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_003159.3:c.2714-1477C>G

Version: 1.0

CA412371856

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 04003c16-8587-49b2-abe3-5fd17cf983ac
Approved on: 2025/9/22
Published on: 2025/9/22

HGVS expressions

NM_003159.3:c.2714-1477C>G
NC_000023.11:g.18644530C>G
CM000685.2:g.18644530C>G
NC_000023.10:g.18662650C>G
CM000685.1:g.18662650C>G
NC_000023.9:g.18572571C>G
NG_008475.1:g.223926C>G
NG_008659.3:g.37919G>C
ENST00000379984.4:c.422G>C
ENST00000379984.3:c.422G>C
ENST00000379989.6:c.2714-1477C>G
ENST00000379996.7:c.2714-1477C>G
ENST00000476595.1:n.913G>C
NM_000330.3:c.422G>C
NM_001037343.1:c.2714-1477C>G
NM_003159.2:c.2714-1477C>G
NM_000330.4:c.422G>C
NM_001037343.2:c.2714-1477C>G

Likely Pathogenic

Met criteria codes 4

PP4 PM5 PP3_Strong PM2_Supporting

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.422G>C (p.Arg141Pro) is a missense variant encoding the substitution of arginine with proline at amino acid 141. Another missense variant in the same codon, NM_000330.4(RS1):c.422G>A (p.Arg141His), (PMID: 29851975, PMID: 34645606, PMID: 30450322, PMID: 29739629, PMID: 35984651, PMID: 30652005, PMID: 19093009, PMID: 30630865, PMID: 30040949, PMID: 17525175, PMID: 30630865, PMID: 30040949) 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 (103) than the comparison variant (29), 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). At least one proband harboring this variant exhibits phenotypes including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 33460243, PP4). The computational predictor REVEL gives a score of 0.955, 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 0.02 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. 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, PM5, and PP4.

Met criteria codes

PP4	✔	At least one proband harboring this variant exhibits phenotypes including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 33460243, PP4).
PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.422G>A (p.Arg141His), (PMID: 29851975, PMID: 34645606, PMID: 30450322, PMID: 29739629, PMID: 35984651, PMID: 30652005, PMID: 19093009, PMID: 30630865, PMID: 30040949, PMID: 17525175, PMID: 30630865, PMID: 30040949) 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 (103) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.955, 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 0.02 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.
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.