

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(CDKL5):c.656A>C (p.Gln219Pro)**

**NM\_001323289.2:c.656A>C**

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**

**PM2\_Supporting** **PS3\_Supporting**

**PP3** **PP4** **PS2** **PS4\_Supporting**

**Not Met criteria codes** **3**

**PS1** **PM1** **PM5**

**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**

***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**

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

**Not Met criteria codes**

|            |                                                                                     |                                                                                     |                                                                                                                            |
|------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
| <b>PS1</b> |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| <b>PM1</b> |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |
| <b>PM5</b> |  |  | No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline |



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