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Variant: NM_001034853.2(RPGR):c.617C>T (p.Thr206Ile)

Version: 1.0

CA412744378

449508 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: e65dda71-2633-4f42-8d6a-608850f47d2b
Approved on: 2025/5/20
Published on: 2025/5/21

HGVS expressions

NM_001034853.2(RPGR):c.617C>T (p.Thr206Ile)
NM_001034853.2:c.617C>T
NC_000023.11:g.38317318G>A
CM000685.2:g.38317318G>A
NC_000023.10:g.38176571G>A
CM000685.1:g.38176571G>A
NC_000023.9:g.38061515G>A
NG_009553.1:g.15218C>T
ENST00000642170.1:n.1027C>T
ENST00000642373.1:c.*196C>T
ENST00000642395.2:c.617C>T
ENST00000642558.1:c.524C>T
ENST00000642739.1:c.617C>T
ENST00000644238.1:c.617C>T
ENST00000644337.1:c.617C>T
ENST00000645032.1:c.617C>T
ENST00000645124.1:c.617C>T
ENST00000646020.1:c.617C>T
ENST00000647261.1:c.617C>T
ENST00000318842.11:c.617C>T
ENST00000339363.7:c.617C>T
ENST00000378505.6:c.617C>T
ENST00000465127.1:c.172-348803G>A
ENST00000470183.1:n.310C>T
ENST00000474584.5:c.617C>T
ENST00000482855.5:c.617C>T
NM_000328.2:c.617C>T
NM_001034853.1:c.617C>T
NM_001367245.1:c.617C>T
NM_001367246.1:c.617C>T
NM_001367247.1:c.617C>T
NM_001367248.1:c.647C>T
NM_001367249.1:c.614C>T
NM_001367250.1:c.617C>T
NM_001367251.1:c.617C>T
NR_159803.1:n.759C>T
NR_159804.1:n.670+89C>T

NR_159805.1:n.759C>T
NR_159806.1:n.759C>T
NR_159807.1:n.759C>T
NR_159808.1:n.1027C>T
NM_000328.3:c.617C>T

Likely Pathogenic

Met criteria codes 5

PP4 PP1_Moderate PP3_Moderate PM2_Supporting PS1_Moderate

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.617C>T (p.Thr206Ile) is a missense variant in the last codon of RPGR exon 6 encoding substitution of threonine with isoleucine at amino acid 206 and potentially affecting RPGR splicing. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.883, 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 0.41 for splice donor loss, which is below the ClinGen X-linked IRD VCEP recommended PP3 threshold of ≥0.2 and but indicates the possibility of a damaging impact on splicing. At least one proband harboring this variant exhibits a phenotype including early onset (1 pt), family pedigree consistent with X-linked inheritance (2 pts), with delayed or milder phenotype in females (1 pt), night blindness (0.5 pts), decreased central visual acuity (0.5 pts), and visual field constriction (0.5 pts), which together are specific for RPGR-related retinopathy (5.5 points, PP4, PMID: 21857984, with author communication of clinical details). The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_Moderate; PMID: 21857984, with author confirmation of unpublished clinical details). This variant is outside the +/- 1,2 dinucleotide and meets the PP3 code and another variant in the same donor/acceptor motif, NM_001034853.2(RPGR):c.619+2T>A, was previously classified as pathogenic for RPGR-related retinopathy by the ClinGen X-linked IRD VCEP (PS1_moderate). 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, PS1_moderate, and PP4. (date of approval 05/16/2025).

Met criteria codes

PP4	✔	At least one proband harboring this variant exhibits a phenotype including early onset (1 pt), family pedigree consistent with X-linked inheritance (2 pts), night blindness (0.5 pts), decreased central vision acuity (0.5 pts), delayed or milder phenotype in females (1 pt), and visual field constriction (0.5 pts), which together are specific for RPGR-related retinopathy (5.5 points, PP4, PMID: 21857984 with author communication of clinical details).
PP1_Moderate	✔	The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_Moderate; PMID: 21857984 with author confirmation of unpublished clinical details).

PP3_Moderate		✔	The computational predictor REVEL gives a score of 0.883, 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 0.41 for splice donor loss, which is below the ClinGen X-linked IRD VCEP recommended PP3 threshold of ≥0.2 and but indicates the possibility of a damaging impact on splicing.
PM2_Supporting		✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PS1_Moderate		✔	This variant is outside the +/- 1,2 dinucleotide and applies the PP3 code and another variant in the same donor/acceptor motif, NM_001034853.2(RPGR):c.619+2T>A, was previously classified as pathogenic for RPGR-related retinopathy by the ClinGen X-linked IRD VCEP (PS1_moderate).

Not Met criteria codes

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 and/or decreased or absent ERG responses (PMIDs: 21857984). A second unrelated proband has not yet been found, so the PS4_Supporting code was not met.

Curation History

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