

Variant: *NM_001034853.2:c.296C>T*

Version: 1.0

CA412745374 [↗](#)

3028605 (ClinVar) [↗](#)

Gene: RPGR ([HGNC:6103](#))

Condition: RPGR-related retinopathy ([MONDO:0100437](#))

Inheritance Mode: X-linked inheritance (dominant (HP:0001423))

UUID: 7b9efe26-e164-4e0b-a4e7-2c5dea66623d

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HGVS expressions

NM_001034853.2:c.296C>T

NC_000023.11:g.38321041G>A

CM000685.2:g.38321041G>A

NC_000023.10:g.38180294G>A

CM000685.1:g.38180294G>A

NC_000023.9:g.38065238G>A

NG_009553.1:g.11495C>T

ENST00000642170.1:n.706C>T

ENST00000642373.1:c.296C>T

ENST00000642395.2:c.296C>T

ENST00000642558.1:c.203C>T

ENST00000642739.1:c.296C>T

ENST00000644238.1:c.296C>T

ENST00000644337.1:c.296C>T

ENST00000645032.1:c.296C>T

ENST00000645124.1:c.296C>T

ENST00000646020.1:c.296C>T

ENST00000647261.1:c.296C>T

ENST00000318842.11:c.296C>T

ENST00000339363.7:c.296C>T

ENST00000378505.6:c.296C>T

ENST00000465127.1:c.172-345080G>A

ENST00000474584.5:c.296C>T

ENST00000482855.5:c.296C>T

NM_000328.2:c.296C>T

NM_001034853.1:c.296C>T

NM_001367245.1:c.296C>T

NM_001367246.1:c.296C>T

NM_001367247.1:c.296C>T

NM_001367248.1:c.326C>T

NM_001367249.1:c.296C>T

NM_001367250.1:c.296C>T

NM_001367251.1:c.296C>T

NR_159803.1:n.438C>T

NR_159804.1:n.438C>T

NR_159805.1:n.438C>T

NR_159806.1:n.438C>T

NR_159807.1:n.438C>T
NR_159808.1:n.706C>T
NM_000328.3:c.296C>T

Likely Pathogenic

Met criteria codes 6

PS4_Supporting PP1_Moderate
PM2_Supporting PP3_Moderate PP4
PM5_Supporting

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.296C>T (p.Thr99Ile) is a missense variant predicted to substitute threonine with isoleucine at amino acid 99. 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), a family history consistent with X-linked inheritance (2 pt), visual field constriction (0.5 pts), and rod involvement greater than cone (1 pt), which together are specific for RPGR-related retinopathy (4.5pts, PMID: 21857984, PP4). This variant has been reported in at least 2 additional apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30 years or decreased or absent cone and/or rod electroretinogram responses (PMID: 32702353, 31213501, 21857984, PS4_supporting). The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1_moderate; PMID: 21857984). Another missense variant in the same codon, NM_001034853.2(RPGR):c.296C>A (p.Thr99Asn), (PMIDs: 32531858, 32702353, 10482958, and 28863407) has previously been classified as likely 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 (89) than the comparison variant (65), and SpliceAI has been used to confirm that neither variant has a predicted impact on RPGR splicing (PM5_Supporting). The computational predictor REVEL gives a score of 0.813, 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 computational splicing predictor SpliceAI gives a delta score of 0.03 for acceptor gain, which is below the ClinGen X-linked IRD VCEP threshold of >0.2 and does not predict that the variant disrupts RPGR splicing. 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, PP1_moderate, PP3_moderate, and PP4. (date of approval 05/16/2025).

Met criteria codes

PS4_Supporting  

This variant has been reported in at least 2 apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30, or decreased or absent cone and/or rod ERG responses (PMID: 32702353, 31213501, 21857984).

PP1_Moderate  

The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1; PMID: 21857984).

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 0.813, 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 computational splicing predictor SpliceAI gives a delta score of 0.03 for acceptor gain, 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 early onset (1 pt), a family history consistent with X-linked inheritance (2 pt), visual field constriction (0.5 pts), and rod involvement greater than cone (1 pt), which together are specific for RPGR-related retinopathy (4.5pts, PMID: 21857984, PP4).
PM5_Supporting			Another missense variant in the same codon, NM_001034853.2(RPGR):c.296C>A (p.Thr99Asn), (PMIDs: 32531858, 32702353, 10482958, and 28863407) has been classified as likely 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 (89) than the comparison variant (65), and SpliceAI has been used to confirm that neither variant has a predicted impact on RPGR splicing (PM5_Supporting).

Curation History 	
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