

Variant: *NM_001034853.2(RPGR):c.492G>T (p.Trp164Cys)*

Version: 1.7

CA412744921 [↗](#)

636203 (ClinVar) [↗](#)

Gene: RPGR ([HGNC:6103](#))

Condition: RPGR-related retinopathy ([MONDO:0100437](#))

Inheritance Mode: X-linked inheritance

UUID: 272ebb11-47f9-4557-a27d-0c3302cec15f

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HGVS expressions

NM_001034853.2(RPGR):c.492G>T (p.Trp164Cys)

NM_001034853.2:c.492G>T

NC_000023.11:g.38317443C>A

CM000685.2:g.38317443C>A

NC_000023.10:g.38176696C>A

CM000685.1:g.38176696C>A

NC_000023.9:g.38061640C>A

NG_009553.1:g.15093G>T

ENST00000642170.1:n.902G>T

ENST00000642373.1:c.*71G>T

ENST00000642395.2:c.492G>T

ENST00000642558.1:c.399G>T

ENST00000642739.1:c.492G>T

ENST00000644238.1:c.492G>T

ENST00000644337.1:c.492G>T

ENST00000645032.1:c.492G>T

ENST00000645124.1:c.492G>T

ENST00000646020.1:c.492G>T

ENST00000647261.1:c.492G>T

ENST00000318842.11:c.492G>T

ENST00000339363.7:c.492G>T

ENST00000378505.6:c.492G>T

ENST00000465127.1:c.172-348678C>A

ENST00000470183.1:n.185G>T

ENST00000474584.5:c.492G>T

ENST00000482855.5:c.492G>T

NM_000328.2:c.492G>T

NM_001034853.1:c.492G>T

NM_001367245.1:c.492G>T

NM_001367246.1:c.492G>T

NM_001367247.1:c.492G>T

NM_001367248.1:c.522G>T

NM_001367249.1:c.489G>T

NM_001367250.1:c.492G>T

NM_001367251.1:c.492G>T

NR_159803.1:n.634G>T

NR_159804.1:n.634G>T

NR_159805.1:n.634G>T
NR_159806.1:n.634G>T
NR_159807.1:n.634G>T
NR_159808.1:n.902G>T
NM_000328.3:c.492G>T

Likely Pathogenic

Met criteria codes 4

PP1 PP3_Moderate PM2_Supporting
PP4_Moderate

Not Met criteria codes 11

BP4 BP3 PS2 PS3 PS4
PM4 PM6 BA1 BS1 BS4
BS3

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.492G>T (p.Trp164Cys) is a missense variant that substitutes tryptophan with cysteine at amino acid 164. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.929, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 0.773 and predicts a damaging effect on RPGR function (PP3_moderate). The computational splicing predictor SpliceAI gives a delta score of 0.08 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. At least one proband harboring this variant exhibits a phenotype including a family history consistent with X-linked inheritance (lacking male-to-male transmission, 2 pts) with milder phenotypes in females (1 pt), genotyping by a retinal dystrophy panel designed to detect 111 genes identifying no alternative basis for disease (2 pts), night blindness (0.5 pts), reduced best corrected visual acuity (0.5 pts), onset at age 7 years (1 pt), nonrecordable electroretinogram (required), and severe myopia (1 pt), which together are highly specific for RPGR-related retinopathy (8 pts, PMID: 30917587, PP4). The variant has been reported to segregate with retinal dystrophy through an affected mother and son from 1 family (PP1; PMID: 30917587). At least two probands harboring this variant exhibited a phenotype consistent with retinopathy, however, the required phenotypes of reduced electroretinogram responses and/or male loss of visual function before age 30 years could only be confirmed in one case, so PS4_Supporting was not met (PMID: 30718709, PMID: 30917587). 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, PP1, PP3_moderate, and PP4_moderate. (date of approval 05/16/2025).

Met criteria codes

PP1



The variant has been reported to segregate with retinal dystrophy through an affected mother and son from 1 family (PP1; PMID: 30917587).

PP3_Moderate



The computational predictor REVEL gives a score of 0.929, which is within the ClinGen X-linked IRD VCEP range between 0.931 to 0.773 and predicts a damaging effect on RPGR function (PP3_moderate). The computational splicing predictor SpliceAI gives a delta score of 0.08 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.

PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP4_Moderate			At least one proband harboring this variant exhibits a phenotype consistent with retinitis pigmentosa including a family history consistent with X-linked inheritance (lacking male-to-male transmission, 2 pts), genotyping by a retinal dystrophy panel designed to detect 111 genes uncovering no secondary findings (2 pts), night blindness (0.5 pts), reduced best corrected visual acuity (0.5 pts), onset at age 7 (1 pt), nonrecordable ERG (required), milder female phenotype (1 pt), and severe myopia (1 pt), which together are highly specific for RPGR-related recessive retinopathy (8 pts, PMID: 30917587, PP4).
Not Met criteria codes			
BP4			REVEL score is: 0.929.
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS4			At least two probands harboring this variant exhibited a phenotype consistent with retinitis pigmentosa, however, the required phenotypes of reduced ERG responses and/or male age of onset before 30 could only be confirmed in one case (PMID: 30917587), so the number of probands was not sufficient to meet PS4_Supporting (PMID: 30718709, PMID: 30917587).
PM4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM6			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BA1			BA1 was not met because the variant frequency was not found in gnomAD.
BS1			BS1 was not met because the variant frequency was not found in gnomAD.
BS4			All family members not genotyped (PMID: 30917587).
BS3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History		
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