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# *Variant: NM_000330.4(RS1):c.266A>G (p.Tyr89Cys)*

Version: 1.0

*CA226645*

*98923 (ClinVar)*

**Gene**: RS1 (HGNC:6247)
**Condition**: X-linked retinoschisis (MONDO:0010725)
**Inheritance Mode**: X-linked inheritance
**UUID:** 8d3f860c-b043-4444-a3c9-44fc4c51ae11
**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.266A>G**
**NM_000330.4(RS1):c.266A>G (p.Tyr89Cys)**
NC_000023.11:g.18647251T>C
CM000685.2:g.18647251T>C
NC_000023.10:g.18665371T>C
CM000685.1:g.18665371T>C
NC_000023.9:g.18575292T>C
NG_008475.1:g.226647T>C
NG_008659.3:g.35198A>G
ENST00000379984.4:c.266A>G
ENST00000379984.3:c.266A>G
ENST00000379989.6:c.2797+1161T>C
ENST00000379996.7:c.2797+1161T>C
ENST00000476595.1:n.757A>G
NM_000330.3:c.266A>G
NM_001037343.1:c.2797+1161T>C
NM_003159.2:c.2797+1161T>C
NM_001037343.2:c.2797+1161T>C
NM_003159.3:c.2797+1161T>C

**Pathogenic**

**Met criteria codes** 6

PP1_Strong PP4_Moderate PP3_Moderate PS3_Supporting PM2_Supporting PS4_Moderate

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 1.0.0*
**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.266A>G (p.Tyr89Cys) variant is a missense variant encoding the substitution of Tyrosine and Cystine at amino acid 89. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.912, 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 0.01 for donor loss and 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. COS-7 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 16361673, PS3_Supporting). At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years and showing retinal detachment, which together are specific for X-linked retinoschisis (PMID: 17987333, PP4_Moderate). This variant has been reported in at least 3 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with XLRS (PMIDs: 10220153, 11035549, 30652005, 19324861, 30551202, PS4_Moderate). The variant has been reported to segregate with retinal dystrophy through >3 meioses in two families (PP1_Strong; PMID: 17987333, 19324861). 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_moderate, PS3_Supporting, PP4_Moderate, PS4_Moderate, and PP1_Strong.**

**Met criteria codes**

| | | |
|---|---|---|
| **PP1_Strong** | ✔ | The variant has been reported to segregate with retinal dystrophy through >3 meioses in two families (PP1_Strong; PMID: 17987333, 19324861). |
| **PP4_Moderate** | ✔ | At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years and showing retinal detachment, which together are specific for X-linked retinoschisis (PMID: 17987333, PP4_Moderate). |
| **PP3_Moderate** | ✔ | The computational predictor REVEL gives a score of 0.912, 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 0.01 for donor loss and 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. |
| **PS3_Supporting** | ✔ | COS-7 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 16361673, PS3_Supporting).<br><br>Wang et al. performed WB analysis on the expression of RS1 in WT and mutations tested from whole cell lysates or the cell culture medium. PubMed:16361673 |
| **PM2_Supporting** | ✔ | This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). |
| **PS4_Moderate** | ✔ | This variant has been reported in at least 3 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with XLRS (PMIDs: 10220153, 11035549, 30652005, 19324861, 30551202, PS4_Moderate). |

Curation History

Showing 1 to 1 of 1 rows

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