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Variant: NM_000330.4(RS1):c.656G>A (p.Cys219Tyr)

Version: 1.0

CA412370061

1700721 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: d64ec4a6-74a5-4a33-9bc6-535b99172a47
Approved on: 2025/10/4
Published on: 2025/10/5

HGVS expressions

NM_000330.4:c.656G>A
NM_000330.4(RS1):c.656G>A (p.Cys219Tyr)
NC_000023.11:g.18642023C>T
CM000685.2:g.18642023C>T
NC_000023.10:g.18660143C>T
CM000685.1:g.18660143C>T
NC_000023.9:g.18570064C>T
NG_008475.1:g.221419C>T
NG_008659.3:g.40426G>A
ENST00000379984.4:c.656G>A
ENST00000379984.3:c.656G>A
ENST00000379989.6:c.2714-3984C>T
ENST00000379996.7:c.2714-3984C>T
ENST00000476595.1:n.1147G>A
NM_000330.3:c.656G>A
NM_001037343.1:c.2714-3984C>T
NM_003159.2:c.2714-3984C>T
NM_001037343.2:c.2714-3984C>T
NM_003159.3:c.2714-3984C>T

Likely Pathogenic

Met criteria codes 4

PM5_Supporting PP4 PP3_Strong PM2_Supporting

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 1.0.0*
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.656G>A (p.Cys219Tyr) is a missense variant encoding the substitution of cysteine with tyrosine 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 (194) 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). 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: 32300273, PMID: 33124204, PP4). The computational predictor REVEL gives a score of 0.979, 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. 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 ACMG/AMP criteria applied, as specified by the ClinGen X-linked IRD VCEP: PM2_Supporting, PP3_Strong, PP4, and PM5_Supporting.

Met criteria codes

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 (194) than the comparison variant (159), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5_Supporting).
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: 32300273, PMID: 33124204, PP4).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.979, 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).

Not Met criteria codes

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.

Curation History

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