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Variant: NM_003159.3:c.2714-3997A>C

Version: 1.0

CA412370008

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: b56d1751-5864-490c-8220-74efe6378ee4
Approved on: 2025/9/19
Published on: 2025/9/19

HGVS expressions

NM_003159.3:c.2714-3997A>C
NC_000023.11:g.18642010A>C
CM000685.2:g.18642010A>C
NC_000023.10:g.18660130A>C
CM000685.1:g.18660130A>C
NC_000023.9:g.18570051A>C
NG_008475.1:g.221406A>C
NG_008659.3:g.40439T>G
ENST00000379984.4:c.669T>G
ENST00000379984.3:c.669T>G
ENST00000379989.6:c.2714-3997A>C
ENST00000379996.7:c.2714-3997A>C
ENST00000476595.1:n.1160T>G
NM_000330.3:c.669T>G
NM_001037343.1:c.2714-3997A>C
NM_003159.2:c.2714-3997A>C
NM_000330.4:c.669T>G
NM_001037343.2:c.2714-3997A>C

Likely Pathogenic

Met criteria codes 3

PM2_Supporting PM5 PM1_Strong

Not Met criteria codes 1

PP3

Evidence Links 0

Expert Panel

X-linked Inherited Retinal Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0*
Criteria Specification Approval History
Criteria Specifications for this VCEP

Evidence submitted by expert panel

X-linked Inherited Retinal Disease VCEP

NM_000330.4(RS1):c.669T>G (p.Cys223Trp) is a missense variant encoding the substitution of cysteine with tryptophan at amino acid 223. This missense variant affects a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435, PM1_Strong). Another missense variant in the same codon, NM_000330.4(RS1):c.667T>C (p.Cys223Arg) (PMID: 30652005, PMID: 33460243, PMID: 10533068, PMID: 34645606, PMID: 16361673), has been classified as pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (215) than the comparison variant (180), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.898, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 0.773 and predicts a damaging effect on RS1 function. However, the PM1_Strong code has been met, which is ineligible to be used in combination with the PP3 code at any strength, so the PP3_Moderate code was not met. The computational splicing predictor SpliceAI gives a delta score of 0.02 for splice gain, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing. In summary, this variant is classified as likely pathogenic for X-linked retinoschisis based on the ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0: PM2_Supporting, PM1_Strong, and PM5.

Met criteria codes

PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PM5	✔	Another missense variant in the same codon, c.667T>C (p.Cys223Arg) (PMID: 30652005, PMID: 33460243, PMID: 10533068, PMID: 34645606, PMID: 16361673) has been classified as pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (215) than the comparison variant (180), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
PM1_Strong	✔	This variant is a missense substitution affecting a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435, PM1_Strong).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.898, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 0.773 and predicts a damaging effect on RS1 function. However, the PM1_Strong code has been met, which is ineligible to be used in combination with the PP3 code at any strength, so the PP3_Moderate code was not met. The computational splicing predictor SpliceAI gives a delta score of 0.02 for splice gain, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing.

Curation History

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