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Variant: NM_000330.4(RS1):c.76G>T (p.Glu26Ter)

Version: 1.0

CA226853

99021 (ClinVar)

Gene: RS1 (HGNC:6247)
Condition: X-linked retinoschisis (MONDO:0010725)
Inheritance Mode: X-linked inheritance (recessive (HP:0001419))
UUID: 8819d4d3-e32b-47e4-8d78-3b6732ffee06
Approved on: 2025/5/19
Published on: 2025/5/20

HGVS expressions

NM_000330.4:c.76G>T
NM_000330.4(RS1):c.76G>T (p.Glu26Ter)
NC_000023.11:g.18657642C>A
CM000685.2:g.18657642C>A
NC_000023.10:g.18675762C>A
CM000685.1:g.18675762C>A
NC_000023.9:g.18585683C>A
NG_008659.3:g.24807G>T
ENST00000379984.4:c.76G>T
ENST00000379984.3:c.76G>T
NM_000330.3:c.76G>T

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

Not Met criteria codes 1

PS4

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.76G>T variant is a nonsense variant in amino acid 26, which results in a premature stop codon and causes a truncated protein. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). This is a nonsense variant that introduces a premature stop codon between amino acids 1-223 that is predicted to either trigger nonsense-mediated decay or to disrupt a critical C-terminal region required for proper multimerization of RS1 (PVS1, PMID: 19849666). This variant has been reported in at least 1 proband meeting the PS4 requirement of a male with diagnosis of X-linked retinoschisis (PMIDs: 9618178). However, PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met. 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: PVS1 and PM2_supporting (date of approval 01/24/2025).

Met criteria codes

PVS1	✔	This is a nonsense variant that introduces a premature stop codon between amino acids 1-223 that is predicted to either trigger nonsense-mediated decay or to disrupt a critical C-terminal region required for proper multimerization of RS1 (PVS1, PMID: 19849666).
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS4	✖	This variant has been reported in at least 1 proband meeting the PS4 requirement of a male with some functional vision impairment by age 5 (PMIDs: 9618178). However, PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met.

Curation History

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