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Variant: NM_005629.4:c.318CTT[1]

Version: 1.0

CA342090

21448 (ClinVar)

Gene: SLC6A8
Condition: creatine transporter deficiency (MONDO:0010305)
Inheritance Mode: X-linked inheritance
UUID: e3d1dfbb-7232-43a1-a23b-0a569a127e3e
Approved on: 2022/6/6
Published on: 2022/10/8

HGVS expressions

NM_005629.4:c.318CTT[1]
NC_000023.11:g.153690433_153690435del
CM000685.2:g.153690433_153690435del
NC_000023.10:g.152955888_152955890del
CM000685.1:g.152955888_152955890del
NC_000023.9:g.152609082_152609084del
NG_012016.1:g.7137_7139del
NG_012016.2:g.7137_7139del
ENST00000253122.10:c.321_323del
ENST00000675713.1:n.75_77del
ENST00000253122.9:c.321_323del
ENST00000430077.6:c.-25_-23del
ENST00000476466.1:n.173_175del
NM_001142805.1:c.321_323del
NM_001142806.1:c.-25_-23del
NM_005629.3:c.321_323del
NM_005629.4:c.321_323del
NM_001142805.2:c.321_323del

Pathogenic

Met criteria codes 5

PM4 PP1_Moderate PP4_Strong PS4 PM2_Supporting

Not Met criteria codes 1

PS3

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*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Cerebral Creatine Deficiency Syndromes VCEP

The NM_005629.4(SLC6A8):c.318_320delCTT variant in SLC6A8 is a 3 nucleotide deletion predicted to lead to the in-frame deletion of a single Phenylalanine at amino acid 107 (p.Phe107del). This variant is absent from gnomAD v2.1.1, therefore PM2_Supporting criteria is applicable. Individuals with this variant have been reported in the literature. In deGrauw, 2002 [PMID:12536364] a family with two affected males, one affected female, and one asymptomatic female (mother) were reported. Individual MB from this family was reported with elevated creatine: creatinine in urine, MRS showing absent creatine and phosphocreatine peak, and is used to fulfill PP4_Strong criteria and therefore not used as PS4 evidence. Segregations from this family are used as PP1 evidence. At least 3 additional affected individuals meeting PP4 criteria have been reported [PMID:19188083, 29435807, 33267903], not including the family from deGrauw. Functional studies have been performed, but do not meet the criteria established for PS3 evidence from the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (creatine <125uM creatine used for creatine transport assay) [PMID: 17465020]. There is a ClinVar entry for this variant (Variation ID:21448). In summary, this variant meets the criteria to be classified as a Pathogenic for Creatine Transporter Deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.1.0): PS4, PP4_Strong, PM4, PP1_Moderate, PM2_Supporting. (Classification approved by the ClinGen CCDS VCEP on June 6, 2022).

Met criteria codes

PM4	✔	The NM_005629.4(SLC6A8):c.318_320delCTT (p.Phe107del) variant in SLC6A8 is a 3 nucleotide deletion predicted to lead to the in-frame deletion of a single Phenylalanine at amino acid 107 (p.Phe107del).
PP1_Moderate	✔	Biochemical studies performed in patient MB from family 2 demonstrated elevated urine Cr/Crn 3174 (nMol/Mol Crn), and MRS demonstrating absence of creatine and phosphocreatine peak. Two affected males will be counted for PP1 evidence. Additionally there is one symptomatic female carrier and one asymptomatic (mother of 3 affected individuals) carrier. [PMID:12536364]
PP4_Strong	✔	Biochemical studies performed in patient MB from family 2 demonstrated elevated urine Cr/Crn 3174 (nMol/Mol Crn), and MRS demonstrating absence of creatine and phosphocreatine peak. This individual is used to fulfill PP4_Strong criteria and is therefore not counted as PS4 evidence [PMID:12536364].
PS4	✔	At least 3 additional affected individuals meeting PP4 criteria have been reported [PMID:19188083, 29435807, 33267903], not including the family from deGrauw [PMID:12536364] who were used to fulfill PP4 criteria.
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1, therefore PM2_Supporting criteria is applicable.

Not Met criteria codes

PS3	✖	Functional studies have been performed, but do not meet the criteria established for PS3 evidence from the ClinGen Cerebral Creatine Deficiency Syndromes Variant Curation Expert Panel (Specifications Version 1.0, creatine <125uM creatine used for creatine transport assay) [PMID: 17465020].

Curation History

Showing 1 to 1 of 1 rows

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