

Discovery of a novel genetic variation in papillorenal syndrome

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Abstract

Renal coloboma syndrome or papillorenal syndrome is an autosomal dominant genetic disorder characterized by congenital renal and ocular disorders associated with variations in the *PAX2* gene. In this case report, a 46-year-old gentleman presented for ocular examination in the setting of systemic hypertension. Past medical history included a kidney transplant due to renal failure. Fundus examination revealed bilateral optic nerve abnormalities with a large central excavation, with numerous vessels radiating from the periphery of the optic disc, consistent with the Morning Glory anomaly. Optical coherence tomography (OCT) disclosed substantial thinning of retinal nerve fiber layer. Genetic studies revealed the heterozygous variant c.398delC in the 3' exon of *PAX2* gene not previously described in the peer-reviewed medical literature (searched using MEDLINE and cross-referenced literature).

Introduction

Renal coloboma syndrome or papillorenal syndrome (PRS) is an autosomal dominant genetic disorder characterized by congenital renal and ocular disorders associated with variations in the *PAX2* gene.^{1,2} This gene is responsible for the embryonic development of the genitourinary tract, the inner ear, the eyes, the spinal cord, the hindbrain, and the midbrain. Genetic variations in the *PAX2* gene may

lead to functional and morphological changes in those organs.³ The main clinical manifestations of PRS are optic nerve coloboma and kidney hypodysplasia.¹

Rieger, *et al.* and Karcher, *et al.* were the first to describe the coexistence of optic nerve anomalies in patients with kidney disorders in advanced stages of PRS.^{4,5} The involved families presented with an alteration of the optic nerve described as a Morning Glory anomaly with an enlarged optic disc that is conically excavated and filled with glial tissue with peripherally-displaced radially emerging disc vessels, in a pattern that resembles a morning glory flower.^{3,4} Subsequently, Weaver, *et al.* described a case of two siblings with optic nerve coloboma on both eyes and end-stage kidney disease.⁶ They observed similarities between their patients and the ones affected by the Morning Glory anomaly previously described by Karcher, *et al.* and Rieger, *et al.* This similarity inspired Weaver, *et al.* to name this disease the renal coloboma syndrome. It is currently preferred to use the term papillorenal syndrome due to the variability in the way the optic nerve is affected: one cannot presume every case is affected by optic nerve coloboma.⁷ It is also important to consider PRS in the differential diagnosis of a patient with both renal and optic nerve disorders.^{8,9} In this case report, a 46-year-old gentleman presented with Morning Glory anomaly of the optic disc, renal failure, and a heterozygous variation in the *PAX2* gene not previously described.

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Case Report

A 46-year-old man presented for ophthalmic examination in the setting of high blood pressure secondary to chronic kidney disease. Past medical history included two renal transplants, where the first was rejected, due to renal hypodysplasia with chronic renal insufficiency for 34 years.

Ophthalmic examination disclosed best corrected visual acuity of 20/20 in the right eye and 20/40 in the left eye. Ishihara color testing was normal in both eyes. Both pupils reacted equally to light and accommodation and there was no relative afferent

pupillary defect in either eye. Intraocular pressures were within normal and slit-lamp biomicroscopy of the anterior segment examination was unremarkable in both eyes.

Fundus examination revealed pathologic optic nerves with a large central excavation, peripherally-displaced radially emerging disc vessels (Figure 1). Optical coherence tomography (OCT) showed substantial thinning of the retinal nerve fiber layer in both eyes (Figures 2 and 3). Humphrey visual field testing confirmed an inferior and superior altitudinal defect in the right eye, as well as a superior nasal step and an increased blind spot in the left eye.

