

Variant: *NM_000330.4(RS1):c.216G>C (p.Glu72Asp)*

Version: 1.0

CA226626 [↗](#)

9889 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: 8dd33067-4bd6-4c1c-a743-a7aa4f44f82c

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.216G>C

NM_000330.4(RS1):c.216G>C (p.Glu72Asp)

NC_000023.11:g.18647301C>G

CM000685.2:g.18647301C>G

NC_000023.10:g.18665421C>G

CM000685.1:g.18665421C>G

NC_000023.9:g.18575342C>G

NG_008475.1:g.226697C>G

NG_008659.3:g.35148G>C

ENST00000379984.4:c.216G>C

ENST00000379984.3:c.216G>C

ENST00000379989.6:c.2797+1211C>G

ENST00000379996.7:c.2797+1211C>G

ENST00000476595.1:n.707G>C

NM_000330.3:c.216G>C

NM_001037343.1:c.2797+1211C>G

NM_003159.2:c.2797+1211C>G

NM_001037343.2:c.2797+1211C>G

NM_003159.3:c.2797+1211C>G

Likely Pathogenic

Met criteria codes **5**

PP3_Moderate

PM1

PM5

PS4_Moderate

PM2_Supporting

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.216G>C (p.Glu72Asp) variant is a missense variant encoding the substitution of Glutamic acid and Aspartic acid 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 0.930, 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 0.03 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 missense variant in the same codon, NM_000330.4(RS1):c.214G>C (p.Glu72Gln), (PMIDs: 19390641, 11295123, 28348004, 36460718, 39462066, 35456481) 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 (45) than the comparison variants (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant p.Glu72, of the RS1 gene, is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531, PM1). 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: 9618178, 34822951, 35456481, 38219857, PS4_Moderate). 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_Moderate, PM5, PM1, and PS4_Moderate.

Met criteria codes

PP3_Moderate			The computational predictor REVEL gives a score of 0.930, 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 0.03 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.
PM1			This variant p.Glu72, of the RS1 gene, is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531, PM1).
PM5			Another missense variant in the same codon, NM_000330.4(RS1):c.214G>C (p.Glu72Gln), (PMIDs: 19390641, 11295123, 28348004, 36460718, 39462066, 35456481) 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 (45) than the comparison variants (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
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: 9618178, 34822951, 35456481, 38219857, PS4_Moderate).
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Curation History 

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