

Variant: NM_000330.4:c.175T>C

Version: 1.0

CA412376061 [↗](#)

Gene: RS1 ([HGNC:6247](#))

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

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

UUID: d8efb972-5f87-4af6-89d7-643484295ab4

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HGVS expressions

NM_000330.4:c.175T>C

NC_000023.11:g.18656662A>G

CM000685.2:g.18656662A>G

NC_000023.10:g.18674782A>G

CM000685.1:g.18674782A>G

NC_000023.9:g.18584703A>G

NG_008659.3:g.25787T>C

ENST00000379984.4:c.175T>C

ENST00000379984.3:c.175T>C

NM_000330.3:c.175T>C

Likely Pathogenic

Met criteria codes **3**

PM1_Strong

PM5

PM2_Supporting

Not Met criteria codes **1**

PP3

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.175T>C (p.Cys59Arg) is a missense variant encoding the substitution of cysteine with arginine at amino acid 59, which is a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435, PM1_Strong). Another missense variant in the same codon, NM_000330.4(RS1):c.175T>A (p.Cys59Ser), (PMIDs: 31174210, 10450864, 17987333, 9618178) 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 (180) than the comparison variant (112), 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 0.833, which is within the ClinGen X-linked IRD VCEP range of 0.931 to 0.773, and predicts a damaging effect on RS1 function. PP3 is not met as this

code is ineligible to be combined with the PM1_Strong code. 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. 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, PM1_Strong, and PM5.

Met criteria codes

PM1_Strong			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, PM1_Strong).
PM5			Another missense variant in the same codon, NM_000330.4(RS1):c.175T>A (p.Cys59Ser), (PMIDs: 31174210, 10450864, 17987333, 9618178) 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 (180) than the comparison variant (112), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.833, which is within the ClinGen X-linked IRD VCEP range of 0.931 to 0.773, and predicts a damaging effect on RS1 function. PP3 is not met as this code is ineligible to be combined with the PM1_Strong code. 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.
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Curation History

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