The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000330.4(RS1):c.575C>G (p.Pro192Arg)

Version: 1.0

CA226789

98991 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: fde3ba46-5090-41fd-8f5b-60320d757492
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:c.575C>G
NM_000330.4(RS1):c.575C>G (p.Pro192Arg)
NC_000023.11:g.18642104G>C
CM000685.2:g.18642104G>C
NC_000023.10:g.18660224G>C
CM000685.1:g.18660224G>C
NC_000023.9:g.18570145G>C
NG_008475.1:g.221500G>C
NG_008659.3:g.40345C>G
ENST00000379984.4:c.575C>G
ENST00000379984.3:c.575C>G
ENST00000379989.6:c.2714-3903G>C
ENST00000379996.7:c.2714-3903G>C
ENST00000476595.1:n.1066C>G
NM_000330.3:c.575C>G
NM_001037343.1:c.2714-3903G>C
NM_003159.2:c.2714-3903G>C
NM_001037343.2:c.2714-3903G>C
NM_003159.3:c.2714-3903G>C

Likely Pathogenic

Met criteria codes 4

PM5 PP3_Strong 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>G (p.Pro192Arg) variant is a missense variant encoding the substitution of Proline and Arginine 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 0.942, 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 0.00 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) and NM_000330.4(RS1):c.575C>T (p.Pro192Leu), (PMIDs: 19093009, 19324861, 28348004, 33124204, 36460718, 32300273) 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 (98 / 74), 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 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with XLRS (PMIDs: 9618178, 37396901, DOI: 10.5772/24453, 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

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) and NM_000330.4(RS1):c.575C>T (p.Pro192Leu), (PMIDs: 19093009, 19324861, 28348004, 33124204, 36460718, 32300273) 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 (98 / 74), 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 0.942, 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 0.00 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.
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 one of the PS4 requirements of a male diagnosed with XLRS (PMIDs: 9618178, 37396901, DOI: 10.5772/24453, PS4_Supporting).

Curation History

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