Evaluation Summary

NM_001034853.2(RPGR):c.730A>T (p.Lys244Ter)

ClinVar VariationID: 98796
ClinGen Allele Registry ID: CA226439
Interpretation owner: X-linked Inherited Retinal Disease
Auto-calculated Classification: Pathogenic
Modified Classification: None
Reason for modified classification: None

Interpretation Status: PROVISIONAL
Date interpretation saved: 2024 Aug 01, 1:28 am
Disease: RPGR-related retinopathy
Mode of Inheritance: X-linked inheritance (dominant)
Specification Document: None

Evidence Summary

NM_001034853.2(RPGR):c.730A>T (p.Lys244Ter) is a nonsense variant that introduces a premature stop codon into exon 7 of 15, and is predicted to lead to nonsense-mediated decay in the RPGR gene in which loss-of-function is an established disease mechanism (PVS1).
This variant is absent from gnomAD v2.1.1 (PM2_supporting).
At least one proband harboring this variant exhibits a phenotype including a family pedigree consistent with X-linked inheritance (2 points), night blindness (0.5 points), delayed or milder phenotype in females (1 point), rod involvement relatively greater than cone involvement (1 point), and peripheral visual field constriction (0.5 points), which together are specific for RPGR-related recessive retinopathy (5 points, PMIDs: 11180598, 21857984, PP4).
The variant has been reported to segregate with retinal dystrophy through at least 4 affected meioses from 1 family (PP1_Moderate).
In summary, this variant is classified as pathogenic for RPGR-related retinopathy based on the ACMG/AMP criteria applied, as specified by the ClinGen X-linked IRD VCEP: PVS1, PM2_supporting, PP1_Moderate, and PP4. (VCEP specifications version PILOT; date of approval 10/3/23)

Criteria meeting an evaluation strength

B/P	Criteria	Criteria Descriptions	Modified	Status	Explanation
✓	PVS1	Predicted null variant in a gene where LOF is a known mechanism of disease	No	met	This is a nonsense variant that introduces a premature stop codon into exon 7 of 15, and is predicted to lead to nonsense-mediated decay in the RPGR gene in which loss-of-function is an established mechanism of disease (PVS1).
✓	PP1	Cosegregation with disease in multiple affected family members	Yes	PP1_moderate	The variant has been reported to segregate with retinal dystrophy through at least 4 affected meioses from 1 family (PP1_Moderate).

B/P	Criteria	Criteria Descriptions	Modified	Status	Explanation
	PP4	Patient's phenotype or FH highly specific for gene	No	met	At least one proband harboring this variant exhibits a phenotype including a family pedigree consistent with X-linked inheritance (2 points), night blindness (0.5 points), delayed or milder phenotype in females (1 point), rod involvement relatively greater than cone involvement (1 point), and peripheral visual field constriction (0.5 points), which together are specific for RPGR-related recessive retinopathy (5 points, PMID: 11180598, PP4).
	PM2	Absent in population databases	Yes	PM2_supporting	This variant is absent from gnomAD v2.1.1

Criteria evaluated as 'Not met'

B/P	Criteria	Criteria Descriptions	Modified	Status	Explanation

Criteria 'Not yet evaluated'

B/P	Criteria	Criteria Descriptions	Modified	Status	Explanation
○	BA1	Allele frequency greater than 5% in a population database	N/A	Not Evaluated	
○	BS1	MAF is too high for disorder	N/A	Not Evaluated	
○	BS2	Observation in controls inconsistent with disease penetrance	N/A	Not Evaluated	
○	BS3	Well-established functional studies show no deleterious effect	N/A	Not Evaluated	
○	BS4	Non-segregation with disease	N/A	Not Evaluated	
○	PS1	Same amino acid change as an established pathogenic variant	N/A	Not Evaluated	
○	PS2	De novo (paternity and maternity confirmed)	N/A	Not Evaluated	
○	PS3	Well-established functional studies show a deleterious effect	N/A	Not Evaluated	
○	PS4	Prevalence in affecteds statistically increased over controls	N/A	Not Evaluated	
○	PM1	Mutational hot spot or well-studied functional domain without benign variation	N/A	Not Evaluated	

B/P	Criteria	Criteria Descriptions	Modified	Status	Explanation
○	PM3	For recessive disorders, detected in trans with a pathogenic variant	N/A	Not Evaluated	
○	PM4	Protein length changing variant	N/A	Not Evaluated	
○	PM5	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before	N/A	Not Evaluated	
○	PM6	De novo (without paternity & maternity confirmed)	N/A	Not Evaluated	
○	BP1	Missense in gene where primarily truncating cause disease	N/A	Not Evaluated	
○	BP2	Observed in trans with path. variant for dominant disorder or cis any inheritance	N/A	Not Evaluated	
○	BP3	In-frame indels in repeat w/out known function	N/A	Not Evaluated	
○	BP4	Multiple lines of computational evidence suggest no impact on gene /gene product	N/A	Not Evaluated	
○	BP5	Found in case with an alternate cause	N/A	Not Evaluated	
○	BP6	Reputable source w/out shared data = benign	N/A	Not Evaluated	

B/P	Criteria	Criteria Descriptions	Modified	Status	Explanation
○	BP7	Silent variant predicted with no splice impact	N/A	Not Evaluated	
○	PP2	Missense in gene with low rate of benign missense variants and path. missenses common	N/A	Not Evaluated	
○	PP3	Multiple lines of computational evidence support a deleterious effect on the gene /gene product	N/A	Not Evaluated	
○	PP5	Reputable source = pathogenic	N/A	Not Evaluated	

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