Cureus
Part of SPRINGER NATURE

Open Access Case Report

Profound Visual Impairment With Limited Retinal Structural Abnormalities: A Case of Suspected Photoreceptor Cilium Actin Regulator (PCARE)-Associated Retinopathy

Kevin Santiago-Narváez [1], Ricardo A. Murati Calderon [1], Natalio Izquierdo [1]

1. Ophthalmology, School of Medicine, Medical Sciences Campus, University of Puerto Rico, San Juan, PRI

Corresponding author: Kevin Santiago-Narváez, kevin.santiago29@upr.edu

Review began 10/15/2026
Review ended 11/01/2026
Published 11/09/2026

© **Copyright** 2026
Santiago-Narváez et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.119344

Abstract

Photoreceptor cilium actin regulator (PCARE)-associated retinopathy is a rare autosomal recessive inherited retinal disorder caused by pathogenic variants in the PCARE (formerly C2orf71) gene and encompasses a wide range of clinical phenotypes. Variability in disease severity and retinal findings, together with the complexity of genetic testing, can make diagnosis challenging. We report a 73-year-old Hispanic female patient referred for genetic evaluation of profound bilateral visual impairment, with a family history of blindness.

The patient's best-corrected visual acuity was no light perception in the right eye (OD) and 20/400 in the left eye (OS), with red-green and blue-yellow color vision deficiencies. Fundus examination demonstrated mild retinal vascular attenuation without prominent peripheral pigmentary changes. Fundus autofluorescence of the OS revealed decreased central macular autofluorescence with surrounding alterations. Optical coherence tomography demonstrated decreased retinal thickness and volume with absence of the normal foveal pit in the OD. In contrast, retinal thickness and volume remained within normal limits in the OS. Central subfield thickness (CST) was 229 µm in the OD and 236 µm in the OS, with macular cube volumes of 8.6 mm^3 and 9.3 mm^3, respectively. Humphrey 24-2 visual field testing of the OS demonstrated profound diffuse visual field loss, with a visual field index of 0% and a reported mean deviation of −31.63 dB. However, the instrument indicated that the mean deviation threshold had been exceeded. Next-generation sequencing identified two heterozygous PCARE variants of uncertain significance, c.1453G>A (p.Glu485Lys) and c.739_740delinsAA (p.Val247Asn), with unknown phase.

The marked discrepancy between visual dysfunction and retinal structural findings, together with inconclusive molecular results, presents a diagnostic challenge. This case highlights the importance of careful genotype-phenotype correlation and consideration of additional genetic evaluation in patients with suspected inherited retinal dystrophies.

Categories: Genetics, Ophthalmology
Keywords: genotype-phenotype correlation, inherited retinal dystrophy, pcare-associated retinopathy, pcare variants, profound visual impairment

Introduction

Collin and co-workers first identified pathogenic variants in the C2orf71 gene, now known as photoreceptor cilium actin regulator (PCARE), in patients with autosomal recessive retinitis pigmentosa linked to chromosome 2p23 [1]. Clinical manifestations of PCARE-associated retinopathy include progressive vision loss, nyctalopia, macular involvement, and outer retinal degeneration demonstrated on multimodal imaging [2-4]. Ophthalmoscopic findings may include retinal vascular attenuation, macular atrophy, and peripheral pigmentary changes [1,3,4]. The clinical spectrum is heterogeneous, with variability in age of onset, disease severity, and progression among affected individuals [2-4].

PCARE-associated retinopathy represents a rare subset of inherited retinal dystrophies. In a large French cohort, C2orf71 mutations accounted for approximately 1% of autosomal recessive retinitis pigmentosa cases [5]. PCARE-associated retinopathy follows an autosomal recessive inheritance pattern, with disease-causing variants identified in both homozygous and compound heterozygous states [1,3,5]. Reported pathogenic variants include missense, nonsense, frameshift, and splice-site mutations [2,3,5]. Although considerable variability in disease severity and progression has been described, genotype-phenotype correlations remain incompletely understood [2-4].

