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# *Variant: NM_003159.3:c.2714-1488C>G*

Version: 1.0

*CA412371778*

**Gene**: CDKL5 (HGNC:6792)
**Condition**: X-linked retinoschisis (MONDO:0010725)
**Inheritance Mode**: X-linked inheritance
**UUID:** 8412f6f3-ea2a-43fd-ad63-78f0be1ad982
**Approved on**: Sat, 26 Sep 2026 00:00:00 +0000
**Published on**: Sat, 26 Sep 2026 00:00:00 +0000

## *HGVS expressions*

**NM_003159.3:c.2714-1488C>G**
NC_000023.11:g.18644519C>G
CM000685.2:g.18644519C>G
NC_000023.10:g.18662639C>G
CM000685.1:g.18662639C>G
NC_000023.9:g.18572560C>G
NG_008475.1:g.223915C>G
NG_008659.3:g.37930G>C
ENST00000379984.4:c.433G>C
ENST00000379984.3:c.433G>C
ENST00000379989.6:c.2714-1488C>G
ENST00000379996.7:c.2714-1488C>G
ENST00000476595.1:n.924G>C
NM_000330.3:c.433G>C
NM_001037343.1:c.2714-1488C>G
NM_003159.2:c.2714-1488C>G
NM_000330.4:c.433G>C
NM_001037343.2:c.2714-1488C>G

**Likely Pathogenic**

**Met criteria codes** 5

PP3_Moderate PP4_Moderate PM2_Supporting PS3_Supporting PS4_Supporting

Evidence Links 1

### 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***

**The NM_000330.4(RS1):c.433G>C (p.Asp145His) variant is a missense variant encoding the substitution of Aspartic acid and Histidine at amino acid 145. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.916, which is within the ClinGen X-linked IRD VCEP range between 0.931 and 0.773 and predicts a damaging effect on RS1 function (PP3_moderate). The computational splicing predictor SpliceAI gives a delta score of 0.04 for acceptor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing. Hek 293, Murine RS1h-/Y retinal and kidney cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 30040949, PS3_Supporting). At least one proband harboring this variant exhibits a phenotype including the appearance of schisis and reduced visual acuity before age 13 years, and showing retinal detachment, which together are highly specific for X-linked retinoschisis (PMID: 7615541, PP4_Moderate). This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 18369700, 32300273, 34624300, PS4_Supporting). 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_Moderate, PS3_Supporting, PP4_Moderate, and PS4_Supporting.**

**Met criteria codes**

| | |
|---|---|
| **PP3_Moderate** ✔ | The computational predictor REVEL gives a score of 0.916, which is within the ClinGen X-linked IRD VCEP range between 0.931 and 0.773 and predicts a damaging effect on RS1 function (PP3_moderate). The computational splicing predictor SpliceAI gives a delta score of 0.04 for acceptor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing. |
| **PP4_Moderate** ✔ | At least one proband harboring this variant exhibits a phenotype including the appearance of schisis and reduced visual acuity before age 13 years, and showing retinal detachment, which together are highly specific for X-linked retinoschisis (PMID: 7615541, PP4_Moderate). |
| **PM2_Supporting** ✔ | This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). |
| **PS3_Supporting** ✔ | Hek 293, Murine RS1h-/Y retinal and kidney cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 30040949, PS3_Supporting).<br><br>Plössl et al. assessed the mutants' ability to bind to the retinal membranes of murine retinal RS1h-/Y and interaction with the retinal Na/K-ATPase. Retinoschisin binding was assessed by subjecting membrane pellets to Western blot analyses with antibodies against retinoschisin. PubMed:30040949 |
| **PS4_Supporting** ✔ | This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 18369700, 32300273, 34624300, PS4_Supporting). |

Curation History

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