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Variant: NM_001034853.2(RPGR):c.2236_2237del (p.Glu746fs)

Version: 1.0

CA645509417

438142 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance (dominant (HP:0001423))
UUID: ae6e2391-bae8-42d9-9522-9188513f030b
Approved on: 2025-05-20
Published on: 2025-05-21

HGVS expressions

NM_001034853.2:c.2236_2237del
NM_001034853.2(RPGR):c.2236_2237del (p.Glu746fs)
NC_000023.11:g.38286765_38286766del
CM000685.2:g.38286765_38286766del
NC_000023.10:g.38146018_38146019del
CM000685.1:g.38146018_38146019del
NC_000023.9:g.38030962_38030963del
NG_009553.1:g.45773_45774del
ENST00000494707.6:c.953+1102_953+1103del
ENST00000642170.1:n.1826+4196_1826+4197del
ENST00000642395.2:c.1905+331_1905+332del
ENST00000642739.1:c.1572+4196_1572+4197del
ENST00000644238.1:c.1386+4196_1386+4197del
ENST00000644337.1:c.1719+331_1719+332del
ENST00000645032.1:c.2236_2237del
ENST00000645124.1:c.*101+331_*101+332del
ENST00000646020.1:c.*594+331_*594+332del
ENST00000318842.11:c.1905+331_1905+332del
ENST00000339363.7:c.2520+331_2520+332del
ENST00000378505.6:c.2236_2237del
ENST00000465127.1:c.172-379356_172-379355del
ENST00000474584.5:c.*37+4196_*37+4197del
ENST00000482855.5:c.1905+331_1905+332del
ENST00000494707.5:c.139+4196_139+4197del
NM_000328.2:c.1905+331_1905+332del
NM_001034853.1:c.2236_2237del
NM_001367245.1:c.1902+331_1902+332del
NM_001367246.1:c.1719+331_1719+332del
NM_001367247.1:c.1572+4196_1572+4197del
NM_001367248.1:c.1602+4196_1602+4197del
NM_001367249.1:c.1569+4196_1569+4197del
NM_001367250.1:c.1569+4196_1569+4197del
NM_001367251.1:c.1386+4196_1386+4197del
NR_159803.1:n.2263+331_2263+332del
NR_159804.1:n.1648+4196_1648+4197del

NR_159805.1:n.1714+4196_1714+4197del
NR_159806.1:n.1866+331_1866+332del
NR_159807.1:n.1622+4196_1622+4197del
NR_159808.1:n.1826+4196_1826+4197del
NM_000328.3:c.1905+331_1905+332del

Pathogenic

Met criteria codes 5

PVS1 PP4 PP1_Strong PS4 PM2_Supporting

Not Met criteria codes 10

BP7 BP4 BP3 BP1 BS3 PP2 PM5 PM4 PS1 PS3

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.2236_2237del (p.Glu746ArgfsTer23) is a frameshift variant that introduces a premature stop codon into exon 15 of 15 before amino acid 1132, which is predicted not to trigger nonsense-mediated decay but rather to disrupt a critical C-terminal region required for proper glutamylation of RPGR (PVS1, PMID: 36445968). This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_supporting). At least one proband harboring this variant exhibits a phenotype including family history consistent with X-linked inheritance (2 pts), with delayed or milder phenotype in females (1 pt), and rod involvement greater than cone (1 pt), which together are specific for RPGR-related retinopathy (4 points, PP4). This variant has been reported in at least 33 apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30 years, or decreased / absent cone and/or rod electroretinogram responses (PMIDs: 20021257, 11950860, 16086276, 17093403, 34745198, 33247286, 33576794, 33090715, 23681342, 31213501, 22807293, 32531858, PS4). The variant has been reported to segregate with retinal dystrophy through at least 4 affected meioses from at least 2 families (PP1_strong; PMID: 21857984, 20021257, 11950860, 16086276, 17093403, 34745198). 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, PS4, PM2_supporting, PP1_strong, and PP4. (date of approval 05/16/2025).

Met criteria codes

PVS1	✔	This is a frameshift variant that introduces a premature stop codon into exon 15 of 15 before amino acid 1132, which is predicted not to trigger nonsense-mediated decay but rather to disrupt a critical C-terminal region required for proper glutamylation of RPGR (PVS1, PMID: 36445968).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including family history consistent with X-linked inheritance (2 pts), with delayed or milder phenotype in females (1 pt), and rod involvement greater than cone (1 pt), which together are specific for RPGR-related retinopathy (4 points, PP4).
PP1_Strong	✔	The variant has been reported to segregate with retinal dystrophy through at least 4 affected meioses from at least 2 families (PP1_Strong; PMID: 21857984, 20021257, 11950860, 16086276, 17093403, 34745198).

PS4		✔	This variant has been reported in at least 33 apparently unrelated probands meeting the PS4 requirement of some functional vision impairment in affected males by age 30, or decreased/absent cone and/or rod ERG responses (PMIDs: 20021257, 11950860, 16086276, 17093403, 34745198, 33247286, 33576794, 33090715, 23681342, 31213501, 22807293, 32531858, PS4).
PM2_Supporting		✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).

Not Met criteria codes

BP7		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BP1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
BS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PP2		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM5		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PM4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS1		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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