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Variant: NM_000330.4(RS1):c.574C>A (p.Pro192Thr)

Version: 1.0

CA226784

98989 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: 4c6bd468-e1cc-4a53-b683-977470fea621
Approved on: Sat, 26 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000330.4(RS1):c.574C>A (p.Pro192Thr)
NM_000330.4:c.574C>A
NC_000023.11:g.18642105G>T
CM000685.2:g.18642105G>T
NC_000023.10:g.18660225G>T
CM000685.1:g.18660225G>T
NC_000023.9:g.18570146G>T
NG_008475.1:g.221501G>T
NG_008659.3:g.40344C>A
ENST00000379984.4:c.574C>A
ENST00000379984.3:c.574C>A
ENST00000379989.6:c.2714-3902G>T
ENST00000379996.7:c.2714-3902G>T
ENST00000476595.1:n.1065C>A
NM_000330.3:c.574C>A
NM_001037343.1:c.2714-3902G>T
NM_003159.2:c.2714-3902G>T
NM_001037343.2:c.2714-3902G>T
NM_003159.3:c.2714-3902G>T

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP4 PS4_Supporting PP1_Strong PP3_Moderate

Not Met criteria codes 1

PM5

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

The NM_000330.4(RS1):c.574C>A (p.Pro192Thr) variant is a missense variant encoding the substitution of Proline and Threonine at amino acid 192. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.913, which is within the ClinGen X-linked IRD VCEP range between 0.931 and 0.773 and predicts a damaging effect on RS1 function (PP3_moderate). 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. Another two missense variant in the same codon, NM_000330.4(RS1):c.574C>T (p.Pro192Ser), (PMIDs: 9326935, 10636421, 17987333, 19093009, 28348004, 30551202, 30652005, 34828422, 39293640, 17515881, 20809529) and NM_000330.4(RS1):c.575C>T (p.Pro192Leu), (PMIDs: 19093009, 19324861, 28348004, 33124204, 36460718, 32300273)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 lower Grantham's distance (38) than the comparison variant (98 / 74), and therefore, the PM5 code does not meet. Sergeev et al. used structure-based analysis to predict structural changes for 15 missense variants from the NEI data set (Data set I) affecting the XLRS phenotype. This variant, P192T, defines an almost 90° turn of the loop connecting β7 and β8 strands. This change will make the conformation of the 90° turn less rigid and could affect protein folding (PMID: 20061330). At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 12457918, PP4). The variant has been reported to segregate with retinal dystrophy through >3 meioses in one family (PP1_Strong; PMID: 12457918). This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 39462066, PS4_Supporting). 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_Moderate, PP4, PP1_Strong, and PS4_Supporting.

Met criteria codes

PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP4	✔	At least one proband harboring this variant exhibits the following phenotypes, including the appearance of schisis and reduced visual acuity before age 13 years, which together are specific for X-linked retinoschisis (PMID: 12457918, PP4).
PS4_Supporting	✔	This variant has been reported in at least 1 proband meeting one of the PS4 requirements of a male diagnosed with XLRS, as well as a second apparently unrelated proband previously used for the PP4 code (PMIDs: 39462066, PS4_Supporting).
PP1_Strong	✔	The variant has been reported to segregate with retinal dystrophy through >3 meioses in one family (PP1_Strong; PMID: 12457918).
PP3_Moderate	✔	The computational predictor REVEL gives a score of 0.913, which is within the ClinGen X-linked IRD VCEP range between 0.931 and 0.773 and predicts a damaging effect on RS1 function (PP3_moderate). 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.

Not Met criteria codes

PM5	✖	Another missense variant in the same codon, NM_000330.4(RS1):c.574C>T (p.Pro192Ser), (PMIDs: 9326935, 10636421, 17987333, 19093009, 28348004, 30551202, 30652005, 34828422, 39293640, 17515881, 20809529) and NM_000330.4(RS1):c.575C>T (p.Pro192Leu), (PMIDs: 19093009, 19324861, 28348004, 33124204, 36460718,

32300273)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 lower Grantham’s distance (38) than the comparison variant (98 / 74), and therefore, the PM5 code does not meet.

Curation History

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