occlusion or retinal ischemia commonly occurs in blood disorders, hypertension, retinal vasculitis, retinopathy of prematurity, and diabetic retinopathy. The retinal lesions in our patient could be excluded from these latter diseases, based on laboratory findings. Ischemic manifestations in the aortic, cerebral, and renal vasculature in association with neurofibromatosis have been reported by Salyer and Salyer. The authors also reported that the ages of the patients ranged from 16 months to 69 years (mean, 32 years) and proposed that the proliferation of Schwann cells within arteries might result in vascular lesions in neurofibromatosis. Peripheral retinal vascular occlusive disease has been found in the right fundus of a 4-year-old boy with neurofibromatosis by Moadel et al and in the left fundus of a 20-year-old man with the disease by Thölen et al. Our patient also was young, had poor vision in her right eye since childhood, and had had peripheral retinal vascular occlusion. Although the exact mechanism is unclear, retinal vascular occlusion associated with neurofibromatosis-1 may occur. Furthermore, neurofibromatosis-1 should be added to the causative list of retinal vascular occlusive disease, particularly in young patients without other risk factors.

Neurofibromatosis of the eyelid and orbit has sometimes been described. Other patient had a left upper eyelid tumor, a left orbital bone defect, good visual acuity in her left eye, and minimal orbital involvement. Our patient had a pale optic disk in her right fundus. It is unlikely that a mass lesion in the orbit may compress the optic nerve, resulting in the pale optic disk, because such a lesion was not found on computed tomography and magnetic resonance imaging.

References

ALBIPUNCTATE RETINOPATHY WITH CONE DYSFUNCTION AND NO ABNORMALITY IN THE RH5 OR RLBP1 GENES

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Fundus albipunctatus (FA) is a hereditary and largely stationary form of night blindness, characterized by diffuse yellow spots and flecks in the fundus and by delayed dark adaptation. It is generally classed as one of the night-blinding disorders because the typical patient shows little rod function during conventional dark adaptation testing. However, after several hours of adaptation, rod sensitivity improves to normal levels. There is a wide clinical spectrum of the disease, however, and some patients described in the older literature have been reported to have rather mild symptoms and only a mild slowing of adaptation. Others have shown varying degrees of associated cone dysfunction and some degree of progression.

RH5 and RLBP1 genes encode 11-cis retinol dehydrogenase and the cellular retinaldehyde binding protein (CRALBP), respectively. In the retinal pigment epithelium, both of these proteins intervine in the conversion of 11-cis retinol to 11-cis retinaldehyde. 11-cis retinol dehydrogenase catalyzes the reaction, while CRALBP promotes it. Recent reports have documented mutations in the retinal dehydrogenase gene (RDH5) in typical FA cases with prolonged dark adaptation. The retinaldehyde-binding protein gene (RLBP1) has been

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implicated in the progressive retinopathy, retinitis punctata albescens, but also in some younger patients with clinical signs similar to those of FA.\(^7\)

We present genetic analysis of the \(RDH5\) and \(RLBP1\) genes in a patient with fundus changes that mimic those of FA, but with only mild abnormality of dark adaptation and with an associated cone dysfunction. Our question is whether these known genes account for this spectrum of functional deficits with albipunctate retinopathy or whether other genes may also be capable of producing these phenotypic characteristics. This patient provides insight into the mechanism and cause of hereditary night-blinding disorders and of albipunctate lesions in the fundus.

**Case Report**

The patient is a 30-year-old man of East Asian heritage. He had been told at age 16 of white dots in his fundus and apparently was unaware for many years of mild difficulty adjusting to the dark. He reported fluctuating vision, stinging, and occasional red eyes. He has four siblings who are unaffected by history and is unaware of any other affected family members. His general medical health has been good.

Corrected visual acuity was 20/20 in the right eye and 20/100 in the left eye. The left cornea had a central posterior stromal opacity, possibly old interstitial keratitis, which was longstanding. The right cornea was healthy, as was the remainder of the anterior segment. There was some peripapillary atrophy consistent with moderate myopia (roughly –8 diopters bilaterally). The right maculae showed normal pigmentation but somewhat ill-defined foveal reflexes. Yellow flecks characteristic of fundus albipunctatus began inside the main arcades and extended to the periphery, becoming less punctate and more flecklike away from the center (Figure 1). Fluorescein angiography did not reveal any dystrophic change in either the macula or the periphery.

Color vision tested normally with the desaturated Panel D-15 test of Lanthony. Goldmann–Weekers dark adaptometry without preadaptation to light showed a normal final threshold in both eyes within approximately 15 minutes. After fundus bleaching for 5 minutes, the dark adaptation curve was monotonic and showed no definable cone limb and reached a normal final threshold in approximately 30 minutes (Figure 2).

Full-field ISCEV standard electroretinograms (Figure 2) showed normal rod responses, but the maximal b-waves were reduced roughly 20% below the normal minimum value. Good oscillatory potentials were seen. The cone b-waves were reduced nearly 50% below the minimum of the adult range, although the waveform and timing of the responses were normal. After more prolonged dark adaptation (45 minutes), the rod responses shortened in implicit time, and the maximal dark-adapted b-waves rose to amplitudes within the normal range. When a photopic background was turned on, the initial cone b-waves were larger than those after a shorter period of dark adaptation, and the amplitude after 10 minutes of light adaptation had risen to roughly 80% of the minimum adult range. A multifocal ERG on the left eye (Figure 2), using the VERIS system, showed normal responses in the foveal zone, but reduced amplitudes beyond 10° of eccentricity. An electrooculogram on the left eye showed dark trough voltages of normal amplitude and a light–dark ratio of 1.96.