Diagnosis relies on clinical suspicion supported by multimodal retinal imaging, including optical coherence tomography and fundus autofluorescence, together with molecular genetic testing to establish the underlying genetic diagnosis [2-4]. The most reported phenotype is retinitis pigmentosa (RP54),

How to cite this article
Santiago-Narváez K, Murati Calderon R A, Izquierdo N (November 09, 2026) Profound Visual Impairment With Limited Retinal Structural Abnormalities: A Case of Suspected Photoreceptor Cilium Actin Regulator (PCARE)-Associated Retinopathy. Cureus 18(11): e119344. DOI 10.7759/cureus.119344

characterized by progressive peripheral visual field constriction, nyctalopia, and eventual central visual impairment [1-4]. Cone-rod dystrophy phenotypes have also been described, with greater involvement of central visual function and cone-mediated responses [2]. More recent natural-history data demonstrate that visual field loss may occur early, while useful natural central vision can persist into late adulthood because of foveal sparing [4].

Experimental studies have shown that disruption of PCARE function can impair photoreceptor outer segment development and visual function [6]. PCARE is a photoreceptor-specific ciliary protein involved in outer segment formation through the regulation of actin assembly at the connecting cilium, including interactions with Wiskott-Aldrich syndrome protein family member 3 (WASF3) [7,8].

Currently, there are no approved genetic therapies specifically targeting PCARE-associated retinopathy. Management remains supportive, focusing on visual rehabilitation, clinical monitoring, and associated complications. Advances in disease modeling and understanding of PCARE function may contribute to future therapeutic development, although these approaches remain investigational [2,4].

We report a patient with profound bilateral visual impairment despite relatively mild funduscopic abnormalities and preserved retinal thickness and volume in the left eye. Genetic testing identified two heterozygous PCARE variants of uncertain significance, raising the possibility of PCARE-associated retinopathy without establishing a definitive molecular diagnosis. This case highlights the discrepancy between visual dysfunction and retinal structural findings, as well as the challenges of interpreting inconclusive genetic results in patients with suspected inherited retinal dystrophies.

Case Presentation

A 73-year-old Hispanic female patient with a medical history of brain aneurysm, rheumatoid arthritis, hypertension, hypercholesterolemia, osteoporosis, and thyroid disease was referred to our clinic by a retina specialist for genetic evaluation of severe bilateral visual impairment. The patient had been considered legally blind, with no retinal, optic nerve, corneal, or other ocular findings on the referring evaluation sufficient to explain the severity of her visual loss. Her ocular history was otherwise unremarkable. Family history was notable for legal blindness in her mother and two aunts, as well as a history of glaucoma. The patient was a former smoker, reported social alcohol use, and denied recreational drug use. Review of systems was otherwise unremarkable.

Upon comprehensive ophthalmic evaluation, the patient's best-corrected visual acuity was no light perception (NLP) in the right eye (OD) and 20/400 in the left eye (OS). Intraocular pressures measured by iCare tonometry were 17 mmHg OD and 16 mmHg OS. Her pupils were equal and round, with a relative afferent pupillary defect (RAPD) in the OD and a reactive pupil in the OS. Extraocular movements were full and ortho in all directions of gaze. Color vision testing using the Hardy-Rand-Rittler (HRR) pseudoisochromatic plates (4th edition; Richmond Products, Boca Raton, USA) demonstrated mild red-green and blue-yellow deficiencies [9].

On anterior segment examination, the patient had clear corneas, deep and quiet anterior chambers without inflammation, and nuclear sclerosis in both lenses. Upon dilated fundus examination, there were relatively mild retinal changes despite the severity of the patient's visual impairment. Ultra-widefield color fundus photography of the OD demonstrated mild retinal vascular attenuation without prominent peripheral pigmentary changes (Figure *1*). Similar findings were observed in the OS (Figure *2*). Fundus autofluorescence imaging of the OS demonstrated decreased autofluorescence involving the central macular region with surrounding autofluorescence changes (Figure *3*).

