

Variant: *NM_000330.4(RS1):c.215A>T (p.Glu72Val)*

Version: 1.0

CA412372957 [↗](#)

1994509 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 633ea9bb-44ad-48e3-83f9-bc84456afb0b

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HGVS expressions

NM_000330.4:c.215A>T

NM_000330.4(RS1):c.215A>T (p.Glu72Val)

NC_000023.11:g.18647302T>A

CM000685.2:g.18647302T>A

NC_000023.10:g.18665422T>A

CM000685.1:g.18665422T>A

NC_000023.9:g.18575343T>A

NG_008475.1:g.226698T>A

NG_008659.3:g.35147A>T

ENST00000379984.4:c.215A>T

ENST00000379984.3:c.215A>T

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

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

ENST00000476595.1:n.706A>T

NM_000330.3:c.215A>T

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

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

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

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

Likely Pathogenic

Met criteria codes **3**

PM2_Supporting

PP3_Strong

PM5

Not Met criteria codes **2**

PS4

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>T (p.Glu72Val) variant is a missense variant encoding the substitution of glutamic acid and Valine 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 0.967, 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 0.12 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. 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 (121) than the comparison variants (29, 56), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). The p.Plu72Val 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. This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with XLRS (PMID: 34645606). PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met. 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, and PM5.

Met criteria codes

PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP3_Strong			The computational predictor REVEL gives a score of 0.967, 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 0.12 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.
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 (121) than the comparison variants (29, 56), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).

Not Met criteria codes

PS4			This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with XLRS (PMID: 34645606). PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met.
PM1			The p.Plu72Val 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.

Curation History 		
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