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Variant: NM_001323289.2(CDKL5):c.656A>C (p.Gln219Pro)

Version: 1.0

CA199370

189549 (ClinVar)

Gene: CDKL5 (HGNC:6792)
Condition: CDKL5 disorder (MONDO:0100039)
Inheritance Mode: X-linked inheritance
UUID: a1b11a90-1c4d-406b-85d8-9c6520d4df7c
Approved on: 2025/8/27
Published on: 2025/9/30

HGVS expressions

NM_001323289.2:c.656A>C
NM_001323289.2(CDKL5):c.656A>C (p.Gln219Pro)
NC_000023.11:g.18588055A>C
CM000685.2:g.18588055A>C
NC_000023.10:g.18606175A>C
CM000685.1:g.18606175A>C
NC_000023.9:g.18516096A>C
NG_008475.1:g.167451A>C
ENST00000623535.2:c.656A>C
ENST00000635828.1:c.656A>C
ENST00000637881.1:c.656A>C
ENST00000674046.1:c.656A>C
ENST00000379989.6:c.656A>C
ENST00000379996.7:c.656A>C
ENST00000463994.4:c.656A>C
ENST00000623535.1:c.656A>C
ENST00000623610.1:n.370A>C
NM_001037343.1:c.656A>C
NM_003159.2:c.656A>C
NM_001323289.1:c.656A>C
NM_001037343.2:c.656A>C
NM_003159.3:c.656A>C

Likely Pathogenic

Met criteria codes 6

PS2 PP3 PP4 PM2_Supporting PS4_Supporting PS3_Supporting

Not Met criteria codes 3

PM1 PM5 PS1

Evidence Links 0

Expert Panel

Rett and Angelman-like Disorders VCEP

Criteria Specification Information

- **Criteria Specification:** *ClinGen Rett and Angelman-like Disorders Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for CDKL5 Version 5.0.0*
- **Criteria Specification Approval History**
- **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Gln219Pro variant has been observed in at least 2 individuals with CDKL5 disorder (PMID 23151060, internal database - Ambry) (PS4_Supporting). The p.Gln219Pro variant in CDKL5 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with CDKL5 disorder (internal database - Ambry) (PS2). The p.Gln219Pro variant in CDKL5 is present in an individual with a clinical phenotype suggestive of CDKL5 disorder (internal database - Ambry) (PP4). The p.Gln219Pro variant in CDKL5 is absent from gnomAD v4.1 (PM2_Supporting). In vitro kinase assay has shown that this variant impacts protein function (PMID: 32034940) (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.Gln219Pro variant in CDKL5 is classified as likely pathogenic for CDKL5 disorder based on the ACMG/AMP criteria (PS4_Supporting, PS2, PP4, PM2_Supporting, PS3_Supporting, PP3). (CDKL5 Specifications v.5.0.0; curation approved on 8/27/2025)

Met criteria codes

PS2	✔	The p.Gln219Pro variant in CDKL5 has been reported as a de novo occurrence (biological parentage confirmed) in an individual with CDKL5 disorder (internal database - Ambry).
PP3	✔	Computational prediction analysis tools suggests a deleterious impact; however, this information does not predict clinical significance on its own (PP3).
PP4	✔	The p.Gln219Pro variant in CDKL5 is present in an individual with a clinical phenotype suggestive of CDKL5 disorder (internal database - Ambry).
PM2_Supporting	✔	The p.Gln219Pro variant in CDKL5 is absent from gnomAD v4.1 (PM2_Supporting).
PS4_Supporting	✔	The p.Gln219Pro variant has been observed in at least 2 individuals with CDKL5 disorder (PMID 23151060, internal database - Ambry).
PS3_Supporting	✔	In vitro kinase assay has shown that this variant impacts protein function (PMID 32034940).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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