

Variant: *NM_000330.4(RS1):c.337C>T (p.Leu113Phe)*

Version: 1.0

CA226697 [↗](#)

98943 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance (recessive (HP:0001419))

UUID: 1aacd4cc-13a1-4be1-88a2-3a036aec6819

Approved on: 2025/5/19

Published on: 2025/5/20

HGVS expressions

NM_000330.4(RS1):c.337C>T (p.Leu113Phe)

NM_000330.4:c.337C>T

NC_000023.11:g.18644615G>A

CM000685.2:g.18644615G>A

NC_000023.10:g.18662735G>A

CM000685.1:g.18662735G>A

NC_000023.9:g.18572656G>A

NG_008475.1:g.224011G>A

NG_008659.3:g.37834C>T

ENST00000379984.4:c.337C>T

ENST00000379984.3:c.337C>T

ENST00000379989.6:c.2714-1392G>A

ENST00000379996.7:c.2714-1392G>A

ENST00000476595.1:n.828C>T

NM_000330.3:c.337C>T

NM_001037343.1:c.2714-1392G>A

NM_003159.2:c.2714-1392G>A

NM_001037343.2:c.2714-1392G>A

NM_003159.3:c.2714-1392G>A

Likely Pathogenic

Met criteria codes **4**

PS3_Supporting

PP3_Moderate

PS4

PM2_Supporting

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.337C>T variant is a missense variant encoding the substitution of Leucine with Phenylalanine at amino acid 113. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.874, 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 0.02 for acceptor gain, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing. HEK293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 30040949, 16361673, PS3_Supporting). This variant has been reported in at least 5 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with X-linked retinoschisis (PMIDs: 11738458, 34645606, 34822951, 28348004, 9618178, 39462066, <https://doi.org/10.1134/S1022795421070139>, PS4). 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, PS3_supporting, PS4 (date of approval 01/24/2025).

Met criteria codes

PS3_Supporting			HEK293 cells exogenously expressing the variant exhibit loss of RS1 secretion into the medium relative to the wild-type control (PMID: 30040949, 16361673, PS3_Supporting).
PP3_Moderate			The computational predictor REVEL gives a score of 0.874, 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 0.02 for acceptor gain, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RS1 splicing.
PS4			This variant has been reported in at least 5 apparently unrelated probands meeting the PS4 requirements of a male diagnosed with XLRS (PMIDs: 11738458, 34645606, 34822951, 28348004, 9618178, 39462066, https://doi.org/10.1134/S1022795421070139 , PS4).
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Curation History

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