

Variant: *NM_000330.4(RS1):c.668G>A (p.Cys223Tyr)*

Version: 1.0

CA16043215 [↗](#)

372497 (ClinVar) [↗](#)

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

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

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

UUID: 2fc8a933-df28-4891-b13a-994884d9f3aa

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HGVS expressions

NM_000330.4(RS1):c.668G>A (p.Cys223Tyr)

NM_000330.4:c.668G>A

NC_000023.11:g.18642011C>T

CM000685.2:g.18642011C>T

NC_000023.10:g.18660131C>T

CM000685.1:g.18660131C>T

NC_000023.9:g.18570052C>T

NG_008475.1:g.221407C>T

NG_008659.3:g.40438G>A

ENST00000379984.4:c.668G>A

ENST00000379984.3:c.668G>A

ENST00000379989.6:c.2714-3996C>T

ENST00000379996.7:c.2714-3996C>T

ENST00000476595.1:n.1159G>A

NM_000330.3:c.668G>A

NM_001037343.1:c.2714-3996C>T

NM_003159.2:c.2714-3996C>T

NM_001037343.2:c.2714-3996C>T

NM_003159.3:c.2714-3996C>T

Pathogenic

Met criteria codes 5

PS4_Moderate

PP4

PM5

PP3_Strong

PM2_Supporting

Not Met criteria codes 2

PP1

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.668G>A variant is a missense variant encoding the substitution of Cysteine with Tyrosine at position 223. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.966, 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 0.01 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 variant has been reported to segregate with retinal dystrophy through 1 meiosis in a family consisting of a mother and an affected son, however, the mother was apparently unaffected so PP1 was not met (PMID: 38317323). At least one proband harboring this variant exhibits a phenotype including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 22245991, PP4). This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMIDs: 20061330, 38317323, 39293640, PS4_moderate). This variant p.Cys223Tyr disrupts a site defined as a critical amino acid residue involved in disulfide bridge formation by the ClinGen X-linked IRD VCEP (PMIDs: 26812435). The PM1_strong code is ineligible to be used in combination with the PP3 code, and therefore, this code was not met. Another missense variant in the same codon, NM_000330.4(RS1):c.667T>C (p.Cys223Arg), (PMIDs: 34645606, 10533068, 30652005, 33460243, 16361673) has 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 (194) than the comparison variant (180), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). 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: PM2_supporting, PP3_strong, PP4, PM5, and PS4_moderate (date of approval 01/24/2025).

Met criteria codes

PS4_Moderate			This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with XLRS (PMIDs: 20061330, 38317323, 39293640, PS4_moderate).
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: 22245991, PP4).
PM5			Another missense variant in the same codon, NM_000330.4(RS1):c.667T>C (p.Cys223Arg), (PMIDs: 34645606, 10533068, 30652005, 33460243, 16361673) has 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 (194) than the comparison variant (180), 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 0.966, 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 0.01 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

PP1			The variant has been reported to segregate with retinal dystrophy through 1 meiosis in a family consisting of a mother and an affected son, however, the mother was apparently unaffected so PP1 was not met (PMID: 38317323).
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PM1

This variant p.Cys223Tyr, of the RS1 gene, is defined as a critical amino acid residue involved in disulfide bridge formation by the ClinGen X-linked IRD VCEP (PMIDs: 26812435). The PM1_strong code is ineligible to be used in combination with the PP3 code, and therefore, the PM1 code was not met.

Curation History

Showing 1 to 1 of 1 rows

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