

Variant: *NM_000330.4(RS1):c.215A>G (p.Glu72Gly)*

Version: 1.0

CA412372956 [↗](#)

992968 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: ec1ee0b5-285e-432f-afe4-97dcf35c631b

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HGVS expressions

NM_000330.4:c.215A>G

NM_000330.4(RS1):c.215A>G (p.Glu72Gly)

NC_000023.11:g.18647302T>C

CM000685.2:g.18647302T>C

NC_000023.10:g.18665422T>C

CM000685.1:g.18665422T>C

NC_000023.9:g.18575343T>C

NG_008475.1:g.226698T>C

NG_008659.3:g.35147A>G

ENST00000379984.4:c.215A>G

ENST00000379984.3:c.215A>G

ENST00000379989.6:c.2797+1212T>C

ENST00000379996.7:c.2797+1212T>C

ENST00000476595.1:n.706A>G

NM_000330.3:c.215A>G

NM_001037343.1:c.2797+1212T>C

NM_003159.2:c.2797+1212T>C

NM_001037343.2:c.2797+1212T>C

NM_003159.3:c.2797+1212T>C

Likely Pathogenic

Met criteria codes 4

PP4

PM5

PP3_Strong

PM2_Supporting

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.215A>G (p.Glu72Gly) variant is a missense variant encoding the substitution of Glutamic acid and Glycine at amino acid 72. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.971, 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 0.05 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. The p.Plu72Gly variant in the NDP gene is a missense substitution that alters a critical cysteine residue involved in disulfide bond formation, as established by the ClinGen X-linked IRD VCEP (PMID: 27114531). While this functional importance supports consideration of PM1, the concurrent application of PP3 at the strong level renders PM1 inapplicable per ACMG/AMP guidelines. As a result, the PM1 criterion is considered unmet for this variant. Another two missense variants in the same codon, NM_000330.4(RS1):c.214G>C (p.Glu72Gln), (PMIDs: 19390641, 11295123, 28348004, 36460718, 39462066, 35456481) and NM_000330.4(RS1):c.214G>A (p.Glu72Lys) (PMIDs: 23288992, 11246454, 30025115, 28348004, 19324861, 22245991, 32531858, 29851975, 12746437) have 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 (98) than the comparison variants (29, 56), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 17631851, PP4). 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 PP4.

Met criteria codes

PP4			At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 17631851, PP4).
PM5			Another two missense variants in the same codon, NM_000330.4(RS1):c.214G>C (p.Glu72Gln), (PMIDs: 19390641, 11295123, 28348004, 36460718, 39462066, 35456481) and NM_000330.4(RS1):c.214G>A (p.Glu72Lys) (PMIDs: 23288992, 11246454, 30025115, 28348004, 19324861, 22245991, 32531858, 29851975, 12746437) have 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 (98) than the comparison variants (29, 56), 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 0.971, 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 0.05 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.
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM1			The p.Plu72Gly variant in the NDP gene is a missense substitution that alters a critical cysteine residue involved in disulfide bond formation, as established by the ClinGen X-linked IRD VCEP (PMID: 27114531). While this functional importance supports consideration of PM1, the concurrent application of PP3 at the strong level renders PM1 inapplicable per ACMG/AMP guidelines. As a result, the PM1 criterion is considered unmet for this variant.
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Curation History 

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