

Variant: *NM_000330.4(RS1):c.329G>A (p.Cys110Tyr)*

Version: 1.0

CA226686 [↗](#)

98938 (ClinVar) [↗](#)

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

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

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

UUID: 95d362eb-2280-44c3-8b0b-f52ee6ad4708

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HGVS expressions

NM_000330.4:c.329G>A

NM_000330.4(RS1):c.329G>A (p.Cys110Tyr)

NC_000023.11:g.18644623C>T

CM000685.2:g.18644623C>T

NC_000023.10:g.18662743C>T

CM000685.1:g.18662743C>T

NC_000023.9:g.18572664C>T

NG_008475.1:g.224019C>T

NG_008659.3:g.37826G>A

ENST00000379984.4:c.329G>A

ENST00000379984.3:c.329G>A

ENST00000379989.6:c.2714-1384C>T

ENST00000379996.7:c.2714-1384C>T

ENST00000476595.1:n.820G>A

NM_000330.3:c.329G>A

NM_001037343.1:c.2714-1384C>T

NM_003159.2:c.2714-1384C>T

NM_001037343.2:c.2714-1384C>T

NM_003159.3:c.2714-1384C>T

Pathogenic

Met criteria codes 5

PM1_Strong

PS3_Supporting

PP1

PS4

PM2_Supporting

Not Met criteria codes 1

PP3

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

NM_000330.4(RS1):c.329G>A (p.Cys110Tyr) is a missense encoding the substitution of cysteine with tyrosine at amino acid 110, which is a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435, PM1_Strong). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 6 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 9618178, PMID: 28348004, PMID: 34822951, PMID: 38219857, PMID: 30551202, PMID: 31456290, PMID: 35456422, PMID: 34645606, PS4). The variant has been reported to segregate with X-linked retinoschisis through two affected brothers from a single family (PP1; PMID: 32856788, PMID: 35456422). The computational predictor REVEL gives a score of 0.882, 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 is not met as the code is ineligible to be used in combination with PM1_Strong. The computational splicing predictor SpliceAI gives a delta score of <0.02 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 due to intracellular retention and failure of the variant protein to properly assemble into multimers (PMID: 19849666, PS3_Supporting). 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, PM1_Strong, PS3_Supporting, PS4, and PP1.

Met criteria codes

PM1_Strong			This variant is a missense substitution affecting a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435, PM1_Strong).
PS3_Supporting			HEK293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control due to intracellular retention and failure of the variant protein to properly assemble into multimers (PMID: 19849666, PS3_Supporting).
PP1			The variant has been reported to segregate with X-linked retinoschisis through two affected brothers from a single family (PP1; PMID: 32856788, PMID: 35456422)
PS4			This variant has been reported in at least 6 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 9618178, PMID: 28348004, PMID: 34822951, PMID: 38219857, PMID: 30551202, PMID: 31456290, PMID: 35456422, PMID: 34645606, PS4).
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PP3			The computational predictor REVEL gives a score of 0.882, 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 is not met as the code is ineligible to be used in combination with PM1_Strong. The computational splicing predictor SpliceAI gives a delta score of <0.02 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.
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