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.2714-3926G>T

Version: 1.0

CA412370312

Gene: CDKL5 (HGNC:6792)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: c0d3279e-f282-47a1-8944-d6a08cc3c91a
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HGVS expressions

NM_003159.3:c.2714-3926G>T
NC_000023.11:g.18642081G>T
CM000685.2:g.18642081G>T
NC_000023.10:g.18660201G>T
CM000685.1:g.18660201G>T
NC_000023.9:g.18570122G>T
NG_008475.1:g.221477G>T
NG_008659.3:g.40368C>A
ENST00000379984.4:c.598C>A
ENST00000379984.3:c.598C>A
ENST00000379989.6:c.2714-3926G>T
ENST00000379996.7:c.2714-3926G>T
ENST00000476595.1:n.1089C>A
NM_000330.3:c.598C>A
NM_001037343.1:c.2714-3926G>T
NM_003159.2:c.2714-3926G>T
NM_000330.4:c.598C>A
NM_001037343.2:c.2714-3926G>T

Pathogenic

Met criteria codes 7

PM2_Supporting PP1 PP4 PM1 PM5 PS4_Supporting PP3_Moderate

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

The NM_000330.4(RS1):c.598C>A (p.Arg200Ser) variant is a missense variant encoding the substitution of Arginine and Serine at amino acid 200. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.925, 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 0.00 for all predictive splice changes, 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 p.Arg200, of the RS1 gene is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531, PM1). Another missense variant in the same codon, NM_000330.4(RS1):c.599G>A (p.Arg200His), (PMIDs: 30652005, 32300273, 30551202, 22245991, 21701876, 28147405, 10533068, 27114531) 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 (110) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 19324861, PP4). The variant has been reported to segregate with retinal dystrophy through two brothers. (PP1; PMID: 19324861). 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 (PMID: 36377647, 34822951, PS4_Supporting). In summary, this variant is classified as 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, PM1, PM5, PP4, PP1, and PS4_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with retinal dystrophy through two brothers. (PP1; PMID: 19324861).
PP4	✔	At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 19324861, PP4).
PM1	✔	This variant p.Arg200, of the RS1 gene is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531, PM1).
PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.599G>A (p.Arg200His), (PMIDs: 30652005, 32300273, 30551202, 22245991, 21701876, 28147405, 10533068, 27114531) 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 (110) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
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 (PMID: 36377647, 34822951, PS4_Supporting).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.925, 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 0.00 for all predictive splice changes, 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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