creatine Deficiency Syndromes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for SLC6A8 Version 1*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_005629.4:c.544G>A variant in SLC6A8 is a missense variant predicted to cause substitution of valine by methionine at amino acid 182 (p.Val182Met). The highest population minor allele frequency in gnomAD v2.1.1 is 0.00084 (16/19086 alleles) in the African/African American population, meeting the CCDS VCEP's allele frequency threshold for BS1 (>0.0002) (BS1). This variant is present in 5 or more hemizygotes in gnomAD v2.1.1 (BS2). Furthermore, the variant did not segregate with intellectual disability in multiple brothers, and the proband with the variant had normal urine creatine and normal cerebral creatine on 1H-magnetic resonance spectroscopy (PMID 16738945). The computational predictor REVEL gives a score of 0.184, evidence that does not predict a damaging effect on SLC6A8 function, and SpliceAI predicts no impact of the variant on splicing (BP4). There is a ClinVar entry for this variant (Variation ID: 465147). In summary, this variant meets the criteria to be classified as benign for creatine transporter deficiency. SLC6A8-specific ACMG/AMP codes met, as specified by the ClinGen CCDS VCEP (Specifications Version 1.1.0): BS1, BS2, BP4. (Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Met criteria codes

BS2	✔	This variant is present in 5 or more hemizygotes (8 African/African American, 1 East Asian, 1 European non-Finnish) and 1 homozygote (African/African American) in gnomAD v2.1.1 (BS2). Furthermore, this variant did not segregate with intellectual disability in multiple brothers and the proband with the variant had normal urine creatine and normal cerebral creatine on 1H-MRS (PMID 16738945).
BS1	✔	The highest population minor allele frequency in gnomAD v2.1.1 is 0.00084 (16/19086 alleles) meeting the ClinGen CCDS VCEP's allele frequency threshold for BS1 (>0.0002) (BS1).
BP4	✔	The computational predictor REVEL gives a score of 0.184, evidence that does not predict a damaging effect on SLC6A8 function, and SpliceAI predicts no impact of the variant on splicing (BP4).

Curation History

Showing 1 to 1 of 1 rows

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