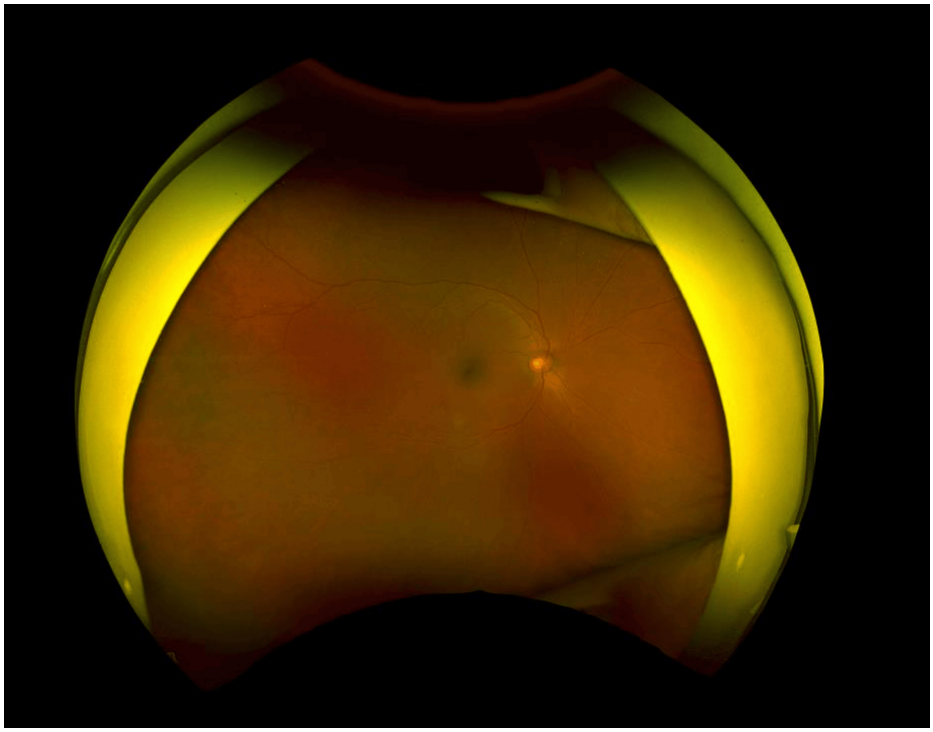


FIGURE 1: Ultra-widefield color fundus photograph of the right eye demonstrating mild retinal vascular attenuation without prominent peripheral pigmentary changes.

