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Variant: NM_000330.4(RS1):c.175T>G (p.Cys59Gly)

Version: 1.1

CA412376057

2159556 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 40bed26c-a1bb-481d-a1b5-de875d47e07c
Approved on: 2025/10/3
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HGVS expressions

NM_000330.4:c.175T>G
NM_000330.4(RS1):c.175T>G (p.Cys59Gly)
NC_000023.11:g.18656662A>C
CM000685.2:g.18656662A>C
NC_000023.10:g.18674782A>C
CM000685.1:g.18674782A>C
NC_000023.9:g.18584703A>C
NG_008659.3:g.25787T>G
ENST00000379984.4:c.175T>G
ENST00000379984.3:c.175T>G
NM_000330.3:c.175T>G

Pathogenic

Met criteria codes 6

PP1_Strong PM2_Supporting PS4_Supporting PM5 PP4 PM1_Strong

Not Met criteria codes 1

PP3

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.175T>G (p.Cys59Gly) is a missense variant encoding the substitution of cysteine with glycine at amino acid 59, which is a critical amino acid residue involved in disulfide bridge formation as defined by the ClinGen X-linked IRD VCEP (PMID: 26812435, PM1_Strong). Another missense variant in the same codon, NM_000330.4(RS1):c.175T>A (p.Cys59Ser), (PMIDs: 31174210, 10450864, 17987333, 9618178) 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 (159) than the comparison variant (112), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). 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: 34645606, PMID: 33460243, PP4). This variant has been reported in at least 1 other proband meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis, in addition to the apparently unrelated proband previously used for the PP4 code (PMIDs: 30652005, PS4_Supporting). The variant has been reported to segregate with X-linked retinoschisis through at least 3 meioses in two families with multiple affected brothers (PP1_Strong; PMID: 30652005). The computational predictor REVEL gives a score of 0.868, which is within the linGen X-linked IRD VCEP range between 0.931 to 0.773 and predicts a damaging effect on RS1 function. PP3 is not met since this code is ineligible in combination with PM1_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. 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, PM1_Strong, PP1_Strong, PP4, and PS4_Supporting.

Met criteria codes

PP1_Strong	✔	The variant has been reported to segregate with X-linked retinoschisis through at least 3 meioses in two families with multiple affected brothers (PP1_Strong; PMID: 30652005).
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PS4_Supporting	✔	This variant has been reported in at least 1 proband meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 30652005, PS4_Supporting).
PM5	✔	Another missense variant in the same codon, NM_000330.4(RS1):c.175T>A (p.Cys59Ser), (PMIDs: 31174210, 10450864, 17987333, 9618178) 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 (159) than the comparison variant (112), and SpliceAI has been used to confirm that neither variant has a predicted impact on RS1 splicing (PM5).
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: 34645606, PMID: 33460243, PP4).
PM1_Strong	✔	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).

Not Met criteria codes

PP3	✖	The computational predictor REVEL gives a score of 0.868, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 0.773 and predicts a damaging effect on RS1 function. 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. The PM1_strong code is ineligible to be combined with PP3 at any strength, therefore, the PP3 code was not met.

Curation History

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