

Variant: *NM_000330.4(RS1):c.575C>A (p.Pro192His)*

Version: 1.0

CA412370412 [↗](#)

1066639 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: b7d788c2-e3b4-45e1-ab0e-0f6739f0b2ef

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HGVS expressions

NM_000330.4(RS1):c.575C>A (p.Pro192His)

NM_000330.4:c.575C>A

NC_000023.11:g.18642104G>T

CM000685.2:g.18642104G>T

NC_000023.10:g.18660224G>T

CM000685.1:g.18660224G>T

NC_000023.9:g.18570145G>T

NG_008475.1:g.221500G>T

NG_008659.3:g.40345C>A

ENST00000379984.4:c.575C>A

ENST00000379984.3:c.575C>A

ENST00000379989.6:c.2714-3903G>T

ENST00000379996.7:c.2714-3903G>T

ENST00000476595.1:n.1066C>A

NM_000330.3:c.575C>A

NM_001037343.1:c.2714-3903G>T

NM_003159.2:c.2714-3903G>T

NM_001037343.2:c.2714-3903G>T

NM_003159.3:c.2714-3903G>T

Likely Pathogenic

Met criteria codes **5**

PP3_Moderate

PP4

PM5

PM2_Supporting

PS4_Supporting

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.575C>A (p.Pro192His) variant is a missense variant encoding the substitution of Proline and Histidine at amino acid 192. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.914, which is within the ClinGen X-linked IRD VCEP range between 0.931 and 0.773 and predicts a damaging effect on RS1 function (PP3_moderate). 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. Another missense variant in the same codon, NM_000330.4(RS1):c.574C>T (p.Pro192Ser), (PMIDs: 9326935, 10636421, 17987333, 19093009, 28348004, 30551202, 30652005, 34828422, 39293640, 17515881, 20809529) 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 (77) than the comparison variant (74), 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 the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 33460243, 31106028, 34645606, PP4). This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 28559085, 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, PP3_moderate, PM5, PP4, and PS4_Supporting.

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.914, which is within the ClinGen X-linked IRD VCEP range between 0.931 and 0.773 and predicts a damaging effect on RS1 function (PP3_moderate). 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.
PP4			At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 33460243, 31106028, 34645606, PP4).
PM5			Another missense variant in the same codon, NM_000330.4(RS1):c.574C>T (p.Pro192Ser), (PMIDs: 9326935, 10636421, 17987333, 19093009, 28348004, 30551202, 30652005, 34828422, 39293640, 17515881, 20809529) 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 (77) than the comparison variant (74), 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).
PS4_Supporting			This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 28559085, PS4_Supporting).

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