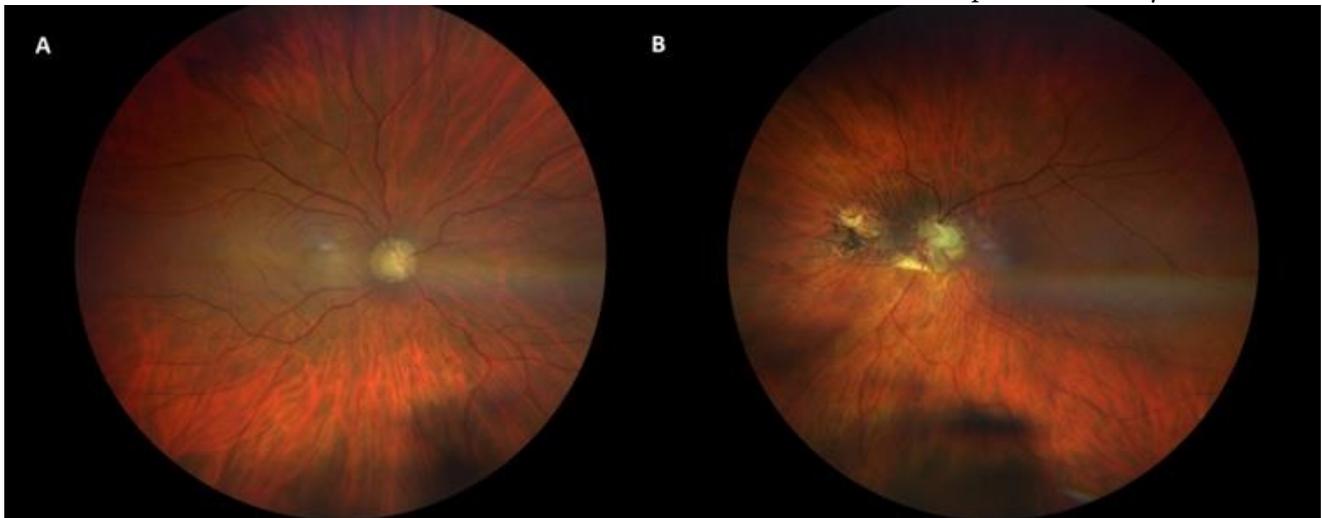


Figure 1
Fundus examination showing pathologic optic nerves with Morning Glory anomaly in the right (A) and left (B) eyes.

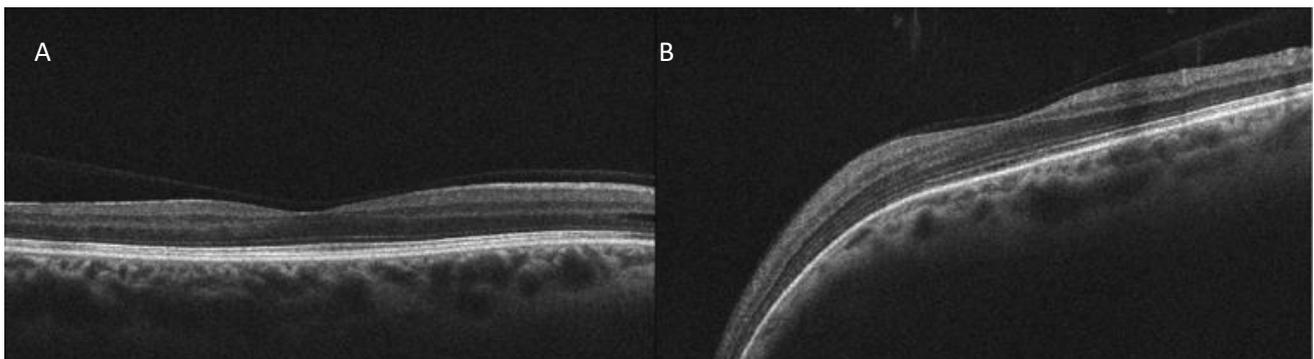


Figure 2
OCT demonstrates mild foveal hypoplasia in the left (B) more than right (A) eye with thinning of retinal nerve fiber layer.

