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Variant: NM_001142805.2:c.541T>C

Version: 1.0

CA415079038

Gene: SLC6A8 (HGNC:6535)
Condition: creatine transporter deficiency (MONDO:0010305)
Inheritance Mode: X-linked inheritance
UUID: a0b22d08-453f-4f8a-9abd-83809fb95ed6
Approved on: 2024/4/11
Published on: 2024/6/12

HGVS expressions

NM_001142805.2:c.541T>C
NC_000023.11:g.153691450T>C
CM000685.2:g.153691450T>C
NC_000023.10:g.152956905T>C
CM000685.1:g.152956905T>C
NC_000023.9:g.152610099T>C
NG_012016.1:g.8154T>C
NG_012016.2:g.8154T>C
ENST00000253122.10:c.541T>C
ENST00000675713.1:n.295T>C
ENST00000253122.9:c.541T>C
ENST00000430077.6:c.196T>C
ENST00000466243.1:n.333T>C
ENST00000467402.1:n.88T>C
NM_001142805.1:c.541T>C
NM_001142806.1:c.196T>C
NM_005629.3:c.541T>C
NM_005629.4:c.541T>C

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PP4_Strong PM2_Supporting PP3

Not Met criteria codes 1

PS4

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.541T>C variant in SLC6A8 is a missense variant that is predicted to result in the substitution of a cysteine for an arginine at amino acid 181 (p.Cys181Arg). This variant has been previously reported in one male individual (PMID: 23644449, PMID: 21660517) who had elevated urinary creatine/creatinine and absent creatine peak on brain MRS (PMID: 21660517) (PP4_Strong). This variant was reported to result in undetectable creatine transport activity when expressed in SLC6A8 deficient fibroblasts. A creatine concentration of 25uM was used, meeting the requirement for the assay to be carried out with less than or equal to 125uM creatine (PMID: 22281021, 23644449) (PS3_Supporting). The variant is absent in gnomAD v2.1.1. (PM2_Supporting). The computational predictor REVEL gives a score of 0.884 which is above the threshold of 0.75, evidence that correlates with impact to SLC6A8 function (PP3). There is no ClinVar entry for this variant. In summary, this variant meets criteria to be classified as likely pathogenic for creatine transporter deficiency. SLC6A8-specific criteria applied, as specified by the ClinGen CCDS VCEP (Specifications Version 1.1.0): PS3_Supporting, PM2_Supporting, PP3, PP4_Strong. (Classification approved by the ClinGen CCDS VCEP on April 11, 2024)

Met criteria codes

PS3_Supporting	✔	This variant was reported to result in undetectable creatine transport activity when expressed in SLC6A8 deficient fibroblasts. A creatine concentration of 25uM was used, meeting the requirement for the assay to be carried out with less than or equal to 125uM creatine (PMID: 22281021, 23644449) (PS3_Supporting).
PP4_Strong	✔	This variant has been previously reported in two unrelated male individuals (PMID: 23644449, PMID: 21660517) (PS4_Supporting), including one who had elevated urinary creatine/creatinine and absent creatine peak on brain MRS (PMID: 21660517) (PP4_Strong).
PM2_Supporting	✔	The variant is absent in gnomAD v2.1.1. (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.884 which is above the threshold of 0.75, evidence that correlates with impact to SLC6A8 function (PP3).

Not Met criteria codes

PS4	✖	This variant has been previously reported in one unrelated male individual (PMID: 23644449, PMID: 21660517) who had elevated urinary creatine/creatinine and absent creatine peak on brain MRS (PMID: 21660517) (PP4_Strong).

Curation History

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