

Variant: *NM_001034853.2:c.593G>A*

Version: 1.0

CA412744485 [↗](#)

3249728 (ClinVar) [↗](#)

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

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

Inheritance Mode: X-linked inheritance

UUID: d8809e89-a4fd-4cab-af74-6d4e8a82c646

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HGVS expressions

NM_001034853.2:c.593G>A

NC_000023.11:g.38317342C>T

CM000685.2:g.38317342C>T

NC_000023.10:g.38176595C>T

CM000685.1:g.38176595C>T

NC_000023.9:g.38061539C>T

NG_009553.1:g.15194G>A

ENST00000642170.1:n.1003G>A

ENST00000642373.1:c.*172G>A

ENST00000642395.2:c.593G>A

ENST00000642558.1:c.500G>A

ENST00000642739.1:c.593G>A

ENST00000644238.1:c.593G>A

ENST00000644337.1:c.593G>A

ENST00000645032.1:c.593G>A

ENST00000645124.1:c.593G>A

ENST00000646020.1:c.593G>A

ENST00000647261.1:c.593G>A

ENST00000318842.11:c.593G>A

ENST00000339363.7:c.593G>A

ENST00000378505.6:c.593G>A

ENST00000465127.1:c.172-348779C>T

ENST00000470183.1:n.286G>A

ENST00000474584.5:c.593G>A

ENST00000482855.5:c.593G>A

NM_000328.2:c.593G>A

NM_001034853.1:c.593G>A

NM_001367245.1:c.593G>A

NM_001367246.1:c.593G>A

NM_001367247.1:c.593G>A

NM_001367248.1:c.623G>A

NM_001367249.1:c.590G>A

NM_001367250.1:c.593G>A

NM_001367251.1:c.593G>A

NR_159803.1:n.735G>A

NR_159804.1:n.670+65G>A

NR_159805.1:n.735G>A

NR_159806.1:n.735G>A
NR_159807.1:n.735G>A
NR_159808.1:n.1003G>A
NM_000328.3:c.593G>A

Likely Pathogenic

Met criteria codes 3

PP3_Strong PM2_Supporting
PS4_Supporting

Not Met criteria codes 15

PS1 PS2 PS3 PP4 PM5
PM4 PM6 BA1 BS2 PVS1
BS1 BS4 BP4 BP3 BP7

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.593G>A (p.Gly198Glu) is a missense variant encoding the substitution of glycine by glutamate at amino acid 198. Another missense variant in the same codon, NM_001034853.2(RPGR):c.592G>A (p.Gly198Arg) (PMIDs: 34985506, 31456290), has been classified as pathogenic for RPGR-related retinopathy based on the ClinGen X-linked IRD VCEP specifications, while no benign missense variants have been identified in this codon. However, the present variant has a lower Grantham’s distance (98) than the comparison variant (125), so the PM5 code has not been applied. 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 (PMID: 18552978, PMID: 32821524, PS4_Supporting). At least one proband harboring the variant exhibits a phenotype including diagnosis at age 25 years, extinguished electroretinogram responses from both rods and cones, night blindness (0.5 pts), visual field defects (0.5 pts), and reduced visual acuity (0.5 pts), which together are not sufficiently specific for RPGR-related retinopathy, so PP4 is not met (1.5 points, PMID: 32821524). The computational predictor REVEL gives a score of 0.980, 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 0.15 for donor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not strongly predict that the variant disrupts RPGR splicing. 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; PS4_Supporting, PP3_Strong, and PM2_Supporting.

Met criteria codes

PP3_Strong



The computational predictor REVEL gives a score of 0.980, 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 0.15 for donor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not strongly predict that the variant disrupts RPGR 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 (PMID: 18552978, PMID: 32821524, PS4_Supporting).

Not Met criteria codes

PS1			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
PP4			At least one proband harboring the variant exhibits a phenotype including diagnosis at age 25 years, extinguished ERG responses from both rods and cones, night blindness (0.5 pts), visual field defects (0.5 pts), fundus findings including attenuated vessels, retinal atrophy (0.5 pts), and bone spicules, and reduced visual acuity (0.5 pts), which together are not sufficiently specific for RPGR-related retinopathy, so PP4 is not met (2 points, PMID: 32821524).
PM5			Another missense variant in the same codon, NM_001034853.2(RPGR):c.592G>A (p.Gly198Arg) (PMIDs: 34985506, 31456290), is classified as pathogenic for RPGR-related retinopathy based on the ClinGen X-linked IRD VCEP specifications, while no benign missense variants have been identified in this codon. The present variant has a lower Grantham’s distance (98) than the comparison variant (125), and therefore, the PM5 code is not applied
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			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS2			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PVS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS1			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS4			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

BP4			REVEL score = 0.980
BP3			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP7			No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History 		
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