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Variant: NM_001034853.2(RPGR):c.2248G>T (p.Glu750Ter)

Version: 1.0

CA327916152

2099208 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 1d14eddf-504c-4239-b7dd-860bbcd06bdb
Approved on: 2025/8/4
Published on: 2025/8/4

HGVS expressions

NM_001034853.2:c.2248G>T
NM_001034853.2(RPGR):c.2248G>T (p.Glu750Ter)
NC_000023.11:g.38286751C>A
CM000685.2:g.38286751C>A
NC_000023.10:g.38146004C>A
CM000685.1:g.38146004C>A
NC_000023.9:g.38030948C>A
NG_009553.1:g.45785G>T
ENST00000494707.6:c.953+1114G>T
ENST00000642170.1:n.1826+4208G>T
ENST00000642395.2:c.1905+343G>T
ENST00000642739.1:c.1572+4208G>T
ENST00000644238.1:c.1386+4208G>T
ENST00000644337.1:c.1719+343G>T
ENST00000645032.1:c.2248G>T
ENST00000645124.1:c.*101+343G>T
ENST00000646020.1:c.*594+343G>T
ENST00000318842.11:c.1905+343G>T
ENST00000339363.7:c.2520+343G>T
ENST00000378505.6:c.2248G>T
ENST00000465127.1:c.172-379370C>A
ENST00000474584.5:c.*37+4208G>T
ENST00000482855.5:c.1905+343G>T
ENST00000494707.5:c.139+4208G>T
NM_000328.2:c.1905+343G>T
NM_001034853.1:c.2248G>T
NM_001367245.1:c.1902+343G>T
NM_001367246.1:c.1719+343G>T
NM_001367247.1:c.1572+4208G>T
NM_001367248.1:c.1602+4208G>T
NM_001367249.1:c.1569+4208G>T
NM_001367250.1:c.1569+4208G>T
NM_001367251.1:c.1386+4208G>T
NR_159803.1:n.2263+343G>T
NR_159804.1:n.1648+4208G>T
NR_159805.1:n.1714+4208G>T
NR_159806.1:n.1866+343G>T

NR_159807.1:n.1622+4208G>T
NR_159808.1:n.1826+4208G>T
NM_000328.3:c.1905+343G>T

Likely Pathogenic

Met criteria codes 2

PVS1 PM2_Supporting

Not Met criteria codes 3

PS4 PP1 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.2248G>T (p.Glu750Ter) is a nonsense variant that substitutes a premature stop in codon for amino acid 750 within exon 15 of 15, which is predicted to disrupt a critical C-terminal region required for proper glutamylation of RPGR (PVS1, PMID: 36445968). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 1 proband meeting one of the PS4 requirements of some functional vision impairment in affected males by age 30 years and/or decreased or absent electroretinogram responses, or a female with functional visual abnormality and documentation of an affected male relative (PMID: 34745198). However, PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met. The variant has been reported in a family in which 3 members are affected with retinal dystrophy, however, only the proband has been genotyped, so the PP1 code is not met (PMID: 34745198). At least one proband harboring this variant exhibits a phenotype including family history consistent with X-linked inheritance (2 pts), early onset (1 pts), night blindness (0.5 pts), reduced visual acuity (0.5 pts), and genetic testing with exome sequencing finding no alternative basis for retinal disease (2 pts), which together are specific for RPGR-related retinopathy (6 points, PMID: 34745198). However, the proband described is a female and PP4 requires a male, so the code is not met. 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; PVS1 and PM2_Supporting. (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).
PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).

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, with decreased or absent cone and/or rod ERG responses or a female with

functional visual abnormality and documentation of a male relative affected with retinitis pigmentosa (PMID: 34745198). However, PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met.

PP1	✖	The variant has been reported in a family in which 3 members are affected with retinal dystrophy, however, only the proband has been genotyped, so the PP1 code is not met (PMID: 34745198).
PP4	✖	At least one proband harboring this variant exhibits a phenotype including genetic testing with WES (2 pts), X-linked inheritance (2 pts), early onset (1 pts), night blindness (0.5 pts), reduced visual acuity (0.5 pts), which together are specific for RPGR-related retinopathy (6 points, PP4). However, using this code requires a male, and the proband is a female.

Curation History

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