

Variant: *NM_000330.4(RS1):c.185-3221G>A*

Version: 1.1

CA412373781 [↗](#)

930627 (ClinVar) [↗](#)

Gene: CDKL5 ([HGNC:6792](#))

Condition: CDKL5 disorder ([MONDO:0100039](#))

Inheritance Mode: X-linked inheritance

UUID: c41c30bb-c109-46b0-b56c-b77809b5aa01

Approved on: 2023/12/6

Published on: 2023/12/8

HGVS expressions

NM_000330.4:c.185-3221G>A

NM_000330.4(RS1):c.185-3221G>A

NC_000023.11:g.18650553C>T

CM000685.2:g.18650553C>T

NC_000023.10:g.18668673C>T

CM000685.1:g.18668673C>T

NC_000023.9:g.18578594C>T

NG_008475.1:g.229949C>T

NG_008659.3:g.31896G>A

ENST00000379984.4:c.185-3221G>A

ENST00000673617.1:n.213C>T

ENST00000379984.3:c.185-3221G>A

ENST00000379989.6:c.2941C>T

ENST00000379996.7:c.2941C>T

NM_000330.3:c.185-3221G>A

NM_001037343.1:c.2941C>T

NM_003159.2:c.2941C>T

NM_001037343.2:c.2941C>T

NM_003159.3:c.2941C>T

Likely Benign

Met criteria codes **1**

BS2

Not Met criteria codes **4**

PS4

PM2

BS1

PVS1

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 3.0.0*

[↗](#) **Criteria Specification Approval History**

[↗](#) **Criteria Specifications for this VCEP**

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

RS1(NM_000330.4) and an alternative transcript of **CDKL5** (NM_003159.2) are overlapping transcripts; however, these variants are in the noncoding 3' region of the main **CDKL5** transcript (NM_001323289.2). The c.2941C>T (p.Arg981Ter) variant in **CDKL5** transcript (NM_003159.2) (**RS1** c.185-3221G>A) is present in 14 XX and 7 XY individuals in gnomAD v4 (0.0043%) (not sufficient to meet **BS1** criteria). The p.Arg981Ter variant in **CDKL5** is predicted to cause a premature stop codon that leads to a truncated or absent protein in a gene where loss-of-function is an established mechanism. While loss-of-function variants are commonly observed in affected individuals in this gene, there is a paucity of these variants in this region of the gene to date (not sufficient to meet **PVS1** criteria). Additionally, the p.Arg981Ter variant is observed in at least 6 unaffected individuals (internal database - Invitae, internal database - GeneDx) (**BS2**). In the absence of conflicting evidence, this is sufficient evidence to classify as likely benign based on the specifications defined by the ClinGen **Rett and Angelman-like Disorders Variant Curation Expert Panel**. In summary, the p.Arg981Ter variant in **CDKL5** (NM_003159.2) is classified as likely benign based on the **ACMG/AMP** criteria (**BS2**).

Met criteria codes

BS2			The p.Arg981Ter variant is observed in at least 6 unaffected individuals (internal database - Invitae, internal database - GeneDx) (BS2).
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Not Met criteria codes

PS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			The p.Arg981Ter variant in CDKL5 is present in 14 X and 7 XY individual(s) in gnomAD (0.0043%) (not sufficient to meet BS1 criteria).
PVS1			The p.Arg981Ter variant in CDKL5 is predicted to cause a premature stop codon that leads to a truncated or absent protein in a gene where loss-of-function is an established mechanism. While loss-of-function variants are commonly observed in affected individuals in this gene, there is a paucity of these variants in this region of the gene to date (not sufficient to meet PVS1 criteria).

Curation History



 

 

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