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Variant: NM_001034853.2(RPGR):c.179G>T (p.Gly60Val)

Version: 2.0

CA226376

9902 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: bdcbb5e9-e036-4b2c-b52f-141135ed6a6e
Approved on: 2025/5/21
Published on: 2025/5/21

HGVS expressions

NM_001034853.2:c.179G>T
NM_001034853.2(RPGR):c.179G>T (p.Gly60Val)
NC_000023.11:g.38322921C>A
CM000685.2:g.38322921C>A
NC_000023.10:g.38182174C>A
CM000685.1:g.38182174C>A
NC_000023.9:g.38067118C>A
NG_009553.1:g.9615G>T
ENST00000642170.1:n.589G>T
ENST00000642373.1:c.179G>T
ENST00000642395.2:c.179G>T
ENST00000642558.1:c.154+478G>T
ENST00000642739.1:c.179G>T
ENST00000644238.1:c.179G>T
ENST00000644337.1:c.179G>T
ENST00000645032.1:c.179G>T
ENST00000645124.1:c.179G>T
ENST00000646020.1:c.179G>T
ENST00000647261.1:c.179G>T
ENST00000318842.11:c.179G>T
ENST00000339363.7:c.179G>T
ENST00000378505.6:c.179G>T
ENST00000465127.1:c.172-343200C>A
ENST00000474584.5:c.179G>T
ENST00000482855.5:c.179G>T
NM_000328.2:c.179G>T
NM_001034853.1:c.179G>T
NM_001367245.1:c.179G>T
NM_001367246.1:c.179G>T
NM_001367247.1:c.179G>T
NM_001367248.1:c.209G>T
NM_001367249.1:c.179G>T
NM_001367250.1:c.179G>T
NM_001367251.1:c.179G>T
NR_159803.1:n.321G>T
NR_159804.1:n.321G>T
NR_159805.1:n.321G>T

NR_159806.1:n.321G>T
NR_159807.1:n.321G>T
NR_159808.1:n.589G>T
NM_000328.3:c.179G>T

Likely Pathogenic

Met criteria codes 5

PP3_Strong PP4 PM2_Supporting PP1_Moderate PS3_Supporting

Not Met criteria codes 21

PS1 PS2 PS4 PP2 PM1 PM3 PM5 PM4 PM6 BA1 BS2 PVS1 BS1 BS4 BS3 BP4 BP3 BP1 BP2 BP5 BP7

Evidence Links 1

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.179G>T (p.Gly60Val) is a missense variant that replaces glycine with valine at amino acid 60. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_supporting). At least one proband harboring this variant exhibits a phenotype including family history consistent with X-linked inheritance (2 pts) with delayed or milder phenotype in females (1 pt), visual field reduction (0.5 pts), central vision problem (0.5 pts) since 6 years of age (1 pt), poor night vision (0.5 pts), pigmentary retinopathy (0.5 pts), and nondetectable electroretinogram responses, which together are specific for RPGR-related retinopathy (6 points, PMID: 9855162, PP4). This variant has been reported in other publications, however, the ability to conclude that the probands described are unrelated was not successful (PMIDs: 28559085, 10937588, 34985506, 9399904, 9855162). The variant has been reported to segregate with retinal dystrophy through at least 4 meioses from at least 1 family (PP1_moderate; PMID: [9855162]). The computational predictor REVEL gives a score of 0.98, 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 acceptor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RPGR splicing. Exogenously expressed RPGR harboring the variant exhibits reduced interaction with RPGRIP1 in a yeast-2-hybrid experiment (PMID: 23213406, 23213406, PS3_supporting). 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_moderate, PP3_strong, PS3_supporting, and PP4. (date of approval 05/16/2025).

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.98, 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 acceptor loss, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RPGR splicing.
PP4	✔	At least one proband harboring this variant exhibits a phenotype including family history consistent with X-linked inheritance (2 pts) with delayed or milder phenotype in females (1 pt), visual field reduction (0.5 pts), central vision problem (0.5 pts) since 6 years of age (1 pt), poor night vision (0.5 pts), pigmentary retinopathy (0.5 pts), and

nondetectable electroretinogram responses, which together are specific for RPGR-related retinopathy (6 points, PMID: 9855162, PP4).

PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP1_Moderate	✔	The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from at least 1 family. (PP1_Moderate; PMID: [9855162]).
PS3_Supporting	✔	Exogenously expressed RPGR harboring the variant exhibits reduced interaction with RPGRIP1 in a yeast-2-hybrid experiment (PMID: 23213406, 23213406, PS3_Supporting) Wild-type or variant RPGR was expressed from the pBD plasmid as the bait in a yeast-two-hybrid system, with co-transfection into yeast with pAD-RPGRIP1. Interaction was measured by transactivation of genes allowing growth in HIS-, LEU-, or TRP-deficient media. Maximum specific growth rate reduced by 25% to 75% relative to the wild-type (E463X) control. PubMed:23213406

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
PS4	✖	This variant has been reported in other publications, however, the ability to conclude that the probands described are unrelated was not successful (PMIDs: 28559085, 10937588, 34985506, 9399904, 9855162).
PP2	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM1	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM3	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
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		✖	This variant is absent in gnomAD v.2.1.1.
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		✖	This variant is absent in gnomAD v.2.1.1.
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
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	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
BP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP5		✖	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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