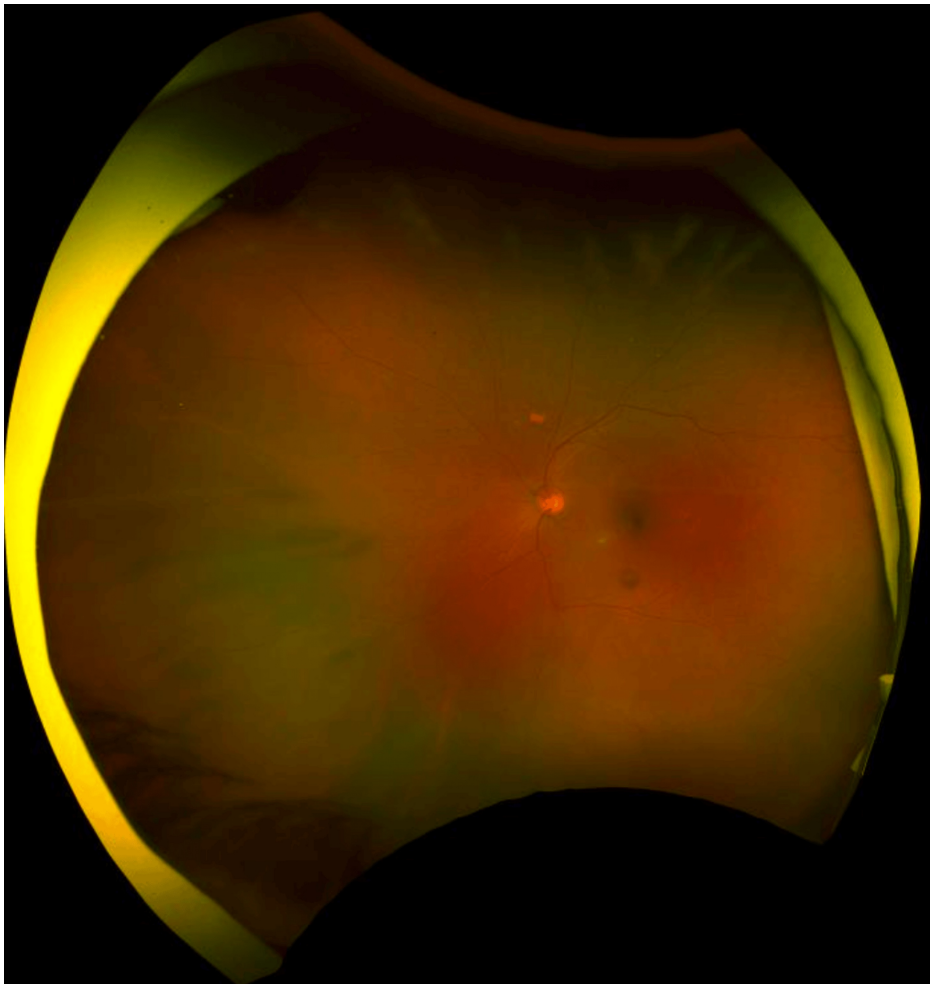


FIGURE 2: Ultra-widefield color fundus photograph of the left eye demonstrating similar findings, with mild retinal vascular attenuation and no prominent peripheral pigmentary changes.



FIGURE 3: Fundus autofluorescence image of the left eye demonstrating decreased autofluorescence involving the central macular region with surrounding autofluorescence changes.

Spectral-domain optical coherence tomography (OCT) of the macula (Cirrus; Carl Zeiss Meditec, Dublin, USA) showed decreased retinal thickness and volume in the OD, with absence of the normal foveal pit, while retinal thickness and volume were within normal limits in the OS. Central subfield thickness (CST) measured 229 µm in the OD and 236 µm in the OS. Cubic volume was decreased in the OD, with a value of 8.6 mm^3, and within the normal range in the OS, with a value of 9.3 mm^3 (Figure *4*).

