

Variant: *NM_003159.3:c.2714-3996C>G*

Version: 1.0

CA412370011 [↗](#)

Gene: CDKL5 ([HGNC:6792](#))

Condition: X-linked retinoschisis ([MONDO:0010725](#))

Inheritance Mode: X-linked inheritance (recessive (HP:0001419))

UUID: 52bebde1-9f03-4961-843d-3bc4fcf8953b

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HGVS expressions

NM_003159.3:c.2714-3996C>G

NC_000023.11:g.18642011C>G

CM000685.2:g.18642011C>G

NC_000023.10:g.18660131C>G

CM000685.1:g.18660131C>G

NC_000023.9:g.18570052C>G

NG_008475.1:g.221407C>G

NG_008659.3:g.40438G>C

ENST00000379984.4:c.668G>C

ENST00000379984.3:c.668G>C

ENST00000379989.6:c.2714-3996C>G

ENST00000379996.7:c.2714-3996C>G

ENST00000476595.1:n.1159G>C

NM_000330.3:c.668G>C

NM_001037343.1:c.2714-3996C>G

NM_003159.2:c.2714-3996C>G

NM_000330.4:c.668G>C

NM_001037343.2:c.2714-3996C>G

Likely Pathogenic

Met criteria codes **4**

PS3_Supporting

PS1_Moderate

PP3_Strong

PM2_Supporting

Not Met criteria codes **2**

PM1

PM5

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

NM_000330.4(RS1):c.668G>C (p.Cys223Ser) is a missense variant encoding the substitution of cystine with serine at amino acid 223. A missense variant encoding the same amino acid substitution, NM_000330.4(RS1):c.667T>A (p.Cys223Ser) has been classified as likely pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PS1_Moderate). 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. However, the present variant has a lower Grantham’s distance(112) than the comparison variant (180), so PM5 cannot be met. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.953, 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 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. HEK293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control, as well as aberrant immunofluorescent localization of RS1 to the ER/Golgi relative to the wild-type control (PMID: 12746437, PS3_Supporting). 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, PS1_Moderate, and PS3_Supporting.

Met criteria codes

PS3_Supporting			HEK293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control, as well as aberrant immunofluorescent localization of RS1 to the ER/Golgi relative to the wild-type control (PMID: 12746437, PS3_Supporting).
			Wu et al. tested the secretion of retinoschisin to the medium. This variant band corresponding to retinoschisin was absent of western blotting. Furthermore, tested disulfide bonds. Any Cys is replaced with a Ser, protein misfolding and aberrant disulfide-mediated aggregation occurs resulting in retention in the ER. PubMed:12746437 
PS1_Moderate			A missense variant encoding the same amino acid substitution, NM_000330.4(RS1):c.667T>A (p.Cys223Ser) has been classified as likely pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PS1_Moderate).
PP3_Strong			The computational predictor REVEL gives a score of 0.953, 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 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.
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM1			This variant p.Cys223Ser, of the RS1 gene, is defined as a critical amino acid residue involved in disulfide bridge formation by the ClinGen X-linked IRD VCEP (PMIDs: 26812435). The PM1_strong code is ineligible to be combined with PP3 at any strength, therefore, the PM1 code was not met.
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. However, the present variant has a

lower Grantham’s distance(112) than the comparison variant (180), so PM5 cannot be met.

Curation History

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Showing 1 to 1 of 1 rows

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