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Variant: NM_005629.4(SLC6A8):c.1473C>G (p.Cys491Trp)

Version: 1.0

CA256015

11704 (ClinVar)

Gene: SLC6A8 (HGNC:6535)
Condition: creatine transporter deficiency (MONDO:0010305)
Inheritance Mode: X-linked inheritance
UUID: 9580d0bc-2081-4ad2-8b07-3a661e24e0ba
Approved on: 2024/3/25
Published on: 2024/3/25

HGVS expressions

NM_005629.4:c.1473C>G
NM_005629.4(SLC6A8):c.1473C>G (p.Cys491Trp)
NC_000023.11:g.153694424C>G
CM000685.2:g.153694424C>G
NC_000023.10:g.152959879C>G
CM000685.1:g.152959879C>G
NC_000023.9:g.152613073C>G
NG_012016.1:g.11128C>G
NG_012016.2:g.11128C>G
ENST00000253122.10:c.1473C>G
ENST00000253122.9:c.1473C>G
ENST00000413787.1:c.402C>G
ENST00000430077.6:c.1128C>G
ENST00000485324.1:n.1694C>G
NM_001142805.1:c.1443C>G
NM_001142806.1:c.1128C>G
NM_005629.3:c.1473C>G
NM_001142805.2:c.1443C>G

Likely Pathogenic

Met criteria codes 4

PS3_Supporting PP4_Strong PM2_Supporting 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.1472G>A variant is a missense variant predicted to cause a substitution of a cysteine for a tryptophan at amino acid position 491 (p.Cys491Trp). This variant has been reported in one hemizygous male individual with elevated urinary creatine/creatinine and absent creatine peak on brain MRS (PMID: 17101918) (PP4_Strong). This variant was reported to result in reduced (<10% of wild-type) creatine transport activity in SLC6A8 deficient fibroblasts, measured with 25uM creatine (PMID: 22281021) (PS3_Supporting). This variant is absent from gnomAD v2.1.1 (PM2_Supporting). The computational predictor REVEL gives a score of 0.751 which is above the threshold of 0.75, evidence that correlates with impact to SLC6A8 function (PP3). There is a ClinVar entry for this variant (Variation ID: 11704). 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 March 25, 2024).

Met criteria codes

PS3_Supporting	✔	This variant was reported to result in reduced (<10% of wild-type) creatine transport activity in SLC6A8 deficient fibroblasts, measured with 25 uM creatine (PMID: 22281021) (PS3_Supporting).
PP4_Strong	✔	This variant has been reported in one hemizygous male individual with elevated urinary creatine/creatinine and absent creatine peak on brain MRS (PMID: 17101918) (PP4_Strong).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.751 which is above the threshold of 0.75, evidence that correlates with impact to GAMT function (PP3).

Curation History

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