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Variant: NM_001034853.2(RPGR):c.283G>A (p.Gly95Arg)

Version: 1.0

CA412745404

2430151 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: d875bbdf-5dd9-426a-b1f6-191b95cdb435
Approved on: 2025/9/5
Published on: 2025/9/5

HGVS expressions

NM_001034853.2(RPGR):c.283G>A (p.Gly95Arg)
NM_001034853.2:c.283G>A
NC_000023.11:g.38321054C>T
CM000685.2:g.38321054C>T
NC_000023.10:g.38180307C>T
CM000685.1:g.38180307C>T
NC_000023.9:g.38065251C>T
NG_009553.1:g.11482G>A
ENST00000642170.1:n.693G>A
ENST00000642373.1:c.283G>A
ENST00000642395.2:c.283G>A
ENST00000642558.1:c.190G>A
ENST00000642739.1:c.283G>A
ENST00000644238.1:c.283G>A
ENST00000644337.1:c.283G>A
ENST00000645032.1:c.283G>A
ENST00000645124.1:c.283G>A
ENST00000646020.1:c.283G>A
ENST00000647261.1:c.283G>A
ENST00000318842.11:c.283G>A
ENST00000339363.7:c.283G>A
ENST00000378505.6:c.283G>A
ENST00000465127.1:c.172-345067C>T
ENST00000474584.5:c.283G>A
ENST00000482855.5:c.283G>A
NM_000328.2:c.283G>A
NM_001034853.1:c.283G>A
NM_001367245.1:c.283G>A
NM_001367246.1:c.283G>A
NM_001367247.1:c.283G>A
NM_001367248.1:c.313G>A
NM_001367249.1:c.283G>A
NM_001367250.1:c.283G>A
NM_001367251.1:c.283G>A
NR_159803.1:n.425G>A
NR_159804.1:n.425G>A
NR_159805.1:n.425G>A

NR_159806.1:n.425G>A
NR_159807.1:n.425G>A
NR_159808.1:n.693G>A
NM_000328.3:c.283G>A

Pathogenic

Met criteria codes 5

PP3_Strong | PP1_Moderate | PM5_Supporting | PP4_Moderate | PM2_Supporting

Not Met criteria codes 3

BA1 | BS1 | 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 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.283G>A (p.Gly95Arg) is a missense variant that replaces glycine with arginine at amino acid 95. Another missense variant in the same codon, NM_001034853.2(RPGR):c.284G>A (p.Gly95Glu) (PMID: 33598457), has been classified as likely 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 (125) than the comparison variant (98), 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). At least one proband harboring this variant exhibits rod-cone dystrophy (1 pt) with onset during the teens (1 pt), genotyping by next-generation sequencing with a 105-gene panel that did not identify an alternative cause of retinal disease (2 pts), family history consistent with X-linked inheritance (2 pt) with female family members showing milder phenotypes (1 pt), reduced visual acuity (0.5 pts), and fundus mid-peripheral atrophy (0.5 pts), which together are highly specific for RPGR-related retinopathy (8 total pts, PMID: 28488341; PMID: 36882936, PP4_Moderate). The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_Moderate; PMID: 28488341, PMID: 36882936). The computational predictor REVEL gives a score of 0.972, 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 0.19 for donor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RPGR splicing. 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, PM5_Supporting, PP1_Moderate, PP3_Strong, and PP4_Moderate.

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.972, 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 0.19 for donor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RPGR splicing.
PP1_Moderate	✔	The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_moderate; PMID: 28488341, PMID: 36882936).

PM5_Supporting	✔	Another missense variant in the same codon, NM_001034853.2(RPGR):c.284G>A (p.Gly95Glu) (PMID: 33598457), has been classified as likely 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 (125) than the comparison variant (98), and SpliceAI has been used to confirm that neither variant has a predicted impact on RPGR splicing (PM5_Supporting).
PP4_Moderate	✔	At least one proband harboring this variant exhibits rod-cone dystrophy (1 pt) with onset during the teens (1 pt), genotyping by next-generation sequencing with a 105-gene panel that did not identify an alternative cause of retinal disease (2 pts), family history consistent with X-linked inheritance (2 pt) with female family members showing milder phenotypes (1 pt), reduced visual acuity (0.5 pts), and fundus mid-peripheral atrophy and pigment (0.5 pts) (8 total pts, PMID: 28488341; PMID: 36882936, PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

BA1	✖	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
PS4	✖	This variant has been reported in at least 1 proband not 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: 28863407).

Curation History

Showing 1 to 1 of 1 rows

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