Variant: NM_001034853.2(RPGR):c.1307G>A (p.Gly436Asp)

Version: 1.0

CA226356

98738 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 259ad801-183d-474f-8b27-8da049e52853
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HGVS expressions

NM_001034853.2:c.1307G>A
NM_001034853.2(RPGR):c.1307G>A (p.Gly436Asp)
NC_000023.11:g.38297391C>T
CM000685.2:g.38297391C>T
NC_000023.10:g.38156644C>T
CM000685.1:g.38156644C>T
NC_000023.9:g.38041588C>T
NG_009553.1:g.35145G>A
ENST00000494707.6:c.511G>A
ENST00000642170.1:n.1561G>A
ENST00000642395.2:c.1307G>A
ENST00000642739.1:c.1307G>A
ENST00000644238.1:c.1121G>A
ENST00000644337.1:c.1121G>A
ENST00000645032.1:c.1307G>A
ENST00000645124.1:c.1307G>A
ENST00000646020.1:c.1367G>A
ENST00000318842.11:c.1307G>A
ENST00000339363.7:c.1307G>A
ENST00000378505.6:c.1307G>A
ENST00000465127.1:c.172-368730C>T
ENST00000474584.5:c.1307G>A
ENST00000482855.5:c.1307G>A
ENST00000494841.1:n.570G>A
NM_000328.2:c.1307G>A
NM_001034853.1:c.1307G>A
NM_001367245.1:c.1304G>A
NM_001367246.1:c.1121G>A
NM_001367247.1:c.1307G>A
NM_001367248.1:c.1337G>A
NM_001367249.1:c.1304G>A
NM_001367250.1:c.1304G>A
NM_001367251.1:c.1121G>A
NR_159803.1:n.1509G>A
NR_159804.1:n.1383G>A
NR_159805.1:n.1449G>A
NR_159806.1:n.1449G>A

NR_159807.1:n.1449G>A
NR_159808.1:n.1561G>A
NM_000328.3:c.1307G>A

Likely Pathogenic

Met criteria codes 5

PM2_Supporting PP3 PP4 PS4_Supporting PP1_Moderate

Not Met criteria codes 2

BP4 PS3

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.1307G>A (p.Gly436Asp) is a missense variant predicted to cause substitution of glycine by aspartate at amino acid 436. The computational predictor REVEL gives a score of 0.271, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.644 and does not predict a damaging effect on RPGR function. However, the splicing impact predictor SpliceAI gives delta scores of 0.48 for acceptor loss and 0.41 for acceptor gain, which are above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predict a deleterious impact on splicing (PP3). This variant is absent from gnomAD v4.1.0 (PM2_Supporting). This variant has been reported in at least 2 apparently unrelated probands 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 (PMID: 26164827, PMID: 36445968, PMID: 32209785, PMID: 32098976, and PMID: 28863407, PS4_Supporting). At least one proband harboring this variant exhibits a phenotype including a family history consistent with X-linked inheritance (2 pts), showing a milder phenotype in affected females (1 pt), reduced visual acuity (0.5 pts), and visual field constriction (0.5 pts), which together are specific for RPGR-related retinopathy (4 points, PMID: 10937588, PP4). The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PMID: 10937588, PP1_Moderate). 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; PP3, PM2_Supporting, PS4_Supporting, PP4, and PP1_Moderate.

Met criteria codes

PM2_Supporting	✔	This variant is absent from gnomAD v4.1.0 (PM2_Supporting).
PP3	✔	The computational predictor REVEL gives a score of 0.271, which is below the ClinGen X-linked IRD VCEP threshold of ≥0.644 and does not predict a damaging effect on RPGR function. The splicing impact predictor SpliceAI gives delta scores of 0.48 for acceptor loss and 0.41 for acceptor gain, which are above the ClinGen X-linked IRD VCEP recommended threshold of ≥0.2 and predict a deleterious impact on splicing (PP3).
PP4	✔	At least one proband harboring this variant exhibits a phenotype including a family history consistent with X-linked inheritance (2 pts), showing a milder phenotype in affected females (1 pt), reduced visual acuity (0.5 pts), and visual field constriction (0.5 pts), which together are specific for RPGR-related retinopathy (4 points, PMID: 10937588, PP4).

PS4_Supporting		✔	This variant has been reported in at least 2 apparently unrelated probands 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 (PMID: 26164827, PMID: 36445968, PMID: 32209785, PMID: 32098976, and PMID: 28863407, PS4_Supporting).
PP1_Moderate		✔	The variant has been reported to segregate with retinal dystrophy through at least 3 affected meioses from 1 family (PMID: 10937588, PP1_Moderate).

Not Met criteria codes

BP4		✖	No code specific comments provided, please refer to the summary above or general recommendations provided in the guideline
PS3		✖	Eye autopsy from a female patient harboring the variant in the heterozygous state exhibits loss of opsin localization within photoreceptor cells and loss of photoreceptor nuclei in comparison to the healthy control eye (PMID: 16935610). This study is relevant to the phenotype of the particular patient but does not directly assess the function of the RPGR variant. Eye autopsy of a female carrier, carrying this variant, shows a Rod and cone opsin mislocalization. The family was described by Sharon et al. PubMed:16935610

Curation History

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