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Variant: NM_000330.4(RS1):c.176G>A (p.Cys59Tyr)

Version: 1.0

CA412376054

866404 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 9d08e945-b042-4b6b-87ce-24007c50268d
Approved on: 2025/5/19
Published on: 2025/5/20

HGVS expressions

NM_000330.4(RS1):c.176G>A (p.Cys59Tyr)
NM_000330.4:c.176G>A
NC_000023.11:g.18656661C>T
CM000685.2:g.18656661C>T
NC_000023.10:g.18674781C>T
CM000685.1:g.18674781C>T
NC_000023.9:g.18584702C>T
NG_008659.3:g.25788G>A
ENST00000379984.4:c.176G>A
ENST00000379984.3:c.176G>A
NM_000330.3:c.176G>A

Likely Pathogenic

Met criteria codes 5

PS4_Supporting PP4 PM5 PM1_Strong 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

The NM_000330.4(RS1):c.176G>A variant is a missense variant encoding the substitution of Cysteine with Tyrosine at amino acid 59 and results in the disruption of the disulfide bridge between Cys59 and Cys223. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant p.Cys59Tyr, 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, PM1_strong). The computational predictor REVEL gives a score of 0.754, 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 PM1_strong code is ineligible to be combined

with PP3 at any strength, therefore, the PP3 code was not met. 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 likely 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 (195) than the comparison variant (112), 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 a phenotype including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 32300273, PP4). This variant has been reported in at least 2 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMIDs: 39462066, 30025115, 22245991, 35456481, PS4_Supporting). 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, PM5, PS4_supporting, and PP4. (date of approval 01/24/2025).

Met criteria codes

PS4_Supporting	✔	This variant has been reported in at least 2 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with XLRS (PMIDs: 39462066, 30025115, 22245991, 35456481, PS4_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 32300273, PP4).
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 (195) 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 p.Cys59Tyr, 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, PM1_strong).
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 0.754, 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 PM1_strong code is ineligible to be combined with PP3 at any strength, therefore, the PP3 code was not met.

Curation History

Showing 1 to 1 of 1 rows

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