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Variant: NM_000330.4(RS1):c.647T>C (p.Leu216Pro)

Version: 1.0

CA226839

99014 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 95ede946-539b-4195-b33e-6ef5ec5cebf1
Approved on: 2025/5/19
Published on: 2025/5/20

HGVS expressions

NM_000330.4(RS1):c.647T>C (p.Leu216Pro)
NM_000330.4:c.647T>C
NC_000023.11:g.18642032A>G
CM000685.2:g.18642032A>G
NC_000023.10:g.18660152A>G
CM000685.1:g.18660152A>G
NC_000023.9:g.18570073A>G
NG_008475.1:g.221428A>G
NG_008659.3:g.40417T>C
ENST00000379984.4:c.647T>C
ENST00000379984.3:c.647T>C
ENST00000379989.6:c.2714-3975A>G
ENST00000379996.7:c.2714-3975A>G
ENST00000476595.1:n.1138T>C
NM_000330.3:c.647T>C
NM_001037343.1:c.2714-3975A>G
NM_003159.2:c.2714-3975A>G
NM_001037343.2:c.2714-3975A>G
NM_003159.3:c.2714-3975A>G

Likely Pathogenic

Met criteria codes 4

PM2_Supporting PS4_Moderate PP3_Strong PP4

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.647T>C variant is a missense variant encoding the substitution of Leucine with Proline at amino acid 216. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.969, 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. 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: 33460243, PP4). This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMIDs: 19324861, 19390641, 34822951, 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_strong, PP4, and PS4_moderate (date of approval 01/24/2025).

Met criteria codes

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 3 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with XLRS (PMIDs: 19324861, 19390641, 34822951, PS4_Moderate)
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.969, 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.
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: 33460243, PP4).

Curation History

Showing 1 to 1 of 1 rows

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