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# *Variant: NM_001034853.2(RPGR):c.3034del (p.Glu1012fs)*

Version: 1.0

*CA2424844266*

*1012646 (ClinVar)*

**Gene**: RPGR (HGNC:6103)
**Condition**: RPGR-related retinopathy (MONDO:0100437)
**Inheritance Mode**: X-linked inheritance
**UUID:** a8e50325-a34e-43a6-878c-8627c01f96ea
**Approved on**: 2025/9/6
**Published on**: 2025/9/7

## *HGVS expressions*

**NM_001034853.2:c.3034del**
**NM_001034853.2(RPGR):c.3034del (p.Glu1012fs)**
NC_000023.11:g.38285965del
CM000685.2:g.38285965del
NC_000023.10:g.38145218del
CM000685.1:g.38145218del
NC_000023.9:g.38030162del
NG_009553.1:g.46571del
ENST00000494707.6:c.953+1900del
ENST00000642170.1:n.1826+4994del
ENST00000642395.2:c.1905+1129del
ENST00000642739.1:c.1572+4994del
ENST00000644238.1:c.1386+4994del
ENST00000644337.1:c.1719+1129del
ENST00000645032.1:c.3034del
ENST00000645124.1:c.*101+1129del
ENST00000646020.1:c.*594+1129del
ENST00000318842.11:c.1905+1129del
ENST00000339363.7:c.2520+1129del
ENST00000378505.6:c.3034del
ENST00000465127.1:c.172-380156del
ENST00000474584.5:c.*37+4994del
ENST00000482855.5:c.1905+1129del
ENST00000494707.5:c.139+4994del
NM_000328.2:c.1905+1129del
NM_001034853.1:c.3034del
NM_001367245.1:c.1902+1129del
NM_001367246.1:c.1719+1129del
NM_001367247.1:c.1572+4994del
NM_001367248.1:c.1602+4994del
NM_001367249.1:c.1569+4994del
NM_001367250.1:c.1569+4994del
NM_001367251.1:c.1386+4994del
NR_159803.1:n.2263+1129del
NR_159804.1:n.1648+4994del
NR_159805.1:n.1714+4994del
NR_159806.1:n.1866+1129del

NR_159807.1:n.1622+4994del
NR_159808.1:n.1826+4994del
NM_000328.3:c.1905+1129del

**Likely Pathogenic**

**Met criteria codes** 2

PVS1 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.3034del (p.Glu1012LysfsTer?) is a frameshift variant due to a 1-nucleotide deletion introducing a premature stop codon in 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 was confirmed to result in a 40% decrease in glutamylation of RPGR when co-transfected into HEK293 cells with the glutamylase TTLL5 (PMID: 36445968), however, PS3_Supporting was not scored as PVS1 has already been met. This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 apparently unrelated probands (PMIDs: 36445968, 30543658). However, the number of individuals meeting the PS4 requirement of some functional vision impairment in affected males by age 30 years, and/or decreased or absent electroretinogram responses was fewer than the requirement of at least 2 unrelated probands, so PS4_Supporting was 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.**

**Met criteria codes**

| | | |
|---|---|---|
| **PVS1** | ✔ | This is a frameshift 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**

| | | |
|---|---|---|
| **PS3** | ✖ | This variant resulted caused a 40% decrease in glutamylation of RPGR when co-transfected into HEK293 cells with the glutamylase TTLL5 (PMID: 36445968), however, PS3_Supporting was not scored as PVS1 has already been met.<br><br>Wild-type or variant RPGR was transfected into HEK293 cells along with a construct for expression of the glutamylase TTLL5. Glutamylation of RPGR by TTLL5 was measured by western blotting with antibodies that recognize RPGR and glutamylated proteins. PubMed:36445968 |

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|---|---|---|---|
| **PS4** | | ✖ | This variant has been reported in at least 2 apparently unrelated probands (PMIDs: 36445968, 30543658). However, the number of individuals 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 was fewer than the requirement of at least 2 unrelated probands, so PS4_Supporting was not met. |

## Curation History

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