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Variant: NM_001034853.2:c.1077T>A

Version: 1.0

CA412740056

3028600 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 67985d9c-a896-4822-9e22-d8e43468c20a
Approved on: 2025/8/1
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HGVS expressions

NM_001034853.2:c.1077T>A
NC_000023.11:g.38299124A>T
CM000685.2:g.38299124A>T
NC_000023.10:g.38158377A>T
CM000685.1:g.38158377A>T
NC_000023.9:g.38043321A>T
NG_009553.1:g.33412T>A
ENST00000494707.6:c.281T>A
ENST00000642170.1:n.1331T>A
ENST00000642395.2:c.1077T>A
ENST00000642558.1:c.984T>A
ENST00000642739.1:c.1077T>A
ENST00000644238.1:c.1060-1672T>A
ENST00000644337.1:c.1060-1672T>A
ENST00000645032.1:c.1077T>A
ENST00000645124.1:c.1077T>A
ENST00000646020.1:c.1137T>A
ENST00000318842.11:c.1077T>A
ENST00000339363.7:c.1077T>A
ENST00000378505.6:c.1077T>A
ENST00000464437.1:c.143T>A
ENST00000465127.1:c.172-366997A>T
ENST00000474584.5:c.1077T>A
ENST00000482855.5:c.1077T>A
ENST00000494841.1:n.340T>A
NM_000328.2:c.1077T>A
NM_001034853.1:c.1077T>A
NM_001367245.1:c.1074T>A
NM_001367246.1:c.1060-1672T>A
NM_001367247.1:c.1077T>A
NM_001367248.1:c.1107T>A
NM_001367249.1:c.1074T>A
NM_001367250.1:c.1074T>A
NM_001367251.1:c.1060-1672T>A
NR_159803.1:n.1279T>A
NR_159804.1:n.1128T>A
NR_159805.1:n.1219T>A

NR_159806.1:n.1219T>A
NR_159807.1:n.1219T>A
NR_159808.1:n.1331T>A
NM_000328.3:c.1077T>A

Pathogenic

Met criteria codes 3

PVS1 PP4_Moderate PM2_Supporting

Not Met criteria codes 1

PP1

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.1077T>A (p.Cys359Ter) is a nonsense variant that substitutes a premature stop codon for amino acid 359 within exon 10 of 15 and is predicted to trigger nonsense-mediated decay (PVS1). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). At least one proband harboring this variant exhibits a phenotype including a family history consistent with X-linked inheritance (2 pts) with a mildly affected female relative (1 pt), childhood onset (1 pt), high myopia (1 pt), night blindness (0.5 pts), reduced visual acuity (0.5 pts), and genotyping by next-generation sequencing panel that did not identify an alternative basis for retinal disease (2 pts) which together are highly specific for RPGR-related retinopathy (8 points, PMID: 30917587, PP4_Moderate). The variant has been reported to segregate with retinal dystrophy through the proband and his carrier mother from 1 family, however, the carrier was reportedly asymptomatic so this was not sufficient to meet the PP1 code (PMID: 30917587). In summary, this variant is classified as 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; PVS1, PM2_supporting, and PP4_moderate. (date of approval 05/16/2025).

Met criteria codes

PVS1	✔	This is a nonsense variant that introduces a premature stop codon between amino acids 1-1132 that is predicted to either trigger nonsense-mediated decay or to disrupt a critical C-terminal region required for proper glutamylation of RPGR (PVS1, PMID: 36445968).
PP4_Moderate	✔	At least one proband harboring this variant exhibits a phenotype including a family history consistent with X-linked inheritance (2 pts) including.a mildly affected female relative (1 pt), childhood-onset (1 pt), high myopia (1 pt), night blindness (0.5 pts), reduced visual acuity (0.5 pts), and genotyping by next-generation sequencing with a panel of genes that did not identify an alternative basis for retinal disease (2 pts) which together are highly specific for RPGR-related retinopathy (8 points, PMID: 30917587, PP4_Moderate).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

PP1	✖	The variant has been reported to segregate with retinal dystrophy through the proband and his carrier mother from 1 family, however, the carrier was reportedly asymptomatic so this was not sufficient to meet the PP1 code (PMID: 30917587).

Curation History

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