

Variant: *NM_000330.4(RS1):c.421C>T (p.Arg141Cys)*

Version: 1.0

CA226728 [↗](#)

98959 (ClinVar) [↗](#)

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

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

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

UUID: 97c4b02e-c195-4cc8-83b2-1099d970ca25

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HGVS expressions

NM_000330.4:c.421C>T

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NC_000023.11:g.18644531G>A

CM000685.2:g.18644531G>A

NC_000023.10:g.18662651G>A

CM000685.1:g.18662651G>A

NC_000023.9:g.18572572G>A

NG_008475.1:g.223927G>A

NG_008659.3:g.37918C>T

ENST00000379984.4:c.421C>T

ENST00000379984.3:c.421C>T

ENST00000379989.6:c.2714-1476G>A

ENST00000379996.7:c.2714-1476G>A

ENST00000476595.1:n.912C>T

NM_000330.3:c.421C>T

NM_001037343.1:c.2714-1476G>A

NM_003159.2:c.2714-1476G>A

NM_001037343.2:c.2714-1476G>A

NM_003159.3:c.2714-1476G>A

Pathogenic

Met criteria codes **6**

PP1_Strong

PS3

PS4

PP4

PP3_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

NM_000330.4(RS1):c.421C>T (p.Arg141Cys) is a missense variant encoding the substitution of arginine with cysteine at amino acid 141. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 5 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMID: 34828422, PMID: 34822951, PMID: 33124204, PMID: 30025115, PMID: 39435478, PS4). 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: 19093009, PP4). The variant has been reported to segregate with X-linked retinoschisis through at least 3 meioses in two families (PP1_Strong; PMID: 19093009). Additional publications report on other families diagnosed with retinitis pigmentosa, however, the genotyped family members were limited to an unaffected mother and the proband, which were not included in the PP1 criterion (PMID: 34828422, PMID: 33124204). The computational predictor REVEL gives a score of 0.817, 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). The computational splicing predictor SpliceAI gives a delta score of 0.01 for donor gain and 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. Knock-in mice harboring the variant exhibited reduced electroretinogram b-wave amplitudes and developed schisis (PMID: 31174210, PS3). 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_Moderate, PS3, PS4, PP4, and PP1_Strong.

Met criteria codes

PP1_Strong			The variant has been reported to segregate with X-linked retinoschisis through at least 3 meioses in two families (PP1_Strong; PMID: 19093009). Additional publications report on other families diagnosed with retinitis pigmentosa, however, the genotyped family members were limited to an unaffected mother and the proband, which were not included in the PP1 criterion (PMID: 34828422, PMID: 33124204).
PS3			Knock-in mice harboring the variant exhibited reduced electroretinogram b-wave amplitudes and developed schisis (PMID: 31174210, PS3).
PS4			This variant has been reported in at least 5 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMID: 34828422, PMID: 34822951, PMID: 33124204, PMID: 30025115, PMID: 39435478, PS4).
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: 19093009, PP4).
PP3_Moderate			The computational predictor REVEL gives a score of 0.817, 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). The computational splicing predictor SpliceAI gives a delta score of 0.01 for donor gain and 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).

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