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Variant: NM_000330.4:c.52G>A

Version: 1.0

CA412378923

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance
UUID: 04282c13-07a5-4da1-99d4-2f0d6b186202
Approved on: Sat, 26 Sep 2026 00:00:00 +0000
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HGVS expressions

NM_000330.4:c.52G>A
NC_000023.11:g.18672017C>T
CM000685.2:g.18672017C>T
NC_000023.10:g.18690137C>T
CM000685.1:g.18690137C>T
NC_000023.9:g.18600058C>T
NG_008659.3:g.10432G>A
ENST00000379984.4:c.52G>A
ENST00000379984.3:c.52G>A
NM_000330.3:c.52G>A

Pathogenic

Met criteria codes 4

PP4 PVS1 PM2_Supporting PP1_Moderate

Not Met criteria codes 2

PS3 PP3

Evidence Links 1

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.52G>A (p.Ala18Thr) variant is a missense variant encoding the substitution of Alanine and Threonine at amino acid 18, located at the end of exon 1. The splicing impact predictor SpliceAI gives the variant a score of 0.31, which is above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. Functional studies confirm that the variant triggers either exon 2 or both exons 1 and 2 skipping in all transcripts (PMID: 20809529). While these in silico and experimental findings would normally be counted under the PP3 and PS3_Supporting codes, respectively, in combination, they have been counted as evidence of a loss-of-function effect (PVS1_RNA). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). 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: 20809529, PP4). The variant has been reported to segregate through

at least 2 meioses in one family (PP1_moderate; PMID: 20809529). 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: PVS1_RNA, PM2_Supporting, PP4, and PP1_Moderate.

Met criteria codes

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: 20809529, PP4).
PVS1	✔	The splicing impact predictor SpliceAI gives the variant a score of 0.31, which is above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. Functional studies confirm that the variant triggers either exon 2 or both exons 1 and 2 skipping in all transcripts (PMID: 20809529). While these in silico and experimental findings would normally be counted under the PP3 and PS3_Supporting codes, respectively, in combination, they have been counted as evidence of a loss-of-function effect (PVS1_RNA).
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP1_Moderate	✔	The variant has been reported to segregate through at least 2 meioses in one family (PP1_moderate; PMID: 20809529).

Not Met criteria codes

PS3	✖	A minigene construct harboring the variant produces mRNA of aberrant size relative to the wild-type control, consistent with a deleterious effect on RS1 splicing (PMID: 20809529). This code was combined with the PP3 code. Vijayasarathy et al. Western blotting with little to no signal, as well as Sanger sequencing of cDNA clones showing skipping of either exon 2 or both exons 1 and 2. PubMed:20809529
PP3	✖	The computational predictor REVEL gives a score of 0.318, which is between the ClinGen X-linked IRD VCEP threshold of 0.290 and 0.664 and does not predict a damaging effect on RS1 function. The splicing impact predictor SpliceAI gives a score of 0.31, which is above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predicts an impact on splicing. This code was combined with PS3_Supporting.

Curation History

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