

Variant: *NM_000330.4(RS1):c.175T>A (p.Cys59Ser)*

Version: 1.0

CA226605 [↗](#)

98908 (ClinVar) [↗](#)

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

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

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

UUID: bd5f6e2f-7f82-4dff-bb6c-660e1895fbc4

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HGVS expressions

NM_000330.4(RS1):c.175T>A (p.Cys59Ser)

NM_000330.4:c.175T>A

NC_000023.11:g.18656662A>T

CM000685.2:g.18656662A>T

NC_000023.10:g.18674782A>T

CM000685.1:g.18674782A>T

NC_000023.9:g.18584703A>T

NG_008659.3:g.25787T>A

ENST00000379984.4:c.175T>A

ENST00000379984.3:c.175T>A

NM_000330.3:c.175T>A

Pathogenic

Met criteria codes **4**

PS3

PM1_Strong

PM2_Supporting

PS4_Supporting

Not Met criteria codes **4**

PS1

PP1

PP3

PP4

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>A (p.Cys59Ser) is a missense variant encoding the substitution of cysteine with serine 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). A missense variant encoding the same amino acid substitution, NM_000330.4(RS1):c.176G>C (p.Cys59Ser), (PMIDs: 12746437, 19849666, 23288992, 35456481, 34645606) 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. SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing. The PS1 code was not considered to avoid circularity. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 apparently unrelated probands meeting the

PS4 requirement of a male diagnosed with XLRs (PMIDs: 10450864, 17987333, 9618178, 35982512, PS4_Supporting). Knock-in mice harboring the variant exhibited reduced electroretinogram b-wave amplitudes and developed schisis (PMID: 31174210, PS3). The computational predictor REVEL gives a score of 0.916, which is within the ClinGen X-linked IRD VCEP range between 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 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, PS3, and PS4_Supporting.

Met criteria codes

PS3			Knock-in mice harboring the variant exhibited reduced electroretinogram b-wave amplitudes and developed schisis (PMID: 31174210, PS3).
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).
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting			This variant has been reported in at least 2 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMIDs: 10450864, 17987333, 9618178, 35982512).

Not Met criteria codes

PS1			A missense variant encoding the same amino acid substitution, NM_000330.4(RS1):c.176G>C (p.Cys59Ser), (PMIDs: 12746437,19849666, 23288992, 35456481, 34645606) 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. SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing. The PS1 code was not considered to avoid circularity.
PP1			The variant has been reported to segregate with retinal dystrophy through 1 meiosis in a mother and an affected son. (PMID: 10450864). The PP1 code was ineligible as the carrier mother is unaffected.
PP3			The computational predictor REVEL gives a score of 0.916, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 0.773 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 PS1 and PP3 codes, therefore, the PP3 code was not met.
PP4			Early onset (required), Negative ERG (2 pts), OCT showing schisis (2 pts), Decreased central vision acuity (0.5), and Local retinal detachment (0.5). The proband's age of onset was not published- the PP4 code is ineligible.

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