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Variant: NM_000330.4(RS1):c.655T>C (p.Cys219Arg)

Version: 1.0

CA226841

99015 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: f559e124-d1f2-4d0e-b199-d15282691f6e
Approved on: 2025/10/4
Published on: 2025/10/5

HGVS expressions

NM_000330.4(RS1):c.655T>C (p.Cys219Arg)
NM_000330.4:c.655T>C
NC_000023.11:g.18642024A>G
CM000685.2:g.18642024A>G
NC_000023.10:g.18660144A>G
CM000685.1:g.18660144A>G
NC_000023.9:g.18570065A>G
NG_008475.1:g.221420A>G
NG_008659.3:g.40425T>C
ENST00000379984.4:c.655T>C
ENST00000379984.3:c.655T>C
ENST00000379989.6:c.2714-3983A>G
ENST00000379996.7:c.2714-3983A>G
ENST00000476595.1:n.1146T>C
NM_000330.3:c.655T>C
NM_001037343.1:c.2714-3983A>G
NM_003159.2:c.2714-3983A>G
NM_001037343.2:c.2714-3983A>G
NM_003159.3:c.2714-3983A>G

Likely Pathogenic

Met criteria codes 6

PS3_Supporting PP3_Strong PP1 PM5_Supporting PS4_Supporting PM2_Supporting

Not Met criteria codes 3

PM6 PM1 PS2

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.655T>C (p.Cys219Arg) is a missense variant encoding the substitution of cysteine with arginine at amino acid 219. Another missense variant in the same codon, NM_000330.4(RS1):c.655T>G (p.Cys219Gly) 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. The present variant has a higher Grantham's distance (180) than the comparison variant (159), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5_Supporting). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 39462066, PMID: 35982512, PMID: 9618178, PS4_Supporting). The variant has been reported to segregate with X-linked retinoschisis through 2 affected family members (PP1; PMID: 39462066). This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual meeting the PS2 phenotype requirement of a male diagnosed with retinoschisis (PMID: 9618178). No description was provided of parental genotyping, so PS2 was not met. COS-1 cells exogenously expressing the variant protein exhibit loss of RS1 secretion into the medium relative to the wild-type control, caused by misfolding, aggregation, and ER retention of the variant protein (PMID: 12746437, PS3_Supporting). The computational predictor REVEL gives a score of 0.978, 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, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing. This variant is a missense substitution affecting a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435). PM1_Strong is not met as this code is ineligible to be used in combination with PP3_Strong. 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, PM5_Supporting, PS3_Supporting, PS4_Supporting, and PP1.

Met criteria codes

PS3_Supporting ✔	COS-1 cells exogenously expressing the variant protein exhibit loss of RS1 secretion into the medium relative to the wild-type control, caused by misfolding, aggregation, and ER retention of the variant protein (PMID: 12746437, PS3_Supporting).
PP3_Strong ✔	The computational predictor REVEL gives a score of 0.978, 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, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.2 and does not predict that the variant disrupts RS1 splicing.
PP1 ✔	The variant has been reported to segregate with X-linked retinoschisis through 2 affected family members (PP1; PMID: 39462066)
PM5_Supporting ✔	Another missense variant in the same codon, NM_000330.4(RS1):c.655T>G (p.Cys219Gly) 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. The present variant has a higher Grantham's distance (180) than the comparison variant (159), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5_Supporting).
PS4_Supporting ✔	This variant has been reported in at least 2 unrelated probands meeting the PS4 requirement of a male diagnosed with XLRS (PMIDs: 39462066, 35982512, 9618178, PS4_supporting).
PM2_Supporting ✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PM6	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	This variant is a missense substitution affecting a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435). PM1_Strong is not met as this code is ineligible to be used in combination with PP3_Strong.
PS2	✖	This variant has been identified as a de novo occurrence with unconfirmed parental relationships in 1 individual meeting the PS2 phenotype requirement of a male diagnosed with retinoschisis (PMID: 9618178). No description was provided of parental genotyping, so PS2 was not met.

Curation History

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