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Variant: NM_000330.4:c.176G>T

Version: 1.2

CA412376047

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: c69a309c-da66-4aa3-a6b1-296ab4689e1f
Approved on: 2025/10/3
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HGVS expressions

NM_000330.4:c.176G>T
NC_000023.11:g.18656661C>A
CM000685.2:g.18656661C>A
NC_000023.10:g.18674781C>A
CM000685.1:g.18674781C>A
NC_000023.9:g.18584702C>A
NG_008659.3:g.25788G>T
ENST00000379984.4:c.176G>T
ENST00000379984.3:c.176G>T
NM_000330.3:c.176G>T

Likely Pathogenic

Met criteria codes 3

PM2_Supporting | PM5 | PM1_Strong

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.176G>T (p.Cys59Phe) is a missense variant encoding the substitution of cysteine with phenylalanine 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 (205) 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 0.757, which is within the ClinGen X-linked IRD VCEP range between 0.772 to 0.644 and predicts a damaging effect on RS1 function. PP3 is

not met since this code is ineligible in combination with PM1_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. 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

PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
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 RS1-related retinopathy 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 (205) than the comparison variant (112), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
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).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.757, which is within the ClinGen X-linked IRD VCEP range between 0.772 to 0.644 and predicts a damaging effect on RS1 function. 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. The use of PP3 code is ineligible in combination with PM1 code, and therefore, the PP3 code in unmet.

Curation History

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