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Variant: NM_001034853.2:c.373G>T

Version: 1.0

CA412745199

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 47029be4-0883-4dd9-9d68-19549e149a90
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HGVS expressions

NM_001034853.2:c.373G>T
NC_000023.11:g.38318925C>A
CM000685.2:g.38318925C>A
NC_000023.10:g.38178178C>A
CM000685.1:g.38178178C>A
NC_000023.9:g.38063122C>A
NG_009553.1:g.13611G>T
ENST00000642170.1:n.783G>T
ENST00000642373.1:c.373G>T
ENST00000642395.2:c.373G>T
ENST00000642558.1:c.280G>T
ENST00000642739.1:c.373G>T
ENST00000644238.1:c.373G>T
ENST00000644337.1:c.373G>T
ENST00000645032.1:c.373G>T
ENST00000645124.1:c.373G>T
ENST00000646020.1:c.373G>T
ENST00000647261.1:c.373G>T
ENST00000318842.11:c.373G>T
ENST00000339363.7:c.373G>T
ENST00000378505.6:c.373G>T
ENST00000465127.1:c.172-347196C>A
ENST00000470183.1:n.66G>T
ENST00000474584.5:c.373G>T
ENST00000482855.5:c.373G>T
NM_000328.2:c.373G>T
NM_001034853.1:c.373G>T
NM_001367245.1:c.373G>T
NM_001367246.1:c.373G>T
NM_001367247.1:c.373G>T
NM_001367248.1:c.403G>T
NM_001367249.1:c.370G>T
NM_001367250.1:c.373G>T
NM_001367251.1:c.373G>T
NR_159803.1:n.515G>T
NR_159804.1:n.515G>T
NR_159805.1:n.515G>T

NR_159806.1:n.515G>T
NR_159807.1:n.515G>T
NR_159808.1:n.783G>T
NM_000328.3:c.373G>T

Pathogenic

Met criteria codes 3

PVS1 PM2_Supporting PP4

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.373G>T (p.Glu125Ter) is a nonsense variant that introduces a premature stop in codon 125 within exon 5 of 15, which 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 presentation with night blindness (0.5 pts) at age 3 years (1 pt), severely reduced visual acuity (0.5 pts), high myopia (1 pt), markedly reduced electroretinogram responses from rods, widespread retinal pigment epithelium degeneration in the fundus with mid-periphery pigment deposits (0.5 pts), optic disc pallor (0.5 pts), severe macular degeneration, and retinal vessel attenuation, with genotyping by next-generation sequencing of a panel of >300 genes identifying no alternative basis for inherited retinal disease (2 pts), which together are specific for RPGR-related retinopathy (6 points, PMID: 36276946, PP4). 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.

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).
PM2_Supporting	✔	This variant is absent from gnomAD v2.1.1 (PM2_Supporting).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including Early onset at age 3 (1 pts), night blindness (first symptom, 0.5 pts), reduced visual acuity- BCVA blind in both eyes (0.5 pts), high myopia (1 pt), diminished responses on ERG (markedly reduced rod responses in all patients.), Fundus appearance shown with widespread retinal pigment epithelium degeneration, mid-periphery pigment deposits (0.5 pts), Optic disc pallor (0.5 pts), severe macular degeneration and artery attenuation. The NGS using IRD panel (HEDEP) of 483 IRD genes (2 pts), which together are specific for RPGR-related retinopathy (6 points, PMID: 36276946, PP4).

Curation History

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