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Variant: NM_000330.4(RS1):c.643G>C (p.Glu215Gln)

Version: 1.0

CA226837

99013 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: e947e4b4-4ce3-4cf2-bf52-966468f9b183
Approved on: Sat, 26 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000330.4(RS1):c.643G>C (p.Glu215Gln)
NM_000330.4:c.643G>C
NC_000023.11:g.18642036C>G
CM000685.2:g.18642036C>G
NC_000023.10:g.18660156C>G
CM000685.1:g.18660156C>G
NC_000023.9:g.18570077C>G
NG_008475.1:g.221432C>G
NG_008659.3:g.40413G>C
ENST00000379984.4:c.643G>C
ENST00000379984.3:c.643G>C
ENST00000379989.6:c.2714-3971C>G
ENST00000379996.7:c.2714-3971C>G
ENST00000476595.1:n.1134G>C
NM_000330.3:c.643G>C
NM_001037343.1:c.2714-3971C>G
NM_003159.2:c.2714-3971C>G
NM_001037343.2:c.2714-3971C>G
NM_003159.3:c.2714-3971C>G

Pathogenic

Met criteria codes 6

PS3_Supporting PP3_Strong PP4 PP1_Strong PS4_Supporting 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

The NM_000330.4(RS1):c.643G>C (p.Glu215Gln) variant is a missense variant encoding the substitution of Glutamic acid and Glutamine at amino acid 215. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.965, 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. Transient Expression in 293 Cells harboring the variant exhibit loss of RS1, showed markedly reduced Tyrosine phosphorylation compared with the wild type, and showed reduced kinase activation but increased collagen binding (PMID: 11598108, PS3_Supporting). At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 19324861, 9618178, PP4). This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 39462066, PS4_Supporting). The variant has been reported to segregate with retinal dystrophy through >3 meioses in one family (PP1_Strong; PMID: 19324861). 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, PS3_Supporting, PP4, PS4_Supporting, and PP1_Strong.

Met criteria codes

PS3_Supporting	✔	Transient Expression in 293 Cells harboring the variant exhibit loss of RS1, showed markedly reduced Tyrosine phosphorylation compared with the wild type, and showed reduced kinase activation but increased collagen binding (PMID: 11598108, PS3_Supporting).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.965, 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 the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 19324861, 9618178, PP4).
PP1_Strong	✔	The variant has been reported to segregate with retinal dystrophy through >3 meioses in one family (PP1_Strong; PMID: 19324861).
PS4_Supporting	✔	This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 39462066, PS4_Supporting).
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Curation History

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