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.598C>T (p.Arg200Cys)

Version: 1.0

CA226806

99000 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: df55fc50-f712-46f6-aaed-0200871d2a94
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.598C>T (p.Arg200Cys)
NM_000330.4:c.598C>T
NC_000023.11:g.18642081G>A
CM000685.2:g.18642081G>A
NC_000023.10:g.18660201G>A
CM000685.1:g.18660201G>A
NC_000023.9:g.18570122G>A
NG_008475.1:g.221477G>A
NG_008659.3:g.40368C>T
ENST00000379984.4:c.598C>T
ENST00000379984.3:c.598C>T
ENST00000379989.6:c.2714-3926G>A
ENST00000379996.7:c.2714-3926G>A
ENST00000476595.1:n.1089C>T
NM_000330.3:c.598C>T
NM_001037343.1:c.2714-3926G>A
NM_003159.2:c.2714-3926G>A
NM_001037343.2:c.2714-3926G>A
NM_003159.3:c.2714-3926G>A

Pathogenic

Met criteria codes 5

PS4_Very Strong | PP1_Strong | PP3_Strong | PS3_Supporting | PM2_Supporting

Evidence Links 1

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*
- **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.598C>T (p.Arg200Cys) variant is a missense variant encoding the substitution of Arginine and Cystine 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 0.944, 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. COS-7 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 20809529, PS3_Supporting). This variant has been reported in at least ≥9 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with XLRS (PMIDs: 10450864, 10636421, 15937075, 17615541, 17631851, 18541843, 29739629, 35456481, 36377647, PS4_Very strong). The variant has been reported to segregate with retinal dystrophy through >3 meioses in more than two families (PP1_Strong; PMIDs: 17615541, 10636421, 17631851). 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, PP3_Strong, PS3_Supporting, PS4_Very_Strong, and PP1_Strong.

Met criteria codes

PS4_Very Strong	✔	This variant has been reported in at least ≥9 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with XLRS (PMIDs: 10450864, 10636421, 15937075, 17615541, 17631851, 18541843, 29739629, 35456481, 36377647, PS4_Very strong).
PP1_Strong	✔	The variant has been reported to segregate with retinal dystrophy through >3 meioses in more than two families (PP1_Strong; PMIDs: 17615541, 10636421, 17631851).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.944, 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.
PS3_Supporting	✔	COS-7 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 20809529, PS3_Supporting). Vijayasarathy et al. tested mutants in COS-7 cells, which produced intracellularly retained misfolded RS1 protein (Fig. 8A). PubMed:20809529
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Curation History

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