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Variant: NM_000330.4(RS1):c.589C>T (p.Arg197Cys)

Version: 1.0

CA226797

98996 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: ac46f5b2-2bbb-4ff0-abc9-cd954fcff377
Approved on: 2025/5/19
Published on: 2025/5/20

HGVS expressions

NM_000330.4:c.589C>T
NM_000330.4(RS1):c.589C>T (p.Arg197Cys)
NC_000023.11:g.18642090G>A
CM000685.2:g.18642090G>A
NC_000023.10:g.18660210G>A
CM000685.1:g.18660210G>A
NC_000023.9:g.18570131G>A
NG_008475.1:g.221486G>A
NG_008659.3:g.40359C>T
ENST00000379984.4:c.589C>T
ENST00000379984.3:c.589C>T
ENST00000379989.6:c.2714-3917G>A
ENST00000379996.7:c.2714-3917G>A
ENST00000476595.1:n.1080C>T
NM_000330.3:c.589C>T
NM_001037343.1:c.2714-3917G>A
NM_003159.2:c.2714-3917G>A
NM_001037343.2:c.2714-3917G>A
NM_003159.3:c.2714-3917G>A

Pathogenic

Met criteria codes 5

PP4_Moderate PP1 PP3_Strong PM2_Supporting PS4_Moderate

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.589C>T variant is a missense variant encoding the substitution of Arginine with Cystine at amino acid 197. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.99, 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 0.00 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. The variant has been reported to segregate with retinal dystrophy through at least 1 meiosis in two unrelated families, each consisting of 2 brothers (PP1; PMID: 29739629, 36377647). Only one family can be counted. At least one 4-year-old proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years and showing detachment, and showing retinal detachment, which together are highly specific for X-linked retinoschisis (PP4_Moderate). This variant has been reported in at least 4 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMIDs: 34645606, 29739629, 30652005, 34624300, PS4_Moderate). 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, PP1, PP4_moderate, and PS4_moderate (date of approval 01/24/2025).

Met criteria codes

PP4_Moderate	✔	At least one 4-year-old proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years and showing detachment, which together are highly specific for X-linked retinoschisis (PP4_Moderate).
PP1	✔	The variant has been reported to segregate with retinal dystrophy through at least 1 meiosis in two unrelated families- 2 brothers (PP1; PMID: 29739629, 36377647). Only one family can be counted.
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.99, 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 0.00 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.
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PS4_Moderate	✔	This variant has been reported in at least 4 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with XLRS (PMIDs: 34645606, 29739629, 30652005, 34624300, PS4_Moderate)

Curation History

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