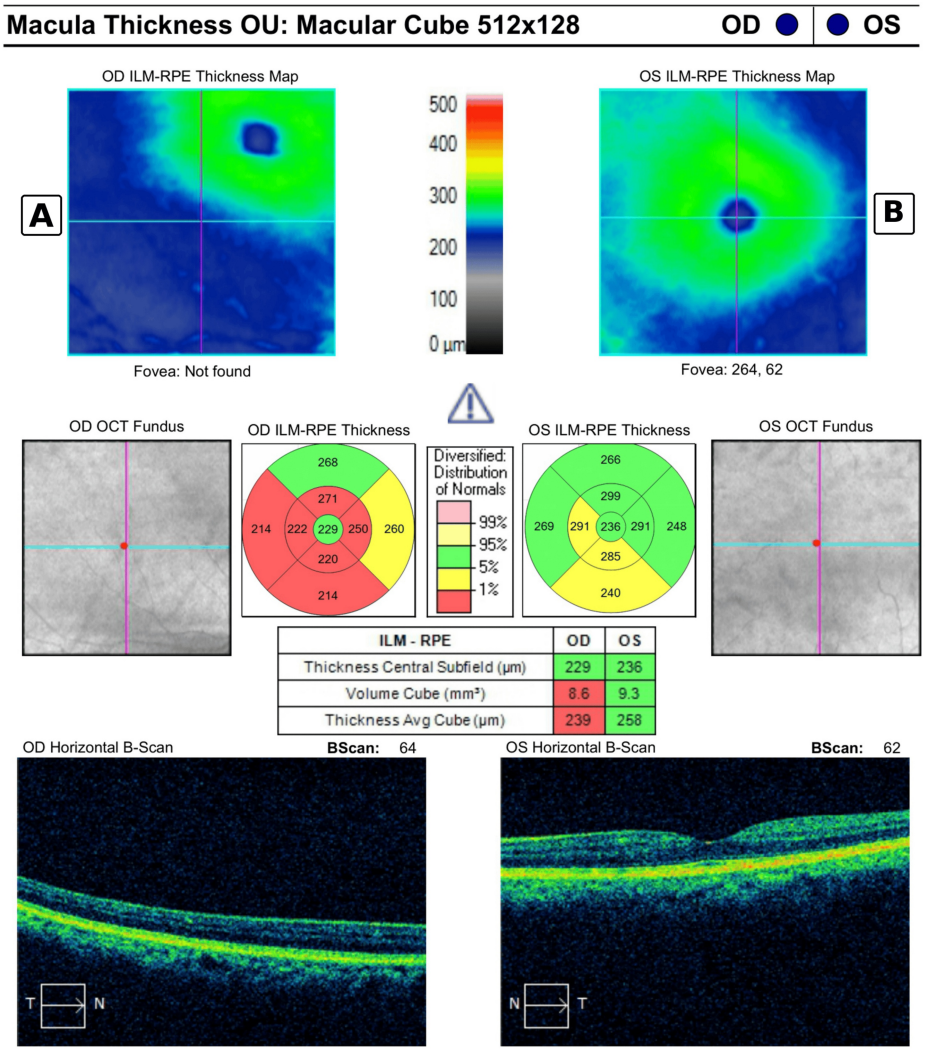


FIGURE 4: Spectral-domain optical coherence tomography of the macula.

(A) OD demonstrating decreased retinal thickness and volume with absence of the normal foveal pit. (B) Left eye (OS), demonstrating relatively preserved retinal thickness and volume. Conventions: The normative color scale indicates values within normal limits (green: 5th–95th percentile), borderline (yellow: 1st–5th percentile), and outside normal limits (red: <1st percentile) compared with the device's age-matched database. OU: oculus uterque; OD: right eye; OS: left eye; OCT: optical coherence tomography; ILM: inner limiting membrane; RPE: retinal pigment epithelium.

As shown in Figure 5, Humphrey 24-2 Swedish Interactive Thresholding Algorithm (SITA) Faster visual field testing (Carl Zeiss Meditec, Dublin, USA) of the OS demonstrated profound diffuse visual field loss, with a response detected at only a single tested location. The visual field index (VFI) was 0%, and the reported mean deviation (MD) was −31.63 dB, although the instrument indicated that the MD threshold had been exceeded.