RNFL y ONH: Optic Disc Cube 200x200

OD ● ● OS

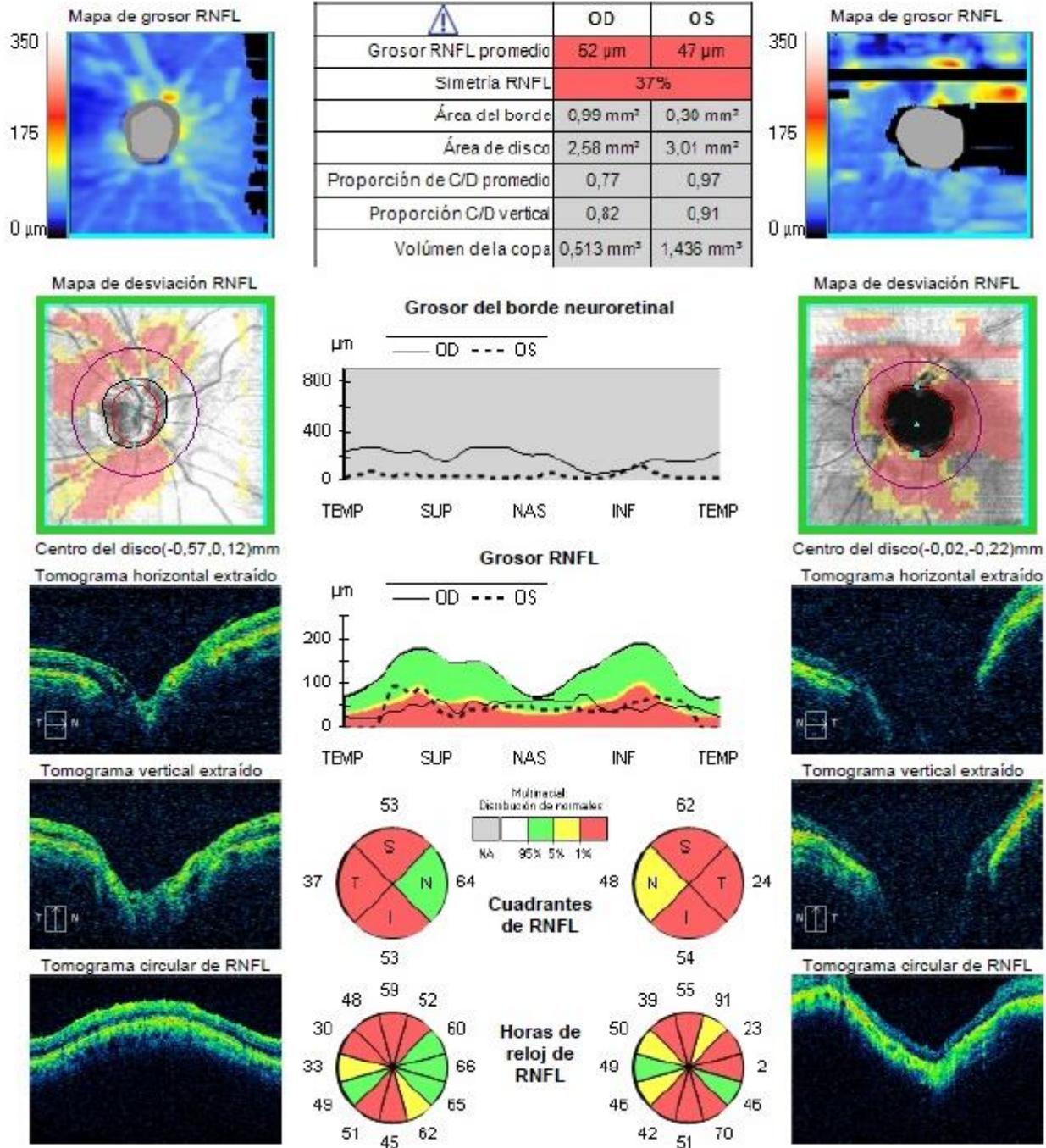


Figure 3
 OCT retinal nerve fiber layer (RNFL) analysis demonstrates thinning of retinal nerve fiber layer in the right (on left side of image) and left (on right) eyes.

MRI of the brain dismissed the presence of the Chiari type 1 malformation. Audiometry disclosed moderate sensorineural hearing loss for the high-pitched sounds. Genetic evaluation from peripheral blood samples were performed using polymerase chain reaction studies (PCR) and next generation sequencing (NGS). The exons and intron flanking sequences of the following genes were analyzed: *PAX2*, *EYA1*, *MUC1*, *REN* and *UMOD*. The result of this genetic study revealed the existence of the heterozygous variant c.398delC in the 3' exon of *PAX2* gene.

Discussion

PRS is a hereditary condition in which both ocular and renal anomalies are caused by the variations in the *PAX2* gene.^{1,2} There are more than 80 published PRS cases associated with variations in the *PAX* gene.^{1,2} It is estimated that any variation in the *PAX2* gene is only detected about 50% of cases, so there is suspicion that other genetic mechanisms may also play a role.^{8,9}

The *PAX2* gene, which is located in the 10q24 chromosomal region, is currently the only identified genetic cause for the PRS. Most of the variations are deletions or duplications of a sole nucleotide, nonsense variations, missense variations, small deletions, or duplications of two or more nucleotides. Pathologic genetic variations appear mostly on the exons from 2 to 4.¹ The c.77dupG is the most frequent *PAX2* gene variation, which has been described in more than 20 reports.^{3,8,9,10} The importance of this study derives from the fact that the variation detected on the 3' exon had not been previously described in the peer-reviewed medical literature (searched using MEDLINE and cross-referenced literature). Due to its nature, as it predicts the existence of a premature codon, this variation is highly prone to be pathologic.

