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Variant: NM_001034853.2(RPGR):c.308C>T (p.Thr103Ile)

Version: 1.0

CA412745351

1356123 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: de426fc2-1cc7-4689-ae73-8b40b12fffbf
Approved on: 2025/5/20
Published on: 2025/5/21

HGVS expressions

NM_001034853.2:c.308C>T
NM_001034853.2(RPGR):c.308C>T (p.Thr103Ile)
NC_000023.11:g.38321029G>A
CM000685.2:g.38321029G>A
NC_000023.10:g.38180282G>A
CM000685.1:g.38180282G>A
NC_000023.9:g.38065226G>A
NG_009553.1:g.11507C>T
ENST00000642170.1:n.718C>T
ENST00000642373.1:c.308C>T
ENST00000642395.2:c.308C>T
ENST00000642558.1:c.215C>T
ENST00000642739.1:c.308C>T
ENST00000644238.1:c.308C>T
ENST00000644337.1:c.308C>T
ENST00000645032.1:c.308C>T
ENST00000645124.1:c.308C>T
ENST00000646020.1:c.308C>T
ENST00000647261.1:c.308C>T
ENST00000318842.11:c.308C>T
ENST00000339363.7:c.308C>T
ENST00000378505.6:c.308C>T
ENST00000465127.1:c.172-345092G>A
ENST00000474584.5:c.308C>T
ENST00000482855.5:c.308C>T
NM_000328.2:c.308C>T
NM_001034853.1:c.308C>T
NM_001367245.1:c.308C>T
NM_001367246.1:c.308C>T
NM_001367247.1:c.308C>T
NM_001367248.1:c.338C>T
NM_001367249.1:c.308C>T
NM_001367250.1:c.308C>T
NM_001367251.1:c.308C>T
NR_159803.1:n.450C>T
NR_159804.1:n.450C>T
NR_159805.1:n.450C>T

NR_159806.1:n.450C>T
NR_159807.1:n.450C>T
NR_159808.1:n.718C>T
NM_000328.3:c.308C>T

Likely Pathogenic

Met criteria codes 4

PP1_Moderate PP4_Moderate PM2_Supporting PP3_Moderate

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.308C>T (p.Thr103Ile) is a missense variant in the final codon of exon 4 and is predicted to encode substitution of threonine with isoleucine in codon 103. The computational predictor REVEL gives a score of 0.819, which is between the ClinGen X-linked IRD VCEP threshold of 0.773 to 0.931 and predicts a damaging effect on RPGR function (PP3_moderate). The splicing impact predictor SpliceAI gives a score of 0.63 for donor loss and 0.59 for acceptor loss, which are above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predict a damaging impact on splicing. 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 early onset (1 pt), family history consistent with X-linked inheritance (2) including delayed or milder phenotype in females (1 pt), genotyping by next-generation sequencing-based retinal panel identifying no alternative cause of disease (2 pts), rod involvement greater than cone (1 pt), decreased central vision acuity (0.5 pts), and bone spicule pigmentation (0.5 pts) which together are highly specific for RPGR-related retinopathy (8 points, communication with clinical researcher regarding unpublished proband, PP4_moderate). The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_moderate; communication with clinical researcher regarding unpublished proband). 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_moderate, and PP4_moderate. (date of approval 05/16/2025).

Met criteria codes

PP1_Moderate	✔	The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_moderate; communication with clinical researcher regarding unpublished proband).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including early onset (1), family history consistent of X-linked inheritance (2), genotyping by next-generation sequencing-based retinal panel identifying no other causes of disease (2), rod involvement higher than cone (1), delayed or milder phenotype in females (1), decreased central vision acuity (0.5), and bone spicule pigmentation (0.5) which together are highly specific for RPGR-related recessive retinopathy (8 points, communication with clinical researcher regarding unpublished proband, PP4_moderate).

PM2_Supporting		✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PP3_Moderate		✔	The computational predictor REVEL gives a score of 0.819, which is between the ClinGen X-linked IRD VCEP threshold of 0.773 to 0.931 and predicts a damaging effect on RPGR function (PP3_Moderate). The splicing impact predictor SpliceAI gives a score of 0.63 for donor loss and 0.59 for acceptor loss, which is above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing.

Curation History

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