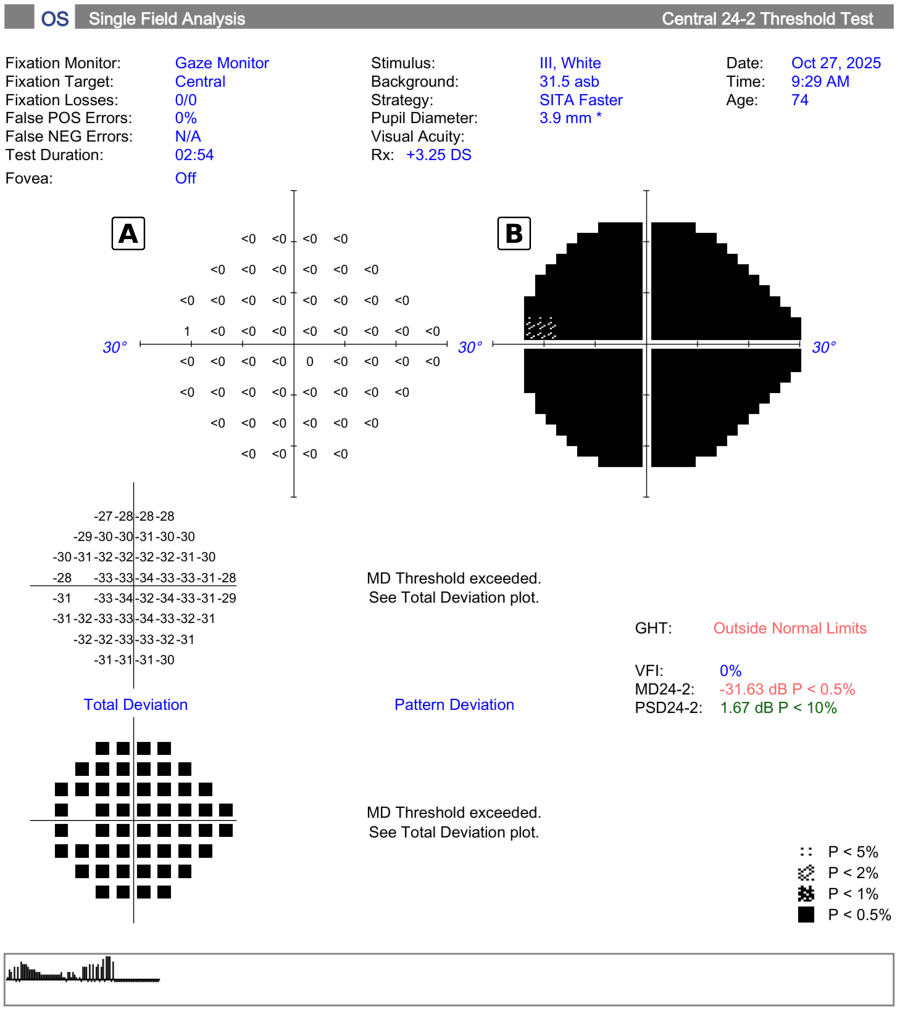


FIGURE 5: Humphrey 24-2 SITA Faster visual field testing of the left eye (OS).

(A) Numerical threshold sensitivity display showing profoundly reduced sensitivity across the tested field, with a response detected at only a single location. (B) Grayscale representation demonstrating severe diffuse visual field loss. The visual field index was 0%, with a reported mean deviation of −31.63 dB and an accompanying instrument warning that the mean deviation threshold had been exceeded. OS: left eye; POS: positive (false-positive responses); NEG: negative (false-negative responses); SITA: Swedish Interactive Thresholding Algorithm; MD: mean deviation; GHT: glaucoma hemifield Test; VFI: visual field index; PSD: pattern standard deviation.

Based on the clinical findings and severe visual impairment, an inherited retinal dystrophy was suspected. Genetic testing was conducted using a buccal swab and a next-generation sequencing (NGS) panel (Invitae Inherited Retinal Disorders Panel; Invitae Corporation, San Francisco, USA), which identified three heterozygous variants of uncertain significance (VUS): DHDDS c.387G>C (p.Leu129Phe), PCARE c.1453G>A (p.Glu485Lys), and PCARE c.739_740delinsAA (p.Val247Asn). The phase of the two PCARE variants could not be determined; therefore, it remains unknown whether they are located on the same or opposite alleles. Given the autosomal recessive inheritance of PCARE-associated retinopathy, these genetic findings do not establish a definitive molecular diagnosis. However, the presence of two heterozygous PCARE variants in the setting of the patient's clinical phenotype raised the possibility of PCARE-associated retinopathy.

Supportive management was continued with monitoring of the patient's residual visual function. The patient was counseled regarding the genetic nature and progressive course of inherited retinal dystrophies and was prescribed lutein and zeaxanthin supplementation. Given the uncertain significance of the identified variants and the inability to determine whether the two PCARE variants were in cis or trans, continued clinical follow-up and further genetic evaluation were recommended.

Discussion

Previous studies have demonstrated substantial phenotypic variability among patients with PCARE-

associated retinopathy, including differences in age of onset, disease severity, and progression [2-4]. Visual acuity may remain relatively preserved during earlier stages of PCARE-associated retinopathy, with useful central vision sometimes retained into later adulthood before progressive deterioration in more advanced disease [3,4]. Cone photoreceptor dysfunction has also been documented in PCARE-associated retinopathy, including cone-rod dystrophy phenotypes [2,3]. Our patient demonstrated profound visual impairment, with no light perception in the OD and markedly reduced visual acuity in the OS, accompanied by both red-green and blue-yellow color vision deficiencies. These findings overlap with the severe visual dysfunction and cone system involvement reported within the phenotypic spectrum of PCARE-associated retinopathy.

Structural abnormalities on optical coherence tomography have been described in PCARE-associated retinopathy, including progressive outer retinal disruption and macular atrophy, with foveal sparing reported in some patients [3,4]. Visual field abnormalities are characterized by progressive peripheral field loss and constriction, which may become severe in advanced disease [3,4]. Funduscopic findings reported in PCARE-associated retinopathy include retinal vascular attenuation, macular atrophy, and peripheral pigmentary changes [1,3,4]. In our patient, OCT demonstrated decreased retinal thickness and volume with absence of the normal foveal pit in the OD, while retinal thickness and volume remained within normal limits in the OS. Despite these relatively preserved structural measurements in the OS, Humphrey 24-2 visual field testing demonstrated nearly complete loss of measurable sensitivity, with residual sensitivity at only a single tested location. Although the reported mean deviation was −31.63 dB, the instrument indicated that the mean deviation threshold had been exceeded, limiting the reliability of this value as a quantitative measure of visual field loss. Funduscopic examination similarly demonstrated relatively mild retinal changes, with only mild vascular attenuation and no prominent peripheral pigmentary abnormalities. The relatively preserved OCT measurements and mild funduscopic changes despite profound visual acuity and visual field loss suggest a notable discordance between retinal structure and visual function in this patient. Given the patient's severe visual impairment and the limited responses obtained with the Goldmann size III stimulus, visual field testing with a larger size V stimulus may have provided a more informative assessment of residual visual function and should be considered in future evaluations.

