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Variant: NM_000330.4(RS1):c.667T>C (p.Cys223Arg)

Version: 1.0

CA254929

9893 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: c5bd1381-d759-4a76-8f06-4488b4c637ca
Approved on: 2025/9/19
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HGVS expressions

NM_000330.4(RS1):c.667T>C (p.Cys223Arg)
NM_000330.4:c.667T>C
NC_000023.11:g.18642012A>G
CM000685.2:g.18642012A>G
NC_000023.10:g.18660132A>G
CM000685.1:g.18660132A>G
NC_000023.9:g.18570053A>G
NG_008475.1:g.221408A>G
NG_008659.3:g.40437T>C
ENST00000379984.4:c.667T>C
ENST00000379984.3:c.667T>C
ENST00000379989.6:c.2714-3995A>G
ENST00000379996.7:c.2714-3995A>G
ENST00000476595.1:n.1158T>C
NM_000330.3:c.667T>C
NM_001037343.1:c.2714-3995A>G
NM_003159.2:c.2714-3995A>G
NM_001037343.2:c.2714-3995A>G
NM_003159.3:c.2714-3995A>G

Pathogenic

Met criteria codes 7

PM2_Supporting PP1 PP4 PS3_Supporting PS4_Moderate PP3_Strong PS2_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 1.0.0*
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>C (p.Cys223Arg) is a missense variant encoding the substitution of cysteine with arginine at amino acid 223. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMID: 34645606, PMID: 10533068, PMID: 30652005, PS4_Moderate). At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 33460243, PP4). This variant has been identified as a de novo occurrence with confirmed parental relationships in an individual meeting the PS2 requirement of some functional vision impairment in affected males by age 13 (1 point, PS2_Moderate, PMID: 33460243). The variant has been reported to segregate with retinal dystrophy through 1 meiosis in a family with two affected brothers (PP1; PMID: 30652005). The computational predictor REVEL gives a score of 0.974, 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. COS-7 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 16361673, PS3_Supporting). 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 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, PP1, PP4, PS2_Moderate, and PS4_Moderate.

Met criteria codes

PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP1	✔	The variant has been reported to segregate with retinal dystrophy through 1 meiosis in a family- two affected brothers (PP1; PMID: 30652005).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 33460243, PP4).
PS3_Supporting	✔	COS-7 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 16361673, PS3_Supporting).
PS4_Moderate	✔	This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMID: 34645606, PMID: 10533068, PMID: 30652005, PS4_Moderate)
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.974, 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.
PS2_Moderate	✔	This variant has been identified as a de novo occurrence with confirmed parental relationships in an individual meeting the PS2 requirement of some functional vision impairment in affected males by age 13 (1 point, PS2_Moderate, PMID: 33460243).

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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