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Variant: NM_003159.2(CDKL5):c.119C>T (p.Ala40Val)

Version: 1.0

CA121521

11502 (ClinVar)

Gene: CDKL5 (HGNC:6792)
Condition: CDKL5 disorder (MONDO:0100039)
Inheritance Mode: X-linked inheritance
UUID: 0e323081-868b-43b4-974c-8893a942d274
Approved on: 2021/3/30
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HGVS expressions

NM_003159.2(CDKL5):c.119C>T (p.Ala40Val)
NM_003159.2:c.119C>T
NC_000023.11:g.18564496C>T
CM000685.2:g.18564496C>T
NC_000023.10:g.18582616C>T
CM000685.1:g.18582616C>T
NC_000023.9:g.18492537C>T
NG_008475.1:g.143892C>T
ENST00000623535.2:c.119C>T
ENST00000635828.1:c.119C>T
ENST00000637881.1:c.119C>T
ENST00000674046.1:c.119C>T
ENST00000379989.6:c.119C>T
ENST00000379996.7:c.119C>T
ENST00000463994.4:c.119C>T
ENST00000623364.3:c.119C>T
ENST00000623535.1:c.119C>T
ENST00000624700.3:c.119C>T
NM_001037343.1:c.119C>T
NM_001323289.1:c.119C>T
NM_001323289.2:c.119C>T
NM_001037343.2:c.119C>T
NM_003159.3:c.119C>T

Pathogenic

Met criteria codes 5

PP3 PS2_Very Strong PM1 PS4 PM2_Supporting

Evidence Links 0

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.Ala40Val variant in CDKL5 has been reported in at least 4 unconfirmed de novo occurrences in patients with CDKL5 disorder (PMID 27779742, 17993579, 22678952, 19793311) (PM6_VS). It is also reported in the mosaic state in a male patient with CDKL5 disorder (PMID 25819767) and therefore confirmed to be de novo (PS2). The p.Ala40Val variant has been observed in at least 10 other individuals with CDKL5 disorder (27779742, 25819767, 17993579, 22678952, 19793311, 21309761, 19780792) (PS4). The variant is absent in gnomAD (PM2_supporting). The variant is located in a well-characterized (ATP binding region: aa 19-43) functional domain of CDKL5 (PMID: 28544139, 17993579, 23064044, 29264392) (PM1). Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3). In summary, the p.Ala40Val in CDKL5 is classified as Pathogenic based on the ACMG/AMP criteria (PM6_very strong, PS2, PS4_strong, PM1, PM2_supporting, PP3).

Met criteria codes

PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3)
PS2_Very Strong	✔	Reported in the mosaic state in a male patient with CDKL5 disorder (PMID 25819767) and therefore confirmed to be de novo (PS2). PM6_VS: The p.Ala40Val variant in CDKL5 has been reported in at least 4 unconfirmed de novo occurrences in patients with CDKL5 disorder (PMID 27779742, 17993579, 22678952, 19793311). While the cases involved did not have parental relationships confirmed (PM6), they did reach the very strong threshold for this type of evidence as defined by the Rett/AS VCEP, and this criterion is being used as a proxy since PM6_very strong is not currently available.
PM1	✔	The variant is located in a critical domain of CDKL5 (ATP binding region: aa 19-43)(PMID: 28544139,17993579) (PM1)
PS4	✔	PS4_S: The p.Ala40Val variant has been observed in at least 10 other individuals with CDKL5 disorder (27779742, 25819767, 17993579, 22678952, 19793311, 21309761, 19780792)
PM2_Supporting	✔	The p.Ala40Val variant is absent in gnomAD and ExAC (PM2_supporting)

Curation History

Showing 1 to 1 of 1 rows

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