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Variant: NM_003159.2(CDKL5):c.215T>C (p.Ile72Thr)

Version: 1.0

CA121523

11503 (ClinVar)

Gene: CDKL5 (HGNC:6792)
Condition: CDKL5 disorder (MONDO:0100039)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: 52d0dedf-0fba-4aeb-b0db-0185cef7c6dd
Approved on: 2021/3/26
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HGVS expressions

NM_003159.2(CDKL5):c.215T>C (p.Ile72Thr)
NM_003159.2:c.215T>C
NC_000023.11:g.18575423T>C
CM000685.2:g.18575423T>C
NC_000023.10:g.18593543T>C
CM000685.1:g.18593543T>C
NC_000023.9:g.18503464T>C
NG_008475.1:g.154819T>C
ENST00000623535.2:c.215T>C
ENST00000635828.1:c.215T>C
ENST00000637881.1:c.215T>C
ENST00000674046.1:c.215T>C
ENST00000379989.6:c.215T>C
ENST00000379996.7:c.215T>C
ENST00000463994.4:c.215T>C
ENST00000623535.1:c.215T>C
NM_001037343.1:c.215T>C
NM_001323289.1:c.215T>C
NM_001323289.2:c.215T>C
NM_001037343.2:c.215T>C
NM_003159.3:c.215T>C

Pathogenic

Met criteria codes 6

PM6 PM5_Strong PS4_Moderate PS3_Supporting PM2_Supporting PP3

Evidence Links 3

Expert Panel

Rett and Angelman-like Disorders VCEP

Criteria Specification Information

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Ile72Thr variant in CDKL5 has been reported as a de novo occurrence (biological parentage unconfirmed) in an individual with CDKL5 disease (PMID 19396824, 19241098) (PM6). The p.Ile72Thr variant in CDKL5 has been reported in at least 3 other individuals with CDKL5 disease (PMID 19396824, 19241098, 25657822, ClinVar) (PS4_moderate). The p.Ile72Thr variant in CDKL5 is absent from gnomAD (PM2). Multiple likely pathogenic missense variants have been previously identified within this codon (p.Ile72Asn; p.Ile72Met) which indicates that this residue is critical to the function of the protein (PMID 28074849, 27779742, 16015284) (PM5_strong). Phosphoproteomic screening of the cellular substrates of CDKL5 (MAP1S, CEP131 and DLG5) has shown that the p.Ile72Thr variant impacts protein function (PMID 30266825) (PS3_supporting). Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own(PP3). In summary, the p.Ile72Thr variant in CDKL5 is classified as Pathogenic for CDKL5 disease based on the ACMG/AMP criteria (PM5_strong, PM6, PS4_moderate, PS3_supporting, PM2_supporting, PP3).

Met criteria codes

PM6 ✔	The p.Ile72Thr variant in CDKL5 has been reported as an unconfirmed de novo occurrence in a female individual with early onset epilepsy, growth retardation, severe developmental delays, and precocious puberty (PMIDs 19396824, 19241098; these articles appear to refer to the same patient). The p.Ile72Thr variant in CDKL5 occurs in the unconfirmed de novo state in this female individual with early onset epilepsy, growth retardation, and severe developmental delays. PubMed:19396824
PM5_Strong ✔	Multiple pathogenic missense variants have been previously identified within this codon which indicates that this residue is critical to the function of the protein (PMID 28074849, 27779742,16015284).
PS4_Moderate ✔	The p.Ile72Thr variant has been observed in at least 3 other individuals with CDKL5 disorder (PMID 19396824, 19241098, 25657822, ClinVar). The p.Ile72Thr variant was observed in an individual with early onset epilepsy, growth retardation, severe developmental delays, and precocious puberty (appears to be the same patient as reported in PMID 19241098). PubMed:19396824 The p.Ile72Thr variant was observed in an individual with early onset epilepsy, growth retardation, severe developmental delays, and precocious puberty (appears to be the same patient as reported in PMID 19396824). PubMed:19241098 The p.Ile72Thr variant was observed in an individual with CDKL5 disorder. PubMed:25657822
PS3_Supporting ✔	Phosphoproteomic screening of the cellular substrates of CDKL5 (MAP1S, CEP131 and DLG5) has shown that the p.Ile72Thr variant impacts CDKL5 phosphorylation in multiple substrates (PMID 30266825).
PM2_Supporting ✔	The p.Ile72Thr variant in CDKL5 is absent from gnomAD.
PP3 ✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own.

Curation History

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