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Variant: NM_001034853.2:c.284G>A

Version: 1.0

CA412745399

3249360 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 962f3480-94ab-44f2-8e4b-744d390132df
Approved on: 2025/9/5
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HGVS expressions

NM_001034853.2:c.284G>A
NC_000023.11:g.38321053C>T
CM000685.2:g.38321053C>T
NC_000023.10:g.38180306C>T
CM000685.1:g.38180306C>T
NC_000023.9:g.38065250C>T
NG_009553.1:g.11483G>A
ENST00000642170.1:n.694G>A
ENST00000642373.1:c.284G>A
ENST00000642395.2:c.284G>A
ENST00000642558.1:c.191G>A
ENST00000642739.1:c.284G>A
ENST00000644238.1:c.284G>A
ENST00000644337.1:c.284G>A
ENST00000645032.1:c.284G>A
ENST00000645124.1:c.284G>A
ENST00000646020.1:c.284G>A
ENST00000647261.1:c.284G>A
ENST00000318842.11:c.284G>A
ENST00000339363.7:c.284G>A
ENST00000378505.6:c.284G>A
ENST00000465127.1:c.172-345068C>T
ENST00000474584.5:c.284G>A
ENST00000482855.5:c.284G>A
NM_000328.2:c.284G>A
NM_001034853.1:c.284G>A
NM_001367245.1:c.284G>A
NM_001367246.1:c.284G>A
NM_001367247.1:c.284G>A
NM_001367248.1:c.314G>A
NM_001367249.1:c.284G>A
NM_001367250.1:c.284G>A
NM_001367251.1:c.284G>A
NR_159803.1:n.426G>A
NR_159804.1:n.426G>A
NR_159805.1:n.426G>A
NR_159806.1:n.426G>A

NR_159807.1:n.426G>A
NR_159808.1:n.694G>A
NM_000328.3:c.284G>A

Likely Pathogenic

Met criteria codes 5

PP3_Strong PS4_Moderate PM2_Supporting PP1 PP4

Not Met criteria codes 1

PM5

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.284G>A (p.Gly95Glu) is a missense variant that replaces glycine with glutamic acid at amino acid 95. Another missense variant in the same codon, NM_001034853.2(RPGR):c.283G>A (p.Gly95Arg; PMID: 28488341) 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. Glycine-to-glutamate has a lower Grantham's distance (98) than the glycine-to-arginine (125), so PM5_Supporting cannot be met. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 3 apparently unrelated probands meeting one of the PS4 requirements of some functional vision impairment in affected males by age 30 years, and/or decreased or absent electroretinogram responses (PMID: 33598457, PMID: 34287692, PMID: 36445968, PS4_Moderate). At least one proband harboring this variant exhibits a phenotype including childhood onset (1 pt), rod-specific b-wave that was reduced or undetectable (1 pt), accumulation of bone spicules (0.5 pts), and reduced visual acuity (0.5 pts), with genotyping by exome sequencing using a 77-gene panel followed by a 161-gene panel that did not identify an alternative basis for retinal disease (2 pts), which together are specific for RPGR-related retinopathy (5 points, PMID 28512305, PP4). The variant has been reported to segregate with retinal dystrophy through at least 2 affected meioses from 1 family (PP1; PMID: [33598457]). The computational predictor REVEL gives a score of 0.983, which is above the ClinGen X-linked IRD VCEP threshold of ≥0.932 and predicts a damaging effect on RPGR function (PP3_Strong). 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, PS4_Moderate, PP3_Strong, PP4, and PP1.

Met criteria codes

PP3_Strong	✔	The computational predictor REVEL gives a score of 0.983, which is above the ClinGen X-linked IRD VCEP threshold of ≥ 0.932 and predicts a damaging effect on RPGR function (PP3_strong).
PS4_Moderate	✔	This variant has been reported in at least 3 apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30, with decreased or absent cone and/or rod ERG responses (PMIDs: 33598457, 34287692, and 36445968, PS4_Moderate).
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: [33598457]).

PP4 ✔

At least one proband harboring this variant exhibits a phenotype including WES sequencing using first a 77-gene panel and then another 161-gene panel (2 pts), Childhood-onset (1 pt), rod-specific b wave that was reduced or undetectable (1 pt), accumulation of bone spicules (0.5 pts), Vision OD hand movement OS 0.3 (0.5 pts), which together are specific for RPGR-related retinopathy (5 points, PMID 28512305, PP4).

Not Met criteria codes

PM5 ✖

Another missense variant in the same codon, NM_001034853.2(RPGR):c.283G>A (p.Gly95Arg; PMID: 28488341) has been classified as a variant of uncertain significance for RPGR-related retinopathy by the ClinGen X-linked IRD VCEP, while no benign missense variants have been identified in this codon. Glycine-to-glutamate has a lower Grantham's distance (98) than the glycine-to-arginine (125), so PM5_Supporting cannot be met.

Curation History

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