The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_001034853.2(RPGR):c.178G>A (p.Gly60Ser)

Version: 1.0

CA412745655

1676154 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: 2e328e2b-d75b-41e5-83fd-345b83e7b508
Approved on: 2025/8/3
Published on: 2025/8/4

HGVS expressions

NM_001034853.2:c.178G>A
NM_001034853.2(RPGR):c.178G>A (p.Gly60Ser)
NC_000023.11:g.38322922C>T
CM000685.2:g.38322922C>T
NC_000023.10:g.38182175C>T
CM000685.1:g.38182175C>T
NC_000023.9:g.38067119C>T
NG_009553.1:g.9614G>A
ENST00000642170.1:n.588G>A
ENST00000642373.1:c.178G>A
ENST00000642395.2:c.178G>A
ENST00000642558.1:c.154+477G>A
ENST00000642739.1:c.178G>A
ENST00000644238.1:c.178G>A
ENST00000644337.1:c.178G>A
ENST00000645032.1:c.178G>A
ENST00000645124.1:c.178G>A
ENST00000646020.1:c.178G>A
ENST00000647261.1:c.178G>A
ENST00000318842.11:c.178G>A
ENST00000339363.7:c.178G>A
ENST00000378505.6:c.178G>A
ENST00000465127.1:c.172-343199C>T
ENST00000474584.5:c.178G>A
ENST00000482855.5:c.178G>A
NM_000328.2:c.178G>A
NM_001034853.1:c.178G>A
NM_001367245.1:c.178G>A
NM_001367246.1:c.178G>A
NM_001367247.1:c.178G>A
NM_001367248.1:c.208G>A
NM_001367249.1:c.178G>A
NM_001367250.1:c.178G>A
NM_001367251.1:c.178G>A
NR_159803.1:n.320G>A
NR_159804.1:n.320G>A
NR_159805.1:n.320G>A

NR_159806.1:n.320G>A
NR_159807.1:n.320G>A
NR_159808.1:n.588G>A
NM_000328.3:c.178G>A

Likely Pathogenic

Met criteria codes 4

PP3_Strong PM2_Supporting PP1 PP4

Not Met criteria codes 12

PM1 PM5 BA1 BS1 BS4 BS3 BS2 BP4 BP1 PS3 PS4 PP2

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.178G>A (p.Gly60Ser) is a predicted missense variant that replaces glycine with serine at amino acid 60. Another missense variant in the same codon, NM_001034853.2(RPGR):c.179G>T (p.Gly60Val), 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. However, the present variant has a lower Grantham's distance (56) than the comparison variant (109), so the PM5_Supporting code is not met. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including diagnosis of rod-cone dystrophy with childhood onset (1 pt), electroretinogram confirmation of rod involvement greater than cone (1pt), genotyping by next-generation sequencing using a 105-gene panel that did not identify an alternative cause of retinal disease (2 pts), family history consistent with X-linked inheritance (2 pts), night blindness (0.5 pts), and photophobia (0.5 pts), which together are specific for RPGR-related retinopathy (7 points, PMID: 28341476, https://c.peervoice.com/programs/505204504/downloads/PV_transcript_CHS_EN.pdf, PP4). The variant has been reported to segregate with retinal dystrophy through at least 2 affected meioses from 1 family (PP1; PMID: 28341476). The computational predictor REVEL gives a score of 0.944, which is above the ClinGen X-linked IRD VCEP threshold of ≥ 0.932 and predicts a damaging effect on RPGR function (PP3_Strong). Also, the computational splicing predictor SpliceAI gives delta scores of 0.35 for acceptor loss and 0.33 for donor loss, which are above the ClinGen X-linked IRD VCEP threshold of >0.2 and predict a damaging impact on 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; PM2_Supporting, PP4, PP1, and PP3_Strong. (date of approval 05/16/2025).

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.944, which is above the ClinGen X-linked IRD VCEP threshold of ≥ 0.932 and predicts a damaging effect on RPGR function (PP3_strong). In addition, the computational splicing predictor SpliceAI gives a delta score of 0.35 for acceptor loss, which is above the ClinGen X-linked IRD VCEP threshold of >0.2 and predicts a damaging impact on splicing.
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP1	✔	

The variant has been reported to segregate with retinal dystrophy through at least 2 affected meioses from 1 family (PP1; PMID: 28341476, https://c.peervoice.com/programs/505204504/downloads/PV_transcript_CHS_EN.pdf).

PP4	✔	At least one proband harboring this variant exhibits a phenotype including diagnosis of childhood-onset (1 pt) rod-cone dystrophy (rod involvement greater than cone, 1pt) with next-generation sequencing-based genotyping using a 105-gene panel that did not find an alternative cause of retinal disease (2 pts), family history consistent with X-linked inheritance (2 pts), night blindness (0.5 pts), and photophobia (0.5 pts), which together are specific for RPGR-related retinopathy (7 points, PMID: 28341476, https://c.peervoice.com/programs/505204504/downloads/PV_transcript_CHS_EN.pdf, PP4).

Not Met criteria codes

PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	The ClinGen X-linked IRD VCEP has previously classified a different amino acid change at the same position (Gly60Val) as likely pathogenic. However, the Grantham's distance for glycine-to-serine is less (56) than for glycine-to-valine (109), so PM5_Supporting is not met.
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
BS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3	✖	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
BP4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1	✖	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	✖	This variant has been reported in at least 1 proband meeting the PS4 requirement of some functional vision impairment in affected males by age 30 (PMID: 28341476). However, PS4_Supporting requires at least 2 unrelated

probands, so this criterion was not met.

PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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