

Variant: NM\_001142805.2:c.1241G>A

Version: 1.0

CA415086699 [↗](#)

3066442 (ClinVar) [↗](#)

**Gene:** SLC6A8 ([HGNC:6535](#))

**Condition:** creatine transporter deficiency ([MONDO:0010305](#))

**Inheritance Mode:** X-linked inheritance

**UUID:** 93926c42-71f7-46a4-a54a-df099ddfdb4e

**Approved on:** 2024/3/29

**Published on:** 2024/3/29

### HGVS expressions

**NM\_001142805.2:c.1241G>A**

NC\_000023.11:g.153694146G>A

CM000685.2:g.153694146G>A

NC\_000023.10:g.152959601G>A

CM000685.1:g.152959601G>A

NC\_000023.9:g.152612795G>A

NG\_012016.1:g.10850G>A

NG\_012016.2:g.10850G>A

ENST00000253122.10:c.1271G>A

ENST00000253122.9:c.1271G>A

ENST00000413787.1:c.258-58G>A

ENST00000430077.6:c.926G>A

ENST00000442457.1:c.325G>A

ENST00000457723.1:c.248G>A

ENST00000485324.1:n.1416G>A

NM\_001142805.1:c.1241G>A

NM\_001142806.1:c.926G>A

NM\_005629.3:c.1271G>A

NM\_005629.4:c.1271G>A

**Likely Pathogenic**

**Met criteria codes** 4

PP3

PP4\_Strong

PP1\_Moderate

PM2\_Supporting

**Not Met criteria codes** 4

BS2

BS4

BS3

PS3

**Evidence Links** 1

### 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**

Cerebral Creatine Deficiency Syndromes VCEP

The NM\_005629.4: c.1271G>A variant in the SLC6A8 is a missense variant in exon 9 predicted to result in substitution of glycine by aspartic acid at position 424 (p.Gly424Asp). This variant has been reported in three male siblings with mild intellectual disability, elevated urine creatine/creatinine, and reduced creatine peak on brain MRS (PP4\_strong). Their mother was heterozygous for the same variant, had a mild reduction of creatine on MRS and indicate the mother had attention deficit, impulsiveness and intelligence below average (PMID: 24137762) (PP1\_moderate). This variant was not found in gnomAD v2.1.1. (PM2\_supporting). In silico predictions suggest this variant will be damaging to the function of the canonical protein (REVEL = 0.90) (PP3). There is no ClinVar entry for this variant. Functional studies of this variant demonstrated residual creatine uptake of 29% of the wildtype transfection level, indicating that this variant may affect the function of the protein but not meeting the threshold required by the ClinGen Cerebral Creatine Deficiency Syndromes VCEP (<10%) (PMID: 22281021) (PS3\_Supporting not met). In summary, this variant meets criteria to be classified as a likely pathogenic variant for creatine transporter deficiency. SLC6A8-specific criteria applied, as specified by the ClinGen CCDS VCEP (Specifications Version 1.1.0) (PP4\_strong, PP1\_moderate, PM2\_supporting, PP3). (Classification approved by the ClinGen Cerebral Cretine Deficiency Syndromes Variant Curation Expert Panel on March 29, 2024).

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                             |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP3            |    |    | The computational predictor REVEL gives a score of 0.909 which is above the threshold of 0.75, evidence that correlates with impact to SLC6A8 function (PP3).                                                                                                               |
| PP4_Strong     |    |    | Phenotypic findings included MRS with reduced creatine peak, increased urinary creatine to creatinine ratio, intellectual disability.                                                                                                                                       |
| PP1_Moderate   |  |  | Segregated in mildly affected mother and three affected brothers. Their mother was heterozygous for the same variant, had a mild reduction of creatine on MRS and indicate the mother had attention deficit, impulsiveness and intelligence below average (PMID: 24137762). |
| PM2_Supporting |  |  | This variant was not found in gnomAD v2.1.1. (PM2_Supporting).                                                                                                                                                                                                              |

Not Met criteria codes

|     |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                              |
|-----|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BS2 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                                                                                                   |
| BS4 |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline                                                                                                                                                                                                                                                                                                   |
| BS3 |                                                                                     |  | Expression of the variant in transfected cells resulted in a residual uptake of 29% wildtype SLC6A8 activity. CCDS VCEP has set a cutoff of >50% creatine uptake for BS3. <div>Expression of the variant in transfected cells resulted in a residual uptake of 29% wildtype SLC6A8 activity.<br/><a href="#">PubMed:22281021</a> </div> |
| PS3 |                                                                                     |  | Expression of the variant in transfected cells resulted in a residual uptake of 29% wildtype SLC6A8 activity. CCDS VCEP has set a cutoff of less than 10% creatine uptake for PS3.                                                                                                                                                                                                                                           |

Expression of the variant in transfected cells resulted in a residual uptake of 29% wildtype SLC6A8 activity.

PubMed:22281021 

Curation History 

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