Pathogenic variants in PCARE have been established as a cause of autosomal recessive inherited retinal dystrophy, with homozygous and compound heterozygous variants reported in affected individuals [1,3-5]. In our patient, next-generation sequencing identified two heterozygous PCARE variants of uncertain significance, c.1453G>A (p.Glu485Lys) and c.739_740delinsAA (p.Val247Asn), in addition to a heterozygous DHDDS variant of uncertain significance, c.387G>C (p.Leu129Phe). The presence of two variants in PCARE, together with the patient's severe visual dysfunction, color vision abnormalities, and family history of visual impairment, raises the possibility of PCARE-associated retinopathy. However, the phase of the two PCARE variants could not be determined, and family members were not available for segregation analysis. Therefore, it remains unknown whether the variants are located in trans, as would be expected for an autosomal recessive disorder, or in cis on the same allele. Furthermore, both variants remain classified as variants of uncertain significance and therefore do not establish a definitive molecular diagnosis [10]. Broader molecular testing may help identify additional variants or alternative genetic causes not detected by the current multigene panel.

In comparison with the published literature, our patient shares several features of the reported PCARE-associated retinopathy spectrum, including severe visual impairment, cone system involvement, and visual field loss [1-4]. However, the relatively mild funduscopic abnormalities and preserved retinal thickness and volume in the OS, despite profound functional impairment, represent a less typical presentation compared with the structural abnormalities reported in established PCARE-associated disease [3,4]. Although two heterozygous PCARE variants were identified, their uncertain clinical significance and unknown phase prevent a definitive molecular association with the patient's phenotype. Nevertheless, the possibility that these variants contribute to the patient's visual impairment, potentially alongside additional undetected genetic factors, cannot be excluded.

Unlike patients with more characteristic presentations of PCARE-associated retinopathy, our patient demonstrated profound visual impairment despite relatively mild funduscopic abnormalities and preserved retinal thickness and volume in the OS. This highlights the importance of considering inherited retinal dystrophies as part of the differential diagnosis in patients with severe visual dysfunction, even when structural findings do not fully explain the degree of visual impairment. Given the discrepancy between the degree of visual impairment and the retinal structural findings, alternative ocular or neurologic causes of visual loss should also be considered. Although the identified PCARE variants raise the possibility of an inherited retinal dystrophy, their uncertain significance and unknown phase prevent us from attributing the patient's visual impairment specifically to PCARE-associated retinopathy. This emphasizes the importance of a comprehensive clinical evaluation alongside genetic testing, particularly when the molecular findings remain inconclusive [10]. Additional molecular investigations, including segregation analysis when feasible and broader sequencing approaches, may help clarify the contribution of PCARE or other retinal dystrophy-associated genes to the patient's phenotype.

Investigations into PCARE function have demonstrated that the protein plays an essential role in photoreceptor outer segment formation by regulating actin assembly at the connecting cilium through

interactions with WASF3 [7,8]. Disruption of this process results in abnormal outer segment development and impaired retinal function [6-8]. As advances in retinal disease research continue to provide potential avenues for future therapies, careful interpretation of genetic findings alongside the clinical phenotype remains important [2,4]. In our patient, supportive management included continued clinical monitoring of residual visual function, counseling regarding the progressive nature of inherited retinal dystrophies, and lutein and zeaxanthin supplementation.

