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Variant: NM_001142805.2:c.1180G>C

Version: 1.0

CA415086484

2583101 (ClinVar)

Gene: SLC6A8 (HGNC:6535)
Condition: creatine transporter deficiency (MONDO:0010305)
Inheritance Mode: X-linked inheritance
UUID: 8b6d83cd-87dc-4fee-939b-7d59e7026e69
Approved on: 2023/6/21
Published on: 2023/8/24

HGVS expressions

NM_001142805.2:c.1180G>C
NC_000023.11:g.153693973G>C
CM000685.2:g.153693973G>C
NC_000023.10:g.152959428G>C
CM000685.1:g.152959428G>C
NC_000023.9:g.152612622G>C
NG_012016.1:g.10677G>C
NG_012016.2:g.10677G>C
ENST00000253122.10:c.1210G>C
ENST00000253122.9:c.1210G>C
ENST00000413787.1:c.258-231G>C
ENST00000430077.6:c.865G>C
ENST00000442457.1:c.264G>C
ENST00000457723.1:c.194G>C
ENST00000485324.1:n.1243G>C
NM_001142805.1:c.1180G>C
NM_001142806.1:c.865G>C
NM_005629.3:c.1210G>C
NM_005629.4:c.1210G>C

Likely Pathogenic

Met criteria codes 3

PP4_Strong PM2_Supporting PM6

Not Met criteria codes 2

BP4 PP3

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 1.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_005629.4:c.1210G>C variant in SLC6A8 is predicted to result in the substitution of alanine by proline at amino acid 404 (p.Ala404Pro). A 3 year old male, hemizygous for this variant, with clinical features consistent with creatine transporter deficiency has been reported who also had elevated urine creatine/creatine on three occassions, reduced creatine peak on brain MRS, and 6% normal creatine uptake in fibroblasts (with 25 uM creatine) (PP4_Strong). The variant was not identified in either of two independent samples from the patient's mother (PM6). The variant is absent in gnomAD v2.1.1. (PM2_Supporting). The computational predictor REVEL gives a score of 0.601 which is neither above nor below the thresholds predicting a damaging (>0.75) or benign (<0.2) impact on SLC6A8 function. SpliceAI predicts that the variant has no impact on splicing. To our knowledge, the results of functional studies on this variant have not been reported. In summary, this variant meets the criteria to be classified as likely pathogenic for creatine transporter deficiency. SLC6A8-specific ACMG/AMP criteria applied, as specified by the ClinGen CCDS VCEP (Specifications Version 1.1.0): PP4_Strong, PM6, PM2_Supporting. (Classification approved by the ClinGen CCDS, June 21, 2023)

Met criteria codes

PP4_Strong	✔	A 3 year old male with clinical features consistent with creatine transporter deficiency has been reported who also had elevated urine creatine/creatine on three occassions, reduced creatine peak on brain MRS, and 6% normal creatine uptake in fibroblasts (with 25 uM creatine) (PP4_Strong).
PM2_Supporting	✔	The variant is absent in gnomAD v2.1.1. (PM2_Supporting).
PM6	✔	The variant was not detected by sequence analysis in either of two independent blood samples from the patient's mother; maternity was not confirmed (PM6).

Not Met criteria codes

BP4	✖	The computational predictor REVEL gives a score of 0.601 which is neither above nor below the thresholds predicting a damaging (>0.75) or benign (<0.2) impact on SLC6A8 function.
PP3	✖	The computational predictor REVEL gives a score of 0.601 which is neither above nor below the thresholds predicting a damaging (>0.75) or benign (<0.2) impact on SLC6A8 function.

Curation History

Showing 1 to 1 of 1 rows

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