The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_003159.2(CDKL5):c.533G>A (p.Arg178Gln)

Version: 1.0

CA199289

94113 (ClinVar)

Gene: CDKL5 (HGNC:6792)
Condition: CDKL5 disorder (MONDO:0100039)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: 1bf4c21f-9836-4b36-9366-021907530816
Approved on: 2021/3/25
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HGVS expressions

NM_003159.2(CDKL5):c.533G>A (p.Arg178Gln)
NM_003159.2:c.533G>A
NC_000023.11:g.18584332G>A
CM000685.2:g.18584332G>A
NC_000023.10:g.18602452G>A
CM000685.1:g.18602452G>A
NC_000023.9:g.18512373G>A
NG_008475.1:g.163728G>A
ENST00000623535.2:c.533G>A
ENST00000635828.1:c.533G>A
ENST00000637881.1:c.533G>A
ENST00000674046.1:c.533G>A
ENST00000379989.6:c.533G>A
ENST00000379996.7:c.533G>A
ENST00000463994.4:c.533G>A
ENST00000623535.1:c.533G>A
NM_001037343.1:c.533G>A
NM_001323289.1:c.533G>A
NM_001323289.2:c.533G>A
NM_001037343.2:c.533G>A
NM_003159.3:c.533G>A

Pathogenic

Met criteria codes 4

PM5_Strong PS4 PS2_Very Strong PM2_Supporting

Not Met criteria codes 1

PP3

Evidence Links 5

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.Arg178Gln variant in CDKL5 has been reported in at least 4 de novo occurrences (biological parentage unconfirmed) in patients with CDKL5 disorder (PMID 26482601, 21770923, 29852413, 29190809, 24564546, 26482601) (PM6_very strong). The variant was present in the mosaic state in one patient, confirming its de novo nature (PMID 26482601) (PS2). The p.Arg178Gln variant in CDKL5 has been reported in at least 7 other individuals with CDKL5 disorder (PMID 26482601, 21770923, 29852413, 29190809, 24564546) (PS4). 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 29100083, 22430159, 19793311, 18809835, 30182498) (PM5_strong). The p.Arg178Gln variant in CDKL5 is absent from gnomAD (PM2_supporting). In summary, the p.Arg178Gln variant in CDKL5 is classified as Pathogenic for CDKL5 disorder based on the ACMG/AMP criteria (PM6_very strong, PS2, PS4, PM5_strong, PM2_supporting).

Met criteria codes

PM5_Strong ✔

Other pathogenic missense variants (p.Arg178Trp, p.Arg178Pro, p.Arg178Leu) have been previously identified within this codon which indicates that this residue is critical to the function of the protein (PMIDs 29100083, 22430159, 19793311, 18809835, 30182498) (PM5_strong).

PS4 ✔

The p.Arg178Gln variant has been observed in at least 7 other individuals with CDKL5 disease (PMIDs 26482601, 21770923, 29852413, 29190809, 24564546, ClinVar Variation ID 94113).

The p.Arg178Gln variant was observed in a male individual with epileptic encephalopathy. PubMed:21770923
The p.Arg178Gln variant was observed in a male individual with CDKL5 disease. PubMed:24564546
The p.Arg178Gln variant was observed in a two individuals with early onset epileptic encephalopathy. PubMed:29852413
The p.Arg178Gln variant was observed in a female individual with epileptic encephalopathy. PubMed:29190809
The p.Arg178Gln variant was observed in a male individual with West syndrome. PubMed:26482601

PS2_Very Strong ✔

The p.Arg178Gln variant in CDKL5 has been reported in the mosaic state in a male patient with epileptic encephalopathy (PMID 26482601). The presence of the variant in the mosaic state confirms its de novo nature (PS2). The p.Arg178Gln variant in CDKL5 has been reported as an unconfirmed de novo occurrence in at least 4 individuals with CDKL5 disorder (PMIDs 21770923, 29852413, 29190809, 24564546) (PM6_very strong). Note that PM6_very strong is not available in the drop-down so PS2_VS is applied instead.

The p.Arg178Gln variant in CDKL5 occurs in the unconfirmed de novo state in a male patient with epileptic encephalopathy. PubMed:21770923
The p.Arg178Gln variant in CDKL5 occurs in the unconfirmed de novo state in a male patient with CDKL5 disorder. PubMed:24564546
The p.Arg178Gln variant in CDKL5 occurs in the unconfirmed de novo state in a female patient with early onset epileptic encephalopathy. PubMed:29852413
The p.Arg178Gln variant in CDKL5 occurs in the unconfirmed de novo state in a female patient with epileptic encephalopathy. PubMed:29190809

PM2_Supporting ✔

The p.Arg178Gln variant in CDKL5 is absent from gnomAD.

Not Met criteria codes

PP3 ✖

No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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