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Variant: NM_001034853.2(RPGR):c.494G>T (p.Gly165Val)

Version: 1.0

CA412744915

1802334 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: fd9da888-326a-4e5f-9568-3d06139dae7e
Approved on: 2025/9/7
Published on: 2025/9/8

HGVS expressions

NM_001034853.2:c.494G>T
NM_001034853.2(RPGR):c.494G>T (p.Gly165Val)
NC_000023.11:g.38317441C>A
CM000685.2:g.38317441C>A
NC_000023.10:g.38176694C>A
CM000685.1:g.38176694C>A
NC_000023.9:g.38061638C>A
NG_009553.1:g.15095G>T
ENST00000642170.1:n.904G>T
ENST00000642373.1:c.*73G>T
ENST00000642395.2:c.494G>T
ENST00000642558.1:c.401G>T
ENST00000642739.1:c.494G>T
ENST00000644238.1:c.494G>T
ENST00000644337.1:c.494G>T
ENST00000645032.1:c.494G>T
ENST00000645124.1:c.494G>T
ENST00000646020.1:c.494G>T
ENST00000647261.1:c.494G>T
ENST00000318842.11:c.494G>T
ENST00000339363.7:c.494G>T
ENST00000378505.6:c.494G>T
ENST00000465127.1:c.172-348680C>A
ENST00000470183.1:n.187G>T
ENST00000474584.5:c.494G>T
ENST00000482855.5:c.494G>T
NM_000328.2:c.494G>T
NM_001034853.1:c.494G>T
NM_001367245.1:c.494G>T
NM_001367246.1:c.494G>T
NM_001367247.1:c.494G>T
NM_001367248.1:c.524G>T
NM_001367249.1:c.491G>T
NM_001367250.1:c.494G>T
NM_001367251.1:c.494G>T
NR_159803.1:n.636G>T
NR_159804.1:n.636G>T

NR_159805.1:n.636G>T
NR_159806.1:n.636G>T
NR_159807.1:n.636G>T
NR_159808.1:n.904G>T
NM_000328.3:c.494G>T

Likely Pathogenic

Met criteria codes 4

PM5 PP3_Strong PM2_Supporting PS4_Supporting

Not Met criteria codes 3

BS3 PS3 PP4

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 RPGR 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_001034853.2(RPGR):c.494G>T (p.Gly165Val) is a missense variant causing substitution of glycine by valine at amino acid 165. Another missense variant in the same codon, NM_001034853.2(RPGR):c.494G>A (p.Gly165Asp), has been classified as pathogenic for RPGR-related retinopathy by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (109) than the comparison variant (94), and SpliceAI has been used to confirm that neither variant has a predicted impact on RPGR splicing (PM5_Supporting). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 apparently unrelated probands meeting one of the PS4 requirements of a male with some functional vision impairment by age 30 years and/or decreased or absent electroretinogram responses, or a female with functional visual abnormality and documentation of a male relative affected with retinitis pigmentosa (PMID: 34745198, PMID: 31630094, PS4_Supporting). The computational predictor REVEL gives a score of 0.982, which is above the ClinGen X-linked IRD VCEP threshold of ≥ 0.932 and predicts a damaging effect on RPGR function (PP3_Strong). The splicing predictor SpliceAI gives a delta score of 0.06 for splice donor loss, which is lower than the threshold of >0.2 and does not strongly predict a disruption of splicing. Injection of human RPGR mRNA harboring the variant into zebrafish embryos rescued ciliary defects associated with rpgr silencing comparably to wild-type RPGR (PMID: 19815619). However, the BS3_Supporting code is not considered applicable for RPGR. In summary, this variant is classified as likely pathogenic for RPGR-related retinopathy based on the ClinGen X-linked Inherited Retinal Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for RPGR Version 1.0.0; PM2_Supporting, PP3_Strong, and PS4_Supporting.

Met criteria codes

PM5	✔	Another missense variant in the same codon, NM_001034853.2(RPGR):c.494G>A (p.Gly165Asp) has been classified as pathogenic for RPGR-related retinopathy by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. The present variant has a higher Grantham's distance (109) than the comparison variant (94), and SpliceAI has been used to confirm that neither variant has a predicted impact on RPGR splicing (PM5_Supporting).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.982, which is above the ClinGen X-linked IRD VCEP threshold of ≥ 0.932 and predicts a damaging effect on RPGR function (PP3_Strong). The splicing predictor SpliceAI gives a

delta score of 0.06 for splice donor loss, which is lower than the threshold of >0.5 and does not strongly predict a disruption of splicing.

PM2_Supporting ✔ This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

PS4_Supporting ✔ This variant has been reported in at least 2 apparently unrelated probands meeting one of the PS4 requirements of a male with some functional vision impairment by age 30 and/or decreased or absent ERG responses, or a female with functional visual abnormality and documentation of a male relative affected with retinitis pigmentosa (PMIDs: 34745198, 31630094, PS4_Supporting).

Not Met criteria codes

BS3 ✖ Injection of human RPGR mRNA harboring the variant into zebrafish embryos rescued ciliary defects associated with rpgr silencing (such as hydrocephaly / edema / kinked tail) comparably to wild-type RPGR (PMID: 19815619). However, the BS3_Supporting code is not considered applicable for RPGR.

Injection of human RPGR mRNA harboring the variant into zebrafish embryos rescued ciliary defects such as hydrocephaly / edema / kinked tail associated with rpgr silencing (Figure 4B). PubMed:19815619

PS3 ✖ Injection of human RPGR mRNA harboring the variant into zebrafish embryos rescued ciliary defects associated with rpgr silencing (such as hydrocephaly / edema / kinked tail) comparably to wild-type RPGR (PMID: 19815619). However, the BS3_Supporting code is not considered applicable for RPGR.

Injection of human RPGR mRNA harboring the variant into zebrafish embryos rescued ciliary defects such as hydrocephaly / edema / kinked tail associated with rpgr silencing (Figure 4B). PubMed:19815619

PP4 ✖ This variant has been reported in at least 1 proband with early-onset severe retinal dystrophy fulfilling the requirements of onset before the age of 30 and abnormalities on ERG. Because phenotypes were absent other than the next generation sequencing-based genotyping excluding alternative causes in other loci (2 pts), this criterion is not met.

Curation History

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