Variant: NM_001034853.2(RPGR):c.494G>A (p.Gly165Asp)

Version: 1.0

CA412744917

812421 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: d6a9f3ed-0190-4450-bb30-a00144e97d09
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HGVS expressions

NM_001034853.2:c.494G>A
NM_001034853.2(RPGR):c.494G>A (p.Gly165Asp)
NC_000023.11:g.38317441C>T
CM000685.2:g.38317441C>T
NC_000023.10:g.38176694C>T
CM000685.1:g.38176694C>T
NC_000023.9:g.38061638C>T
NG_009553.1:g.15095G>A
ENST00000642170.1:n.904G>A
ENST00000642373.1:c.*73G>A
ENST00000642395.2:c.494G>A
ENST00000642558.1:c.401G>A
ENST00000642739.1:c.494G>A
ENST00000644238.1:c.494G>A
ENST00000644337.1:c.494G>A
ENST00000645032.1:c.494G>A
ENST00000645124.1:c.494G>A
ENST00000646020.1:c.494G>A
ENST00000647261.1:c.494G>A
ENST00000318842.11:c.494G>A
ENST00000339363.7:c.494G>A
ENST00000378505.6:c.494G>A
ENST00000465127.1:c.172-348680C>T
ENST00000470183.1:n.187G>A
ENST00000474584.5:c.494G>A
ENST00000482855.5:c.494G>A
NM_000328.2:c.494G>A
NM_001034853.1:c.494G>A
NM_001367245.1:c.494G>A
NM_001367246.1:c.494G>A
NM_001367247.1:c.494G>A
NM_001367248.1:c.524G>A
NM_001367249.1:c.491G>A
NM_001367250.1:c.494G>A
NM_001367251.1:c.494G>A
NR_159803.1:n.636G>A
NR_159804.1:n.636G>A

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

Pathogenic

Met criteria codes 4

PP3_Strong PP1_Strong PS4_Moderate PM2_Supporting

Not Met criteria codes 3

PP4 PM5 PM6

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 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>A (p.Gly165Asp) is a missense variant predicted to cause substitution of glycine by aspartate at amino acid 165. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). At least one male proband harboring this variant has onset before age 30 years (required), macular integrity assessment of 0, optic nerve pallor (0.5 pts), pigmentary retinopathy (0.5 pts), nyctalopia (0.5 pts), decreased central vision acuity (0.5 pts), and high myopia (1 pt), combined with panel-based genotyping that excludes alternative causes in other relevant loci (2 pts), but cannot meet PP4 due to the absence of the reduced electroretinogram requirement (5 pts total, PMID: 27596865). This variant has been identified as a de novo occurrence in this proband, with an assumed but unconfirmed maternal relationship (0.25 pts, PMID: 27596865), however, de novo points were not sufficient to meet PS2_Supporting. This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30 years, with decreased or absent cone and/or rod electroretinogram responses (PMIDs: 31456290, 27596865, 30887160, PS4_Moderate).The variant has been reported to segregate with retinal dystrophy through at least 4 affected meioses total from at least 2 families (PP1_Strong; PMIDs: 30887160, 31456290). Another missense variant in the same codon, NM_001034853.2(RPGR):c.494G>T (p.Gly165Val), has a higher Grantham score than this variant, so PM5 has not been considered. The computational predictor REVEL gives a score of 0.968, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RPGR function (PP3_strong). In summary, this variant is classified as 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, PP1_strong, PS4_moderate, and PP3_strong. (date of approval 05/16/2025).

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.968, which is above the ClinGen X-linked IRD VCEP threshold of >0.932 and predicts a damaging effect on RPGR function (PP3_strong). The computational splicing predictor SpliceAI gives a delta score of 0.12 for donor gain, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RPGR splicing.
PP1_Strong	✔	The variant has been reported to segregate with retinal dystrophy through at least 4 affected meioses total from at least 2 families (PP1_Strong; PMIDs: 30887160, 31456290).

PS4_Moderate	✔	This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30, with decreased or absent cone and/or rod ERG responses (PMIDs: 31456290, 27596865, 30887160, PS4_Moderate).
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PP4	✖	At least one male proband diagnosed with X-linked retinitis pigmentosa has onset before age 30 (required), macular integrity assessment of 0, optic nerve pallor (0.5 pts), pigmentary retinopathy (0.5 pts), nyctalopia (0.5 pts), decreased central vision acuity (0.5 pts), and high myopia (1 pt), combined with panel-based genotyping that excludes alternative causes in other relevant loci (2 pts), but cannot meet PP4 due to the absence of the reduced ERG requirement (5 pts total, PMID: 27596865). A second proband diagnosed with X-linked retinitis pigmentosa has a family history consistent with X-linked inheritance (2 pts), whole exome genotyping without identification of an alternative cause of disease (2 pts), abnormal best corrected visual acuity test (0.5 pts), nyctalopia (0.5 pts, male only), and high myopia (1 pt), but lacks the required details confirming functional vision impairment by age 30, with decreased or absent cone and/or rod ERG responses, so PP4 is not met (PMID: 34745198).
PM5	✖	Another missense variant, NM_001034853.2(RPGR):c.494G>T (p.Gly165Val), in the same codon has a higher Grantham score than this variant, so PM5 is not met. This comparison variant has been classified as likely pathogenic for RPGR-related retinopathy by the ClinGen X-linked IRD VCEP.
PM6	✖	This variant has been identified as a de novo occurrence with an assumed but unconfirmed maternal relationship in 1 individual with a phenotype consistent with RPGR-related retinopathy (0.25 points, PMID: 27596865).

Curation History

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