Variant: NM_001034853.2(RPGR):c.3423G>T (p.Trp1141Cys)

CA412726237

1012373 (ClinVar)

Gene: RPGR (HGNC:6103)
Condition: RPGR-related retinopathy (MONDO:0100437)
Inheritance Mode: X-linked inheritance
UUID: 3e7c061f-0f70-4498-a216-729cf5d2fb9e
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HGVS expressions

NM_001034853.2:c.3423G>T
NM_001034853.2(RPGR):c.3423G>T (p.Trp1141Cys)
NC_000023.11:g.38285576C>A
CM000685.2:g.38285576C>A
NC_000023.10:g.38144829C>A
CM000685.1:g.38144829C>A
NC_000023.9:g.38029773C>A
NG_009553.1:g.46960G>T
ENST00000494707.6:c.953+2289G>T
ENST00000642170.1:n.1826+5383G>T
ENST00000642395.2:c.1905+1518G>T
ENST00000642739.1:c.1572+5383G>T
ENST00000644238.1:c.1386+5383G>T
ENST00000644337.1:c.1719+1518G>T
ENST00000645032.1:c.3423G>T
ENST00000645124.1:c.*101+1518G>T
ENST00000646020.1:c.*594+1518G>T
ENST00000318842.11:c.1905+1518G>T
ENST00000339363.7:c.2520+1518G>T
ENST00000378505.6:c.3423G>T
ENST00000465127.1:c.172-380545C>A
ENST00000474584.5:c.*37+5383G>T
ENST00000482855.5:c.1905+1518G>T
ENST00000494707.5:c.139+5383G>T
NM_000328.2:c.1905+1518G>T
NM_001034853.1:c.3423G>T
NM_001367245.1:c.1902+1518G>T
NM_001367246.1:c.1719+1518G>T
NM_001367247.1:c.1572+5383G>T
NM_001367248.1:c.1602+5383G>T
NM_001367249.1:c.1569+5383G>T
NM_001367250.1:c.1569+5383G>T
NM_001367251.1:c.1386+5383G>T
NR_159803.1:n.2263+1518G>T
NR_159804.1:n.1648+5383G>T
NR_159805.1:n.1714+5383G>T

NR_159806.1:n.1866+1518G>T
NR_159807.1:n.1622+5383G>T
NR_159808.1:n.1826+5383G>T
NM_000328.3:c.1905+1518G>T

Uncertain Significance

Met criteria codes 2

BP4 PM2_Supporting

Not Met criteria codes 2

PS4 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.3423G>T (p.Trp1141Cys) is a missense variant encoding substitution of tryptophan with cysteine at residue 1141. This variant is absent from hemizygous individuals in gnomAD v4.1.0 (PM2_Supporting). The computational predictor REVEL gives a score of 0.2, which is below the ClinGen X-linked IRD VCEP threshold of <0.290 and predicts a non-damaging effect on RPGR function. Additionally, the splicing impact predictor SpliceAI gives a delta score of 0.00, which is below the ClinGen X-linked IRD VCEP recommended threshold of <0.1 and does not strongly predict an impact on splicing (BP4). This variant has been reported in at least 1 proband meeting the PS4 requirement of some functional vision impairment in an affected male by age 30 years, with decreased fundus autofluorescence responses (PMID: 32278709). However, PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met. In summary, this variant is classified as a variant of uncertain significance 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; PM2_Supporting and BP4. (date of approval 05/16/2025).

Met criteria codes

BP4	✔	The computational predictor REVEL gives a score of 0.2, which is below the ClinGen X-linked IRD VCEP threshold of < 0.290 and predicts a non-damaging effect on RPGR function. Additionally, the splicing impact predictor SpliceAI gives a delta score of 0.00, which is below the ClinGen X-linked IRD VCEP recommended threshold of <0.1 and does not strongly predict an impact on splicing (BP4).
PM2_Supporting	✔	This variant is present in gnomAD v.4.1.0 at a frequency of 0.00 among hemizygous individuals, with 0 variant alleles / 399138 total hemizygous alleles, which is lower than the ClinGen X-linked IRD VCEP PM2_Supporting threshold of < 0.0000005 (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/FAF responses (PMID:

32278709). However, PS4_Supporting requires at least 2 unrelated probands, so this criterion was not met.

PP4		✖	This variant has been reported in at least 1 proband with some functional vision impairment in an affected male by age 30, decreased FAF responses, and bull's eye macular lesion (PMID: 32278709). These phenotypes were not sufficient to meet PP4.

Curation History

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