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_001323289.2(CDKL5):c.2152G>A (p.Val718Met)

Version: 1.0

CA199279

143796 (ClinVar)

Gene: CDKL5 (HGNC:6792)
Condition: CDKL5 disorder (MONDO:0100039)
Inheritance Mode: X-linked inheritance
UUID: 285d3afa-2703-4819-af6e-ee9e40fc0071
Approved on: 2025/5/7
Published on: 2025/6/30

HGVS expressions

NM_001323289.2:c.2152G>A
NM_001323289.2(CDKL5):c.2152G>A (p.Val718Met)
NC_000023.11:g.18609570G>A
CM000685.2:g.18609570G>A
NC_000023.10:g.18627690G>A
CM000685.1:g.18627690G>A
NC_000023.9:g.18537611G>A
NG_008475.1:g.188966G>A
ENST00000623535.2:c.2152G>A
ENST00000635828.1:c.2152G>A
ENST00000674046.1:c.2152G>A
ENST00000379989.6:c.2152G>A
ENST00000379996.7:c.2152G>A
ENST00000463994.4:c.2152G>A
ENST00000623535.1:c.2152G>A
NM_001037343.1:c.2152G>A
NM_003159.2:c.2152G>A
NM_001323289.1:c.2152G>A
NM_001037343.2:c.2152G>A
NM_003159.3:c.2152G>A

Pathogenic

Met criteria codes 5

PM6_Strong PS4 PP4 PM2_Supporting PS3_Supporting

Not Met criteria codes 1

PP3

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 4.1.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

Rett and Angelman-like Disorders VCEP

The p.Val718Met variant in CDKL5 has been reported in at least 2 de novo occurrences (biological parentage unconfirmed) in individuals with a CDKL5-related disorder (PMID 18790821, 27599155) (PM6_strong). The p.Val718Met variant has been observed at least 5 individuals with CDKL5-related disorders (PMID 31313283, 18790821, 27599155, GeneDx internal database) (PS4), including in an individual with a clinical phenotype very specific to a CDKL5-related disorder (PMID 27599155) (PP4). Additionally, an in vitro study using a minigene splicing assay showed that splicing is disrupted, resulting in exon 14 being omitted from the transcript (PMID: 29264392) (PS3_supporting). The p.Val718Met variant in CDKL5 is absent from gnomAD v4.1 (PM2_Supporting). In summary, the p.Val718Met variant in CDKL5 is classified as pathogenic for CDKL5-related disorders based on the ACMG/AMP criteria (PM6_strong, PS4, PP4, PS3_supporting, PM2_supporting). (CDKL5 Specifications v.4.1; curation approved on [5/7/2025])

Met criteria codes

PM6_Strong	✔	The p.Val718Met variant in CDKL5 has been reported in at least 2 de novo occurrences (biological parentage unconfirmed) in individuals with a CDKL5-related disorder. (PMID 18790821, 27599155).
PS4	✔	The p.Val718Met variant has been observed at least 5 individuals with CDKL5-related disorders (PMID 31313283, 18790821, 27599155, GeneDx internal database) (PS4).
PP4	✔	The p.Val718Met variant in CDKL5 has been reported in an individual with a clinical phenotype suggestive of a CDKL5-related disorder (PMID 27599155)
PM2_Supporting	✔	The p.Val718Met variant in CDKL5 is absent from gnomAD v4.1 (PM2_Supporting).
PS3_Supporting	✔	An in vitro study using a minigene splicing assay showed that splicing is disrupted, resulting in exon 14 being omitted from the transcript (PMID: 29264392).

Not Met criteria codes

PP3	✖	Computational prediction analysis tools are inconclusive for this variant.

Curation History

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