Genomic DNA was isolated from 1 mL of blood using the QiaAMP Blood kit (Qiagen). The four coding exons (numbers 2–5) for the \(RDH5\) gene were amplified by polymerase chain reaction from genomic DNA using intronic primers at 94°C for 2 minutes, followed by 40 cycles at 94°C for 20 seconds, 58°C for 30 seconds, and 68°C for 1 minute, finishing with a final extension at 68°C for 7 minutes. The seven coding exons (numbers 2–8) for the \(RLBP1\) gene were amplified by polymerase chain reaction from genomic DNA using intronic primers at 94°C for 2 minutes, followed by 35 cycles at 96°C for 20 seconds, 55°C for 30 seconds, and 68°C for 1 minute, finishing with a final extension at 68°C for 7 minutes. Each exon was directly sequenced in both directions using the BigDye Terminator Cycle Sequencing Kit (Applied Biosystems). No disease-associated mutations were identified in the coding regions of either the \(RDH5\) or the \(RLBP1\) gene.

**Discussion**

Fundus albipunctatus and retinitis punctata albescens are characterized by the presence of multiple...

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**Fig. 1.** Fundus photograph (left) and fluorescein angiogram (right) of the patient’s right eye. The white spots are not seen on the angiogram.
yellow-white dots throughout the retina, except the fovea. However, retinitis punctata albescens is a severely progressive disorder and results in marked constriction of the peripheral visual field unlike FA, which is stationary or only minimally progressive. FA is clinically associated with prolonged dark adaptation, so it is not surprising that the genes that have been shown to cause the disease (RDH5 and RLBP1) involve proteins of the visual pigment renewal cycle, 11-cis retinol dehydrogenase and cellular retinaldehyde-binding protein. A broad variety of mutations in the RDH5 gene have been associated with FA. Mutations in the RLBP1 gene have been associated with retinitis punctata albescens and also with recessive retinitis pigmentosa and Bothnia dystrophy. Recently, mutations in the RLBP1 gene have also been reported to be associated with an FA phenotype in younger individuals.

In our study, we have genetically analyzed these two genes in a patient with retinal lesions similar to those of FA but with unusually mild abnormality of dark adaptation and with a degree of diffuse cone dysfunction. No mutations were detected in the coding regions of these two genes. The untranslated and intronic sequences of RDH5 and RLBP1 have not been sequenced. Therefore, we cannot exclude that, although rare, a mutation or deletion in the promoter of these genes or in their introns might affect the expression or splicing of the genes. However, we think it most likely that another gene is affected in this patient.

The absence of mutations in the RDH5 and RLBP1 genes of this patient suggests that there is further genetic heterogeneity to conditions associated with diffuse white dots in the fundus. Clinical variation has been evident in the literature, including a wide range of severity in the prolongation of dark adaptation and also in the degree of diffuse cone dysfunction. Our patient suggests some milder forms of albipunctate retinopathy may involve different genes than the more severe ones. The relationship of other genes to cone dysfunction remains to be determined. As Cideciyan et al have pointed out, the appearance of mild
cone dysfunction electroretinographically in FA patients with RDH5 mutations may be a consequence of a loss of cone outer segments or incomplete visual pigment regeneration under photopic conditions. White dots in the fundus have most often been associated with rather severe disorders of vitamin A metabolism, such as typical FA, prolonged vitamin A deficiency, and retinitis punctata albescens. That they may also appear with milder dark adaptation abnormalities adds to the challenge of explaining this intriguing fundus abnormality.

References

INTERFERON-ASSOCIATED COMBINED BRANCH RETINAL ARTERY AND CENTRAL RETINAL VEIN OBSTRUCTION

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Interferon alpha (IFNα) is commonly used in the treatment of many viral and neoplastic diseases because of its antiviral, antiproliferative, and immunomodulatory effects. Ocular complications associated with IFNα therapy have been increasingly reported over the past decade. A characteristic retinopathy associated with IFNα therapy has been well described and consists of multiple cotton-wool spots associated with retinal hemorrhages. Although isolated cases of a branch retinal artery, branch retinal vein, or central retinal vein obstruction have been associated with IFNα, a central retinal vein obstruction occurring together with a simultaneous branch retinal artery obstruction has not been previously reported with IFNα therapy. We describe a case of a branch retinal artery obstruction combined with a nonischemic central vein obstruction in a 51-year-old man with chronic hepatitis C undergoing treatment with IFNα.

Case Report

In April 2001, a 51-year-old man was evaluated for sudden and painless decreased vision in his left eye. Since July 2000, he had been receiving 150 μg (1.5 μg/kg) of pegylated IFNα-2b once weekly subcutaneous injections in conjunction with oral ribavirin 600 mg daily for chronic hepatitis C. He denied a previous history of diabetes or hypertension. He also reported stable liver function studies including a recent liver biopsy showing no cirrhosis. Ocular history was significant only for rosacea treated with oral tetracycline.

On examination, he was noted to have a visual acuity of 20/20 in his right eye and counting fingers in his left eye. There was a 4+ left afferent pupillary defect, and intraocular pressure was within normal limits in both eyes. Anterior segment examination of both eyes was unremarkable with no evidence of iris neovascularization. Dilated fundus examination of the right eye was unremarkable. Examination of the left fundus revealed pronounced retinal opacification and edema along the distribution of the inferior temporal