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Variant: NM_000330.4(RS1):c.644A>T (p.Glu215Val)

Version: 1.0

CA412370114

1359440 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 01180726-a2b6-4c50-b1ac-045994463498
Approved on: Sat, 26 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000330.4:c.644A>T
NM_000330.4(RS1):c.644A>T (p.Glu215Val)
NC_000023.11:g.18642035T>A
CM000685.2:g.18642035T>A
NC_000023.10:g.18660155T>A
CM000685.1:g.18660155T>A
NC_000023.9:g.18570076T>A
NG_008475.1:g.221431T>A
NG_008659.3:g.40414A>T
ENST00000379984.4:c.644A>T
ENST00000379984.3:c.644A>T
ENST00000379989.6:c.2714-3972T>A
ENST00000379996.7:c.2714-3972T>A
ENST00000476595.1:n.1135A>T
NM_000330.3:c.644A>T
NM_001037343.1:c.2714-3972T>A
NM_003159.2:c.2714-3972T>A
NM_001037343.2:c.2714-3972T>A
NM_003159.3:c.2714-3972T>A

Pathogenic

Met criteria codes 5

PP4 PM5 PP3_Strong PM2_Supporting PS4_Moderate

Not Met criteria codes 1

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*
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.644A>T (p.Glu215Val) variant is a missense variant encoding the substitution of Glutamate with Valine 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 0.988, 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. Another missense variant in the same codon, NM_000330.4(RS1):c.643G>C (p.Glu215Gln), (PMIDs: 19324861, 11598108, 9618178, 39462066) 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 (121) than the comparison variant (29), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant p.Glu215Val, of the RS1 gene, is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531). The PP3_strong code is ineligible to be used in combination with the PM1 code at any strength, and therefore, this code was not met. At least one proband harboring this variant exhibits a phenotype of the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 19324861, PP4). This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with XLRS (PS4_Moderate, PMIDs: 19324861, 17852193, Department of Genetics, Fundacion Jimenez Diaz, Madrid, Spain). Another missense variant in the same codon, NM_000330.4(RS1):c.643G>A (p.Glu215Lys), (PMIDs: 10450864, 33460243, 27114531) has been classified as likely pathogenic for X-linked retinoschisis by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. 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, PM5, PP4, and PS4_ Moderate.

Met criteria codes

PP4	✔	At least one proband harboring this variant exhibits a phenotype of the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 19324861, PP4).
PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.643G>C (p.Glu215Gln), (PMIDs: 19324861, 11598108, 9618178, 39462066) 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 (121) than the comparison variant (29), 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 [0.988], 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 [0.04] for [Splice loss] and [0.01] for [Splice 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).
PS4_Moderate	✔	This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with XLRS (PS4_moderate, PMIDs: 19324861, 17852193, Department of Genetics, Fundacion Jimenez Diaz, Madrid, Spain).

Not Met criteria codes

PM1	✖	This variant p. Glu215, of the RS1 gene, is a missense substitution affecting an established residue involved in cross-linking the adjacent RS1 subunit defined by the ClinGen X-linked IRD VCEP (PMID: 27114531). The PP3_strong code

is ineligible to be used in combination with the PM1 code at any strength, and therefore, this code was not met.

Curation History

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