While the prevalence of PRS is low, there are studies which confirm that many patients go undetected during the ophthalmic and renal examination. Therefore, it is suspected that there are more cases of PRS than the ones known and described.³

The diagnostic basis of PRS has not still been established for the PRS. Bower, *et al.* and Schimmenti, *et al.* estimate that around 50% of the patients presenting with optic nerve dysplasia and renal hypoplasia have a variation in the *PAX2* gene.^{1,8,9} It is recommended that patients with renal hypoplasia be checked by an ophthalmologist to evaluate for optic nerve malformations which are found in PRS. Likewise, patients who suffer from optic nerve dysplasia should have a renal ultrasound and an analysis of renal function as well as having blood pressure checked.

The Human Phenotype Ontology (HPO) database describes a list of the possible phenotypical associations that can be present in this syndrome. The ocular manifestations are present in 77% of those affected by the *PAX2* gene variation.¹ Typical ocular findings including the Morning Glory anomaly: an enlarged optic disc that is conically excavated and filled with glial tissue with peripherally-displaced radially emerging disc vessels, as in the case reported. Ocular findings can be unilateral or bilateral and vary in extent, including Morning Glory anomaly, optic nerve aplasia, optic disc pit, optic nerve coloboma, retinal coloboma, chorioretinal atrophy, microphthalmos, cataract, lens luxation, macular degeneration, macular hyperpigmentation, retinal detachment, or retrobulbar cyst formation.¹

In regard to renal function, it is altered in around 92% of the patients.¹ The most frequent anomaly is the renal hypoplasia (65%), as in the case presented. It is characterized by small kidneys with a reduced number of nephrons and disorganized renal tissue.¹ Other renal manifestations include multicystic renal dysplasia, oligomeganephronia (reduced number of nephrons and glomerular and tubular hypertrophy), horseshoe kidney, renal malrotation, and vesicoureteral reflux.¹ Most of the published cases show that renal anomalies appear before the ocular disorders.^{3,8} Hypertension and renal insufficiency are common in patients with PRS due to the renal genitourinary abnormalities.¹

Other infrequent manifestations caused by variation in the *PAX2* gene in the PRS are hearing loss for the high-pitched sounds (present in about 7% of

patients with PRS), as found in the case of this study, and other nervous system abnormalities (which are not found in the case of this study): mental retardation, seizures, gliosis, ligamentous laxity or Arnold-Chiari type 1 malformation.^{1,3,8} Other rare findings in PRS include hyperextensible skin and joint laxity.

Differential diagnosis of combined ocular and renal pathology include: CHARGE syndrome, the branchio-oto-renal syndrome, the Joubert syndrome, distal deletion of 4p, HNF1 β gene variations, the cat eye syndrome, or the tetraploid 22q.⁸ Several syndromes are characterized by ocular and renal abnormalities. Differential diagnosis includes CHARGE syndrome (Coloboma of the eye, Heart malformations, Atresia choanae, Retardation of growth, Genital anomalies, Ear and hearing abnormalities), Joubert syndrome, and Joubert syndrome with hepatic fibrosis also known as COACH syndrome (Cerebellar vermis aplasia, Oligophrenia, congenital Ataxia, Coloboma of the eye, and Hepatic fibrosis).⁸

Conclusion

In conclusion, the PRS is an uncommon disorder, but it should be taken into account when both ocular and renal disorders occur at the same time.¹ Cooperation among the relevant medical specialists is the key to discovering the multisystem pathology.⁸ Family genetic counseling must be performed due to the hereditary autosomal dominant genetic character of the disorder.² Renal function will determine the prognosis of this disorder because of its irreversible and progressive degradation.⁹ The current case demonstrates a previously unreported variation of the *PAX2* gene where the multidisciplinary approach is necessary for proper diagnosis and management. This unique variation in the *PAX2* gene should be

included in the locus specific variation database for PRS.

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