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Variant: NM_003159.3:c.2714-3996C>A

Version: 1.2

CA412370010

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: f24bd4f8-cf33-4ddc-b57b-ec868d021397
Approved on: 2025/9/19
Published on: 2025/9/19

HGVS expressions

NM_003159.3:c.2714-3996C>A
NC_000023.11:g.18642011C>A
CM000685.2:g.18642011C>A
NC_000023.10:g.18660131C>A
CM000685.1:g.18660131C>A
NC_000023.9:g.18570052C>A
NG_008475.1:g.221407C>A
NG_008659.3:g.40438G>T
ENST00000379984.4:c.668G>T
ENST00000379984.3:c.668G>T
ENST00000379989.6:c.2714-3996C>A
ENST00000379996.7:c.2714-3996C>A
ENST00000476595.1:n.1159G>T
NM_000330.3:c.668G>T
NM_001037343.1:c.2714-3996C>A
NM_003159.2:c.2714-3996C>A
NM_000330.4:c.668G>T
NM_001037343.2:c.2714-3996C>A

Likely Pathogenic

Met criteria codes 3

PP3_Strong PM2_Supporting PM5

Not Met criteria codes 1

PM1

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.668G>T (p.Cys223Phe) is a missense variant encoding the substitution of phenylalanine with cysteine at amino acid 223. Another missense variant in the same codon, NM_000330.4(RS1):c.667T>C (p.Cys223Arg), (PMIDs: 34645606, 10533068, 30652005, 33460243, 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 (205) 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 0.934, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_Strong). The computational splicing predictor SpliceAI gives a delta score of 0.00, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing. 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). However, the PP3_Strong code has been met, which is ineligible to be used in combination with the PM1 code at any strength, so the PM1 code was not met. 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, PP3_Strong, and PM5.

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.934, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_Strong). The computational splicing predictor SpliceAI gives a delta score of 0.00, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing.
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.667T>C (p.Cys223Arg), (PMIDs: 34645606, 10533068, 30652005, 33460243, 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 (205) than the comparison variant (180), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).

Not Met criteria codes

PM1	✖	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). However, the PP3_Strong code has been met, which is ineligible to be used in combination with the PM1 code at any strength, so the PM1 code was not met.

Curation History

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See Report	Preferred Variant Title	Classification	Condition	Published Date	Version	Criteria Specification	Gene
View		Likely Pathogenic	X-Linked Retinoschisis	2025-09-19	1.2	ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0	CDKL5
View		Likely Pathogenic	X-Linked Retinoschisis	2025-09-19	1.1	ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0	CDKL5
View		Likely Pathogenic	X-Linked Retinoschisis	2025-09-19	1.0	ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RS1 Version 1.0.0	CDKL5

Showing 1 to 3 of 3 rows

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