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Variant: NM_000330.4(RS1):c.599G>C (p.Arg200Pro)

Version: 1.0

CA412370309

2009641 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: 40322d2a-5da9-4d03-bca1-d5f29b88c454
Approved on: Sat, 26 Sep 2026 00:00:00 +0000
Published on: Sat, 26 Sep 2026 00:00:00 +0000

HGVS expressions

NM_000330.4(RS1):c.599G>C (p.Arg200Pro)
NM_000330.4:c.599G>C
NC_000023.11:g.18642080C>G
CM000685.2:g.18642080C>G
NC_000023.10:g.18660200C>G
CM000685.1:g.18660200C>G
NC_000023.9:g.18570121C>G
NG_008475.1:g.221476C>G
NG_008659.3:g.40369G>C
ENST00000379984.4:c.599G>C
ENST00000379984.3:c.599G>C
ENST00000379989.6:c.2714-3927C>G
ENST00000379996.7:c.2714-3927C>G
ENST00000476595.1:n.1090G>C
NM_000330.3:c.599G>C
NM_001037343.1:c.2714-3927C>G
NM_003159.2:c.2714-3927C>G
NM_001037343.2:c.2714-3927C>G
NM_003159.3:c.2714-3927C>G

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS4_Supporting PM5 PP3_Strong

Not Met criteria codes 1

PM1

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.599G>C (p.Arg200Pro) variant is a missense variant encoding the substitution of Arginine and Proline at amino acid 200. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.974, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_strong). The computational splicing predictor SpliceAI gives a delta score of 0.01 for acceptor gain, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing. This variant p.Arg200His, of the RS1 gene, is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531). The combination of PP3_strong and PM1 code at any strength is ineligible, and therefore, the PM1 code was not met. Another missense variant in the same codon, NM_000330.4(RS1):c.599G>A (p.Arg200His), (PMIDs: 30652005, 32300273, 30551202, 22245991, 21701876, 28147405, 10533068, 27114531) 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 (103) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant has been reported in at least 2 probands meeting the PS4 requirement of a male diagnosed with XLRS [PMID: 34865595, and Jun Kong, Wei Sun, Tingyu Yan, Xinxin Zhang, Na Yang, Neil Bressler; Identification of Two Potentially Novel Mutations in X-linked Juvenile Retinoschisis. Invest. Ophthalmol. Vis. Sci. 2017;58(8):4511, 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_Strong, PM5, and PS4_Supporting.

Met criteria codes

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 probands meeting the PS4 requirement of a male diagnosed with XLRS [PMID: 34865595, and Jun Kong, Wei Sun, Tingyu Yan, Xinxin Zhang, Na Yang, Neil Bressler; Identification of Two Potentially Novel Mutations in X-linked Juvenile Retinoschisis. Invest. Ophthalmol. Vis. Sci. 2017;58(8):4511, PS4_Supporting].
PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.599G>A (p.Arg200His), (PMIDs: 30652005, 32300273, 30551202, 22245991, 21701876, 28147405, 10533068, 27114531) 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 (103) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.974, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RS1 function (PP3_strong). The computational splicing predictor SpliceAI gives a delta score of 0.01 for acceptor gain, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing.

Not Met criteria codes

PM1	✖	This variant p. Arg200His, of the RS1 gene, is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531). The combination of PP3_strong and PM1 code at any strength is ineligible, and therefore, the PM1 code was not met.

Curation History

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