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Variant: NM_005629.4(SLC6A8):c.1216TTC[2] (p.Phe408del)

Version: 1.0

CA341129

11698 (ClinVar)

Gene: SLC6A8 (HGNC:6535)
Condition: creatine transporter deficiency (MONDO:0010305)
Inheritance Mode: X-linked inheritance
UUID: 29079020-d5eb-44ab-95bc-4c9fd389a141
Approved on: 2023/8/22
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HGVS expressions

NM_005629.4(SLC6A8):c.1216TTC[2] (p.Phe408del)
NM_005629.4:c.1222_1224del
NC_000023.11:g.153693985_153693987del
CM000685.2:g.153693985_153693987del
NC_000023.10:g.152959440_152959442del
CM000685.1:g.152959440_152959442del
NC_000023.9:g.152612634_152612636del
NG_012016.1:g.10689_10691del
NG_012016.2:g.10689_10691del
ENST00000253122.10:c.1222_1224del
ENST00000253122.9:c.1222_1224del
ENST00000413787.1:c.258-219_258-217del
ENST00000430077.6:c.877_879del
ENST00000442457.1:c.276_278del
ENST00000457723.1:c.206_208del
ENST00000485324.1:n.1255_1257del
NM_001142805.1:c.1192_1194del
NM_001142806.1:c.877_879del
NM_005629.3:c.1222_1224del
NM_001142805.2:c.1192_1194del

Pathogenic

Met criteria codes 6

PS3_Supporting PP4_Strong PM2_Supporting PM4 PS4 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.1222_1224del variant in SLC6A8 is predicted to cause a change in the length of the protein (p.Phe408del)) due to an in-frame deletion of 1 amino acid in a non-repeat region (PM4). This variant is one of the most common variants in SLC6A8 identiified in individuals with Creatine transporter deficiency. It has been reported in at least 10 individuals with clinical symptoms consistent with creatine transporter deficiency and elevated urine creatine/creatinine ratio from various countires including Italy, Spain, China, India, and Turkey (PMIDs: 12210795, 16169544, 21140503, 22551696, 23644449, 23660394, 29396939, 33656256, 34974949) (PS4_Very Strong). One male patient had clinical features consistent with creatine transporter deficiency, marked reduction of brain creatine peak on MRS. elevated urine creatine/creatinine ratio, and undetectable creatine uptake in fibroblasts with 25 µmol/L creatine (PMID: 16601898) (PP4_Strong). In gnomAD v2.1.1, the highest population minor allele frequency is 0.00009370 (1/10672 alleles) in the European non-Finnish population which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.00002). This is the only allele reported in any population in gnomAD v2.1.1. and there are 0 homozygotes and 0 hemizygotes (PM2_Supporting). The variant was introduced into SLC6A8 cDNA by site-directed mutagenesis and expressed in Xenopus oocytes. Creatine transport was measured in the presence of 20uM creatine and was "severely impaired" (PMID: 22644605) (PS3_Supporting). Mutation Taster predicts that the variant is "disease-causing". 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 Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): PM4, PS4_VeryStrong, PP4_Strong,, PP3, PS3_Supporting, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP, August 22, 2023)

Met criteria codes

PS3_Supporting ✔	The variant was introduced into SLC6A8 cDNA by site-directed mutagenesis and expressed in Xenopus oocytes. Creatine transport was measured in the presence of 20uM creatine and was "severely impaired" (PMID: 22644605) (PS3_Supporting).
PP4_Strong ✔	A male patient with clinical features consistent with creatine transporter deficiency, marked reduction of brain creatine peak on MRS. elevated urine creatine/creatinine ratio, and undetectable creatine uptake in fibroblasts with 25 µmol/L creatine (PMID: 16601898) (PP4_Strong).
PM2_Supporting ✔	In gnomAD v2.1.1, the highest population minor allele frequency is 0.00009370 (1/10672 alleles) in the European non-Finnish population which is lower than the ClinGen CCDS VCEP's threshold for PM2_Supporting (<0.00002). This is the only allele reported in any population in gnomAD v2.1.1. and there are 0 homozygotes and 0 hemizygotes (PM2_Supporting).
PM4 ✔	The NM_005629.4:c.1222_1224del variant in SLC6A8 is predicted to cause a change in the length of the protein (p.Phe408del)) due to an in-frame deletion of 1 amino acid in a non-repeat region (PM4).
PS4 ✔	This variant is one of the most common variants in SLC6A8 identiified in individuals with Creatine transporter deficiency. It has been reported in at least 10 individuals with clinical symptoms consistent with creatine transporter deficiency and elevated urine creatine/creatinine ratio from various countires including Italy, Spain, China, India, and Turkey (PMIDs: 12210795, 16169544, 21140503, 22551696, 23644449, 23660394, 29396939, 33656256, 34974949) (PS4_Very Strong))
PP3 ✔	Mutation Taster predicts that the variant is "disease-causing". No impact on splicing predicted by SpliceAI.

Curation History

Showing 1 to 1 of 1 rows

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