

Variant: *NM_005629.4(SLC6A8):c.1661C>T (p.Pro554Leu)*

Version: 1.0

CA345036 [↗](#)

65693 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 3c251870-1145-4f3d-b6c8-a8eafb2d9656

Approved on: 2025/1/7

Published on: 2025/1/9

HGVS expressions

NM_005629.4:c.1661C>T

NM_005629.4(SLC6A8):c.1661C>T (p.Pro554Leu)

NC_000023.11:g.153694783C>T

CM000685.2:g.153694783C>T

NC_000023.10:g.152960238C>T

CM000685.1:g.152960238C>T

NC_000023.9:g.152613432C>T

NG_012016.1:g.11487C>T

NG_012016.2:g.11487C>T

ENST00000253122.10:c.1661C>T

ENST00000253122.9:c.1661C>T

ENST00000430077.6:c.1316C>T

ENST00000485324.1:n.1968C>T

NM_001142805.1:c.1631C>T

NM_001142806.1:c.1316C>T

NM_005629.3:c.1661C>T

NM_001142805.2:c.1631C>T

Pathogenic

Met criteria codes 5

PM2_Supporting

PP4_Strong

PS4_Moderate

PP3

PP1_Moderate

Not Met criteria codes 1

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**

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_005629.4:c.1661C>T variant in SLC6A8 is predicted to result in the substitution of proline by leucine at amino acid 554 (p.Pro554Leu). This variant has been reported in a hemizygous male with clinical features consistent with creatine transporter deficiency, elevated urine creatine/creatinine ratio, and deficient creatine uptake in fibroblasts (PMID: 15690373, 21556832, 24789340) (PP4_Strong). This variant has also been reported in another 4 unrelated probands, all with clinical features consistent with creatine transporter deficiency. Two of these individuals (one male, one female) have biochemical and/or brain magnetic resonance spectroscopy (MRS) data to support the diagnosis (PMID: 15154114, 17465020, 21836662; 33164824) (PS4_Moderate). Supportive biochemical, MRS, or creatine uptake results are not available for the other two patients (PMID: 23660394, 30293248). One proband has an affected brother, with elevated creatine/creatinine ratio in urine and deficient creatine transport in fibroblasts; their mother is heterozygous for the variant and has mild learning difficulties (PMID: 15690373) (2 segregations, PP1_Moderate). Segregation of the clinical symptoms with the variant has been reported in other families, but no biochemical, MRS, or creatine uptake studies were performed in the affected individuals and, therefore, this data will not be counted towards PP1 (PMID: 15154114 - 5 segregations; PMID: 33164824). The variant is not in gnomAD v2.1.1. and v4.1.0. (PM2_Supporting). Overexpression of the variant in SLC6A8-deficient fibroblasts did not result in a significant increase in creatine transport. Studies were carried out with 500uM creatine (PMID: 17465020). The CCDS VCEP requires that studies are carried out with <125uM creatine. Therefore, PS3 is not met. The computational predictor REVEL gives a score of 0.937 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 (Variant ID: 65693). In summary, this variant meets the criteria to be classified as pathogenic for creatine transporter deficiency. SLC6A8-specific ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel (Specifications Version 1.1.0): PP4_Strong, PS4_Moderate, PP1_Moderate, PP3, PM2_Supporting.)Classification approved by the ClinGen Cerebral Creatine Deficiencies Variant Curation Expert Panel on Jan 7, 2025).

Met criteria codes		
PM2_Supporting	 	The variant is not in gnomAD v2.1.1. or v4.1.0. (PM2_Supporting).
PP4_Strong	 	This variant has been reported in a hemizygous male with clinical features consistent with creatine transporter deficiency, elevated urine creatine/creatinine ratio, and deficient creatine uptake in fibroblasts (PMID: 15690373, 21556832, 24789340) (PP4_Strong).
PS4_Moderate	 	This variant has been reported in 5 unrelated probands, all with clinical features consistent with creatine transporter deficiency. Three of these individuals (two male, one female) have biochemical, brain magnetic resonance spectroscopy (MRS), and/or fibroblast creatine uptake data to support the diagnosis (PMID: 15690373, 21556832, 24789340; 15154114, 17465020, 21836662; 33164824) (PP4_Strong, PS4_Moderate). Supportive biochemical, MRS, or creatine uptake results are not available for the other two patients (PMID: 23660394, 30293248).
PP3	 	The computational predictor REVEL gives a score of 0.937 which is above the threshold of 0.75, evidence that correlates with impact to SLC6A8 function (PP3). SpliceAI predicts that the variant has no impact on splicing.
PP1_Moderate	 	One proband has an affected brother, with elevated creatine/creatinine ratio in urine and deficient creatine transport in fibroblasts; their mother is heterozygous for the variant and has mild learning difficulties (PMID: 15690373) (2 segregations, PP1_Moderate). Segregation of the clinical symptoms with the variant has been reported in other families, but no biochemical, MRS, or creatine uptake studies were performed in the affected individuals and, therefore, this data will not be counted towards PP1 (PMID: 15154114 - 5 segregations; PMID: 33164824).

Not Met criteria codes		
PS3		Overexpression of the variant in SLC6A8-deficient fibroblasts did not result in a significant increase in creatine transport. Studies were carried out with 500uM creatine (PMID: 17465020). The CCDS VCEP requires that studies are carried out with <125uM creatine. Therefore, PS3 is not met.

Overexpression of the variant in SLC6A8-deficient fibroblasts did not result in a significant increase in creatine transport (Fig 1). Transient transfection with wild-type SLC6A8 resulted in a six-fold increase in creatine uptake, but there was no significant difference in creatine uptake between the nontransfected cells an mock transfectants (PMID: 17465020) [PubMed:17465020](#)

Curation History [↗](#)

▼

▼

Showing 1 to 1 of 1 rows

--

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.