

Variant: *NM_000330.4(RS1):c.544C>T (p.Arg182Cys)*

Version: 1.0

CA226778 [↗](#)

98986 (ClinVar) [↗](#)

Gene: RS1 ([HGNC:6247](#))

Condition: X-linked retinoschisis ([MONDO:0010725](#))

Inheritance Mode: X-linked inheritance

UUID: b7d65277-f3a1-4377-aaec-d7e6e8a00809

Approved on: 2025/9/23

Published on: 2025/9/23

HGVS expressions

NM_000330.4:c.544C>T

NM_000330.4(RS1):c.544C>T (p.Arg182Cys)

NC_000023.11:g.18642135G>A

CM000685.2:g.18642135G>A

NC_000023.10:g.18660255G>A

CM000685.1:g.18660255G>A

NC_000023.9:g.18570176G>A

NG_008475.1:g.221531G>A

NG_008659.3:g.40314C>T

ENST00000379984.4:c.544C>T

ENST00000379984.3:c.544C>T

ENST00000379989.6:c.2714-3872G>A

ENST00000379996.7:c.2714-3872G>A

ENST00000476595.1:n.1035C>T

NM_000330.3:c.544C>T

NM_001037343.1:c.2714-3872G>A

NM_003159.2:c.2714-3872G>A

NM_001037343.2:c.2714-3872G>A

NM_003159.3:c.2714-3872G>A

Pathogenic

Met criteria codes **3**

PS3_Supporting

PS4_Very Strong

PP3_Moderate

Not Met criteria codes **2**

BS1

PM2

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.544C>T (p.Arg182Cys) is a missense variant encoding the substitution of arginine with cysteine at amino acid 182. This variant is present in gnomAD v.4.1.0 at a frequency of 0.000002506 among hemizygous individuals, with 1 variant alleles / 399013 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2_Supporting and BS1 threshold of 0.000002 to 0.00002 and fails to meet these criteria. The computational predictor REVEL gives a score of 0.917, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 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. COS7 cells exogenously expressing the variant exhibit reduced RS1 secretion into the medium relative to the wild-type control (PMID: 16361673, PMID: 29851975, PS3_Supporting). This variant has been reported in at least 9 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 19568363, PMID: 34645606, PMID: 29851975, PMID: 34828422, PMID: 30652005, PMID: 34822951, PMID: 36377647, PMID: 39462066, PMID: 33546218, PS4_VeryStrong). 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: PP3_Moderate, PS3_Supporting, and PS4_VeryStrong.

Met criteria codes

PS3_Supporting			COS7 cells exogenously expressing the variant exhibit reduced RS1 secretion into the medium relative to the wild-type control (PMID: 16361673, 29851975, PS3_Supporting).
PS4_Very Strong			This variant has been reported in at least 9 apparently unrelated probands meeting the PS4 requirement of a male diagnosed with X-linked retinoschisis (PMID: 19568363, PMID: 34645606, PMID: 29851975, PMID: 34828422, PMID: 30652005, PMID: 34822951, PMID: 36377647, PMID: 39462066, PMID: 33546218, PS4_VeryStrong).
PP3_Moderate			The computational predictor REVEL gives a score of 0.917, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 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

BS1			This variant is present in gnomAD v.4.1.0 at a frequency of 0.000002506 among hemizygous individuals, with 1 variant alleles / 399013 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2_Supporting and BS1 threshold of 0.000002 to 0.00002and fails to meet these criteria.
PM2			This variant is present in gnomAD v4.1.0 at a frequency of 0.000002506 among hemizygous individuals, with 1 variant allele / 399,013 total hemizygous alleles, which is between the ClinGen X-linked IRD VCEP PM2_Supporting threshold of <0.000002 and BS1 threshold of >0.00002 and fails to meet these criteria.

Curation History 

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