

Variant: *NM\_000330.4(RS1):c.214G>A (p.Glu72Lys)*

Version: 1.0

CA226621 [↗](#)

9888 (ClinVar) [↗](#)

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

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

**Inheritance Mode:** X-linked inheritance (recessive (HP:0001419))

**UUID:** 95356f66-b18e-41aa-8a7a-37d6d3af7f5c

**Approved on:** 2025/5/19

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### *HGVS expressions*

**NM\_000330.4(RS1):c.214G>A (p.Glu72Lys)**

**NM\_000330.4:c.214G>A**

NC\_000023.11:g.18647303C>T

CM000685.2:g.18647303C>T

NC\_000023.10:g.18665423C>T

CM000685.1:g.18665423C>T

NC\_000023.9:g.18575344C>T

NG\_008475.1:g.226699C>T

NG\_008659.3:g.35146G>A

ENST00000379984.4:c.214G>A

ENST00000379984.3:c.214G>A

ENST00000379989.6:c.2797+1213C>T

ENST00000379996.7:c.2797+1213C>T

ENST00000476595.1:n.705G>A

NM\_000330.3:c.214G>A

NM\_001037343.1:c.2797+1213C>T

NM\_003159.2:c.2797+1213C>T

NM\_001037343.2:c.2797+1213C>T

NM\_003159.3:c.2797+1213C>T

**Pathogenic**

**Met criteria codes** 6

PP1\_Strong

PS4

PP4

PM1

PP3\_Moderate

PS3\_Supporting

**Not Met criteria codes** 2

PM2

BS1

**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.214G>A variant is a missense variant encoding the substitution of Glutamic acid with Lysine at amino acid 72. This variant is present in gnomAD v.4.1.0 at a frequency of 0.000002508 among hemizygous individuals, with 1 variant alleles / 398646 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2\_Supporting and BS1 thresholds of <0.000002 and >0.00002 and fails to meet these criteria. The computational predictor REVEL gives a score of 0.921, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 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. HEK293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 12746437, PS3\_Supporting). This variant p.Glu72Lys, of the RS1 gene, is an established residue involved in cross-linking the adjacent RS1 subunit by the ClinGen X-linked IRD VCEP (PMID: 27114531, PM1). The variant has been reported to segregate with retinal dystrophy through at least 3 meioses in the same family (PP1\_Strong; PMID: 11246454, 38317323, 19324861). At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 23288992, PP4). This variant has been reported in at least 6 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMIDs: 30025115, 28348004, 19324861, 22245991, 32531858, 29851975, PS4). 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: PP3\_moderate, PP1\_strong, PP4, PS4, PS3\_supporting, and PM1 (date of approval 01/24/2025).

Met criteria codes

|                |                                                                                     |                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|----------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PP1_Strong     |    |    | The variant has been reported to segregate with retinal dystrophy through at least 3 meioses in the same family (PP1_Strong; PMID: 11246454, 38317323, 19324861).                                                                                                                                                                                                                                                                            |
| PS4            |  |  | This variant has been reported in at least 6 apparently unrelated probands meeting one of the PS4 requirements of a male diagnosed with XLR5 (PMIDs: 30025115, 28348004, 19324861, 22245991, 32531858, 29851975, PS4).                                                                                                                                                                                                                       |
| PP4            |  |  | At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 23288992, PP4).                                                                                                                                                                                                                |
| PM1            |  |  | This variant p.Glu72Lys, of the RS1 gene, is an established residue involved in cross-linking the adjacent RS1 subunit by the ClinGen X-linked IRD VCEP (PMID: 27114531, PM1_moderate).                                                                                                                                                                                                                                                      |
| PP3_Moderate   |  |  | The computational predictor REVEL gives a score of 0.921, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 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. |
| PS3_Supporting |  |  | 293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 12746437, PS3_Supporting).                                                                                                                                                                                                                                                                               |
|                |                                                                                     |                                                                                     | Wu et al. tested mutated Human RS1 cDNA which was subcloned into the pCEP4 vector (WT or mutant) and tested the secretion of Retinoschisin in 293 cells. <a href="#">PubMed:12746437</a>                                                                                                                                                                |

Not Met criteria codes

|            |                                                                                   |                                                                                   |                                                                                                                                                                                                                                                                                                          |
|------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>PM2</b> |     |     | This variant is present in gnomAD v.4.1.0 at a frequency of 0.000002508 among hemizygous individuals, with 1 variant alleles / 398646 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2_Supporting and BS1 threshold of 0.000002 to 0.00002 and fails to meet these criteria. |
| <b>BS1</b> |  |  | This variant is present in gnomAD v.4.1.0 at a frequency of 0.000002508 among hemizygous individuals, with 1 variant alleles / 398646 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2_Supporting and BS1 threshold of 0.000002 to 0.00002 and fails to meet these criteria. |

| Curation History  |  |  |                                                |
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