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Variant: NM_001034853.2(RPGR):c.823G>T (p.Gly275Cys)

Version: 1.0

CA412741594

2118600 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 008fde91-e932-4956-901c-e2ad7c8c1e7a
Approved on: 2025/9/7
Published on: 2025/9/8

HGVS expressions

NM_001034853.2(RPGR):c.823G>T (p.Gly275Cys)
NM_001034853.2:c.823G>T
NC_000023.11:g.38304746C>A
CM000685.2:g.38304746C>A
NC_000023.10:g.38163999C>A
CM000685.1:g.38163999C>A
NC_000023.9:g.38048943C>A
NG_009553.1:g.27790G>T
ENST00000494707.6:c.27G>T
ENST00000642170.1:n.1189-3375G>T
ENST00000642373.1:c.*402G>T
ENST00000642395.2:c.823G>T
ENST00000642558.1:c.730G>T
ENST00000642739.1:c.823G>T
ENST00000644238.1:c.823G>T
ENST00000644337.1:c.823G>T
ENST00000645032.1:c.823G>T
ENST00000645124.1:c.823G>T
ENST00000646020.1:c.823G>T
ENST00000647261.1:c.823G>T
ENST00000318842.11:c.823G>T
ENST00000339363.7:c.823G>T
ENST00000378505.6:c.823G>T
ENST00000465127.1:c.172-361375C>A
ENST00000474584.5:c.823G>T
ENST00000482855.5:c.823G>T
ENST00000494841.1:n.86G>T
NM_000328.2:c.823G>T
NM_001034853.1:c.823G>T
NM_001367245.1:c.820G>T
NM_001367246.1:c.823G>T
NM_001367247.1:c.823G>T
NM_001367248.1:c.853G>T
NM_001367249.1:c.820G>T
NM_001367250.1:c.820G>T
NM_001367251.1:c.823G>T
NR_159803.1:n.965G>T

NR_159804.1:n.874G>T
NR_159805.1:n.965G>T
NR_159806.1:n.965G>T
NR_159807.1:n.965G>T
NR_159808.1:n.1189-3375G>T
NM_000328.3:c.823G>T

Likely Pathogenic

Met criteria codes 3

PM5_Supporting PP3_Strong PM2_Supporting

Not Met criteria codes 1

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.823G>T (p.Gly275Cys) is a missense variant causing substitution of glycine by cysteine at amino acid 275. Another missense variant in the same codon, NM_001034853.2:c.823G>A (p.Gly275Ser) (PMID: 17480003, PMID: 31456290, PMID: 17724181, PMID: 16969763, PMID: 8817343), 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. The present variant has a higher Grantham's distance (159) than the comparison variant (56), 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). This variant has been reported in at least 2 apparently unrelated probands diagnosed with retinitis pigmenosa (PMID: 37217489). However, neither individual meets one of the PS4 requirements of some functional vision impairment in affected males by age 30 years, or decreased or absent electroretinogram responses, so PS4_Supporting was not met. The computational predictor REVEL gives a score of 0.968, 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, PM5_Supporting, and PP3_Strong.

Met criteria codes

PM5_Supporting	✔	Another missense variant in the same codon, NM_001034853.2:c.823G>A (p.Gly275Ser), (PMIDs: 17480003, 31456290, 17724181, 16969763, and 8817343) 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. The present variant has a higher Grantham's distance (159) than the comparison variant (56), and SpliceAI has been used to confirm that neither variant has a predicted impact on RPGR splicing (PM5_Supporting).
PP3_Strong	✔	The computational predictor REVEL gives a score of 0.968, which is above the ClinGen X-linked IRD VCEP threshold of ≥ 0.932 and predicts a damaging effect on RPGR function (PP3_Strong). The splicing impact predictor SpliceAI gives a score of 0.02 for splice acceptor gain, which is below the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and does not predict a damaging impact on splicing.

PM2_Supporting		✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PS4		✖	This variant has been reported in at least 2 apparently unrelated probands diagnosed with retinitis pigmenosa (PMID: 37217489). However, neither individual meets one of the PS4 requirements of some functional vision impairment in affected males by age 30, or decreased or absent cone and/or rod ERG responses, so PS4_Supporting was not met.

Curation History

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