Conclusions

This case describes an adult patient with profound bilateral visual impairment and two heterozygous PCARE variants of uncertain significance, highlighting the diagnostic complexity of suspected PCARE-associated retinopathy. Although the patient's severe visual dysfunction and family history of blindness raise suspicion for an inherited retinal dystrophy, the relatively mild retinal structural abnormalities, uncertain pathogenicity of the identified variants, and inability to determine whether they are in cis or trans prevent a definitive molecular diagnosis. Furthermore, alternative ocular or neurologic causes of visual impairment have not been excluded, and the possible association with PCARE-associated retinopathy remains tentative. These findings reinforce the importance of careful genotype-phenotype correlation, comprehensive clinical evaluation, and consideration of expanded molecular testing when suspicion for an inherited retinal dystrophy remains despite inconclusive genetic findings.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Kevin Santiago-Narváez , Natalio Izquierdo

Acquisition, analysis, or interpretation of data: Kevin Santiago-Narváez , Natalio Izquierdo, Ricardo A. Murati Calderon

Drafting of the manuscript: Kevin Santiago-Narváez , Natalio Izquierdo

Critical review of the manuscript for important intellectual content: Kevin Santiago-Narváez , Natalio Izquierdo, Ricardo A. Murati Calderon

Supervision: Natalio Izquierdo

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. University of Puerto Rico, Medical Sciences Campus Institutional Review Board issued approval 2610677156 (protocol number). The University of Puerto Rico, Medical Sciences Campus Institutional Review Board reviewed this case report. It determined that IRB oversight and approval were not required, as the submission does not meet the federal definition of research or human subjects research under 45 CFR 46.102. The IRB issued this determination on October 14, 2026, under protocol number 2610677156. Case Reports are ruled exempt, per the IRB Committee. IRB Exemption letter will be submitted under "Files for Editor Review". . **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Collin RW, Safieh C, Littink KW, et al.: Mutations in C2ORF71 cause autosomal-recessive retinitis pigmentosa. Am J Hum Genet. 2010, 86:783-8. 10.1016/j.ajhg.2010.03.016
2. Zufiaurre-Seijo M, García-Arumí J, Duarri A: Clinical and molecular aspects of C2orf71/PCARE in retinal diseases. Int J Mol Sci. 2023, 24: 10.3390/ijms241310670
3. Gerth-Kahlert C, Tiwari A, Hanson JV, et al.: C2orf71 mutations as a frequent cause of autosomal-recessive retinitis pigmentosa: clinical analysis and presentation of 8 novel mutations. Invest Ophthalmol Vis Sci. 2017, 58:3840-50. 10.1167/iovs.17-21597
4. Bianco L, Antropoli A, Benadji A, et al.: PCARE-associated retinopathy - genetics, clinical characteristics, and natural history. Invest Ophthalmol Vis Sci. 2025, 66:61. 10.1167/iovs.66.4.61
5. Audo I, Lancelot ME, Mohand-Saïd S, et al.: Novel C2orf71 mutations account for ~1% of cases in a large French arRP cohort. Hum Mutat. 2011, 32:E2091-103. 10.1002/humu.21460
6. Corral-Serrano JC, Messchaert M, Dona M, Peters TA, Kamminga LM, van Wijk E, Collin RW:

C2orf71a/pcare1 is important for photoreceptor outer segment morphogenesis and visual function in zebrafish. Sci Rep. 2018, 8:9675. 10.1038/s41598-018-27928-7

7. Corral-Serrano JC, Lamers IJ, van Reeuwijk J, et al.: PCARE and WASF3 regulate ciliary F-actin assembly that is required for the initiation of photoreceptor outer segment disk formation. Proc Natl Acad Sci U S A. 2020, 117:9922-31. 10.1073/pnas.1903125117
8. Afanasyeva TA, Schnellbach YT, Gibson TJ, Roepman R, Collin RW: PCARE requires coiled coil, RP62 kinase-binding and EVH1 domain-binding motifs for ciliary expansion. Hum Mol Genet. 2022, 31:2560-70. 10.1093/hmg/ddac057
9. Hardy-Rand-Rittler (HRR) pseudoisochromatic plates (4th ed.) . (2026). Accessed: 26 September 2026: https://www.optometryweb.com/6394-HRR-Hardy-Rand-Rittlers-Pseudoisochromatic-Test/58133-HRR-4th-Edition-Test-with-Spa....
10. Richards S, Aziz N, Bale S, et al.: Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015, 17:405-24. 10.1038/gim.2015.30