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Variant: NM_001034853.2(RPGR):c.1753G>A (p.Glu585Lys)

Version: 1.0

CA412736653

866825 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 75684f8c-dabc-479d-9d21-5091cea42680
Approved on: 2025/7/31
Published on: 2025/7/31

HGVS expressions

NM_001034853.2:c.1753G>A
NM_001034853.2(RPGR):c.1753G>A (p.Glu585Lys)
NC_000023.11:g.38287861C>T
CM000685.2:g.38287861C>T
NC_000023.10:g.38147114C>T
CM000685.1:g.38147114C>T
NC_000023.9:g.38032058C>T
NG_009553.1:g.44675G>A
ENST00000494707.6:c.953+4G>A
ENST00000642170.1:n.1826+3098G>A
ENST00000642395.2:c.1753G>A
ENST00000642739.1:c.1572+3098G>A
ENST00000644238.1:c.1386+3098G>A
ENST00000644337.1:c.1567G>A
ENST00000645032.1:c.1753G>A
ENST00000645124.1:c.1573-616G>A
ENST00000646020.1:c.*442+4G>A
ENST00000318842.11:c.1753G>A
ENST00000339363.7:c.1753G>A
ENST00000378505.6:c.1753G>A
ENST00000465127.1:c.172-378260C>T
ENST00000474584.5:c.*37+3098G>A
ENST00000482855.5:c.1753G>A
ENST00000494707.5:c.139+3098G>A
NM_000328.2:c.1753G>A
NM_001034853.1:c.1753G>A
NM_001367245.1:c.1750G>A
NM_001367246.1:c.1567G>A
NM_001367247.1:c.1572+3098G>A
NM_001367248.1:c.1602+3098G>A
NM_001367249.1:c.1569+3098G>A
NM_001367250.1:c.1569+3098G>A
NM_001367251.1:c.1386+3098G>A
NR_159803.1:n.2111+4G>A
NR_159804.1:n.1648+3098G>A
NR_159805.1:n.1714+3098G>A
NR_159806.1:n.1715-616G>A

NR_159807.1:n.1622+3098G>A
NR_159808.1:n.1826+3098G>A
NM_000328.3:c.1753G>A

Pathogenic

Met criteria codes 3

PP4 PM2_Supporting PVS1

Not Met criteria codes 3

PP3 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.1753G>A (p.Glu585Lys) is a missense variant located in the final nucleotide of exon 14, and encodes the substitution of glutamic acid with lysine at amino acid 585. The splicing impact predictor SpliceAI gives a score of 0.52 for donor gain, which is above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing. In vitro splicing studies confirm that the variant disrupts splicing of RPGR ORF15 and causes loss of transcript heterogeneity (PMID: 32788070). While these in silico and experimental findings would normally be counted under the PP3 and PS3_Supporting codes, respectively, they have been counted in combination as evidence of a loss-of-function effect (PVS1_RNA). 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 onset in first decade of life (1 pt), decreased visual acuity (0.5 pts), night blindness (0.5 pts), severe, diffuse, granular appearance and atrophy of retinal pigment epithelium (0.5 pts), bone-spicule pigmentation (0.5 pts), and arteriolar attenuation in mid-peripheral retina (0.5 pts), with genotyping by previous exome sequencing (2 pts), which together are highly specific for RPGR-related retinopathy (5.5 points, PMID: 32788070, 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_RNA, PM2_Supporting, and PP4. (date of approval 05/16/2025).

Met criteria codes

PP4	✔	At least one proband harboring this variant exhibits a phenotype including previous exome sequencing (2pts), onset in first decade (1pt), decreased visual acuity (.5pt), night blindness (.5 pt), severe, diffuse, granular appearance and atrophy of retinal pigment epithelium (.5 pts), bone-spicule pigmentation (.5 pts), arteriolar attenuation in mid-peripheral retina (.5 pts) which together are highly specific for RPGR-related retinopathy (5.5 points, PMID: 32788070, PP4)
PM2_Supporting	✔	This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting).
PVS1	✔	The RPGR E585K mutation disrupts splicing of RPGR ORF15 and causes loss of transcript heterogeneity (PMID: 32788070). While these in silico and experimental findings would normally be counted under the PP3 and PS3_Supporting codes, respectively, in combination, they have been counted as evidence of a loss-of-function effect (PVS1_RNA).

Not Met criteria codes

PP3	✖	The splicing impact predictor SpliceAI gives a score of 0.52 for donor gain, which is above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predicts a damaging impact on splicing (PP3)
PS3	✖	The RPGR E585K mutation disrupts splicing of RPGR ORF15 and causes loss of transcript heterogeneity. (PMID: 32788070) The RPGR E585K mutation disrupts splicing of RPGR ORF15 and causes loss of transcript heterogeneity. PubMed:32788070
PS4	✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline

Curation History

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