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Variant: NM_000330.4(RS1):c.667T>G (p.Cys223Gly)

Version: 1.0

CA412370013

1511265 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 902f0975-deb2-4086-9093-85a473dee359
Approved on: 2025/9/19
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HGVS expressions

NM_000330.4:c.667T>G
NM_000330.4(RS1):c.667T>G (p.Cys223Gly)
NC_000023.11:g.18642012A>C
CM000685.2:g.18642012A>C
NC_000023.10:g.18660132A>C
CM000685.1:g.18660132A>C
NC_000023.9:g.18570053A>C
NG_008475.1:g.221408A>C
NG_008659.3:g.40437T>G
ENST00000379984.4:c.667T>G
ENST00000379984.3:c.667T>G
ENST00000379989.6:c.2714-3995A>C
ENST00000379996.7:c.2714-3995A>C
ENST00000476595.1:n.1158T>G
NM_000330.3:c.667T>G
NM_001037343.1:c.2714-3995A>C
NM_003159.2:c.2714-3995A>C
NM_001037343.2:c.2714-3995A>C
NM_003159.3:c.2714-3995A>C

Likely Pathogenic

Met criteria codes 3

PM5_Supporting 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.667T>G (p.Cys223Gly) is a missense variant encoding the substitution of cysteine with glycine at amino acid 223. Another missense variant in the same codon, NM_000330.4(RS1):c.668G>C (p.Cys223Ser), (PMID: 12746437) 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 (159) than the comparison variant (112), 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). The computational predictor REVEL gives a score of 0.951, 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). However, the PP3_Strong code has been met, which is ineligible to be used in combination with the PM1 code at any strength, so the PM1 code was not met. 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, and PM5_Supporting.

Met criteria codes

PM5_Supporting	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.668G>C (p.Cys223Ser), (PMID: 12746437) 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 (159) than the comparison variant (112), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5_Supporting).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.951, 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.
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). However, the PP3_Strong code has been met, which is ineligible to be used in combination with the PM1 code at any strength, so the PM1 code was not met.

Curation History

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