

Variant: NM_001034853.2(RPGR):c.922G>C (p.Ala308Pro)

Version: 1.0

CA270037 [↗](#)

143094 (ClinVar) [↗](#)

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

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

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

UUID: 1ec84574-6253-4687-af4b-51eb058a0e23

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HGVS expressions

NM_001034853.2:c.922G>C

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NC_000023.11:g.38304647C>G

CM000685.2:g.38304647C>G

NC_000023.10:g.38163900C>G

CM000685.1:g.38163900C>G

NC_000023.9:g.38048844C>G

NG_009553.1:g.27889G>C

ENST00000494707.6:c.126G>C

ENST00000642170.1:n.1189-3276G>C

ENST00000642395.2:c.922G>C

ENST00000642558.1:c.829G>C

ENST00000642739.1:c.922G>C

ENST00000644238.1:c.922G>C

ENST00000644337.1:c.922G>C

ENST00000645032.1:c.922G>C

ENST00000645124.1:c.922G>C

ENST00000646020.1:c.922G>C

ENST00000647261.1:c.922G>C

ENST00000318842.11:c.922G>C

ENST00000339363.7:c.922G>C

ENST00000378505.6:c.922G>C

ENST00000465127.1:c.172-361474C>G

ENST00000474584.5:c.922G>C

ENST00000482855.5:c.922G>C

ENST00000494841.1:n.185G>C

NM_000328.2:c.922G>C

NM_001034853.1:c.922G>C

NM_001367245.1:c.919G>C

NM_001367246.1:c.922G>C

NM_001367247.1:c.922G>C

NM_001367248.1:c.952G>C

NM_001367249.1:c.919G>C

NM_001367250.1:c.919G>C

NM_001367251.1:c.922G>C

NR_159803.1:n.1064G>C

NR_159804.1:n.973G>C

NR_159805.1:n.1064G>C
NR_159806.1:n.1064G>C
NR_159807.1:n.1064G>C
NR_159808.1:n.1189-3276G>C
NM_000328.3:c.922G>C

Likely Pathogenic

Met criteria codes 4

PP1_Moderate PP4 PP3_Moderate
PM2_Supporting

Not Met criteria codes 2

PS3 PS4

Evidence Links 1

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.922G>C (p.Ala308Pro) is a missense variant encoding substitution of alanine with proline at amino acid 308. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.904, which is between the ClinGen X-linked IRD VCEP thresholds 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 0.01 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. At least one proband harboring this variant exhibits a phenotype including early onset (1 pt) of night blindness (0.5 pts), decreased central visual acuity (0.5 pts), visual field constriction (0.5 pts), family history consistent with X-linked inheritance (2 pts), delayed or milder phenotype in females (1 pt), and next-generation sequencing-based genotyping identifying no alternative causes of retinal disease (2 pts), which together are specific for RPGR-related retinopathy (7.5 pts, PP4, PMID: 25324289). The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PP1; PMID: 26316687, PMID: 25324289). The variant has been included in multiple publications (PMIDs: 25324289, 26316687, and 26427425), however these have reported the same family, so PS4_Supporting was not met. In summary, this variant meets the criteria to be 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_supporting. (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; PMID: [26316687, 25324289]).
PP4			At least one proband harboring this variant exhibits a phenotype including early onset (1 pt) of night blindness (0.5 pts), decreased central vision acuity (0.5 pts), visual field constriction (0.5 pts), family history consistent with X-linked inheritance (2 pts), delayed or milder phenotype in females (1 pt), and next-generation sequencing-based genotyping identifying no alternative causes of retinal disease (2 pts), which together are specific for RPGR-related recessive retinopathy (7.5 pts, PP4, PMID: 25324289).

PP3_Moderate			The computational predictor REVEL gives a score of 0.904, 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 0.01 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.
PM2_Supporting			This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
Not Met criteria codes			
PS3			<p>Gerasimavicius et al. tried to predict variant effects by protein structural information and molecular mechanisms. This variant was tested as well (PMID: 32958805).</p> <p>Gerasimavicius et al. tried to predict variant effects by protein structural information and molecular mechanisms. This variant was tested as well. PubMed:32958805 </p>
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, with decreased or absent cone and/or rod ERG responses (PMIDs: 25324289, 26316687, 26427425). Since all three papers have reported the same family, PS4_Supporting was not met.

Curation History 			
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