Young Monozygotic Twin Sisters With Fundus Albipunctatus and Cone Dystrophy

Makoto Nakamura, MD; Jian Lin, MD; Yozo Miyake, MD

Objective: To describe young monozygotic twin sisters with fundus albipunctatus (a type of autosomal recessive stationary night blindness caused by mutations of the 11-cis retinol dehydrogenase gene [RDH5]) associated with cone dystrophy, previously reported in elderly men.

Methods: Ophthalmologic examinations were performed, and the RDH5 gene was analyzed by direct genomic sequencing.

Results: Twin 23-year-old sisters with high myopic refractive errors of approximately −13 diopters were diagnosed as having fundus albipunctatus. Their photopic electroretinographic responses were markedly reduced, and cone dystrophy was diagnosed. One twin had macular degeneration with reduced best-corrected visual acuity, while the other twin had normal maculae with good visual acuity. A compound heterozygous mutation, Val32Met and Arg280His, in the RDH5 gene was found in both sisters.

Conclusions: Cone dystrophy can be present in patients with fundus albipunctatus, not only elderly men but also young women. The clinical severity differed between monozygotic twins with fundus albipunctatus and cone dystrophy.

Clinical Relevance: The patient’s sex is not critical for the presence of cone dystrophy in patients with fundus albipunctatus. The discordant findings in the twins indicate that factors other than genetics influenced the phenotype.

Arch Ophthalmol. 2004;122:1203-1207

FUNDUS ALBIPUNCTATUS (FA) IS a type of congenital stationary night blindness with an autosomal recessive transmission. The fundi of patients with FA have a characteristic appearance with a large number of discrete, small, round or elliptical, yellow-white lesions at the level of the retinal pigment epithelium. The electrophysiologic responses are also distinctive because unusually long dark-adaptation periods are required to obtain the maximum scotopic responses. The 11-cis retinol dehydrogenase gene, RDH5, has been identified as the mutated gene in patients with FA.

Patients with FA complain of night blindness from early childhood, and the clinical course has been considered to be stationary with normal visual acuity, visual fields, and color vision. However, we have found that some patients with FA develop cone dystrophy (CD), resulting in progressive visual loss. Cone dystrophy is characterized by an initial degeneration of cone photoreceptor cells causing progressive impairment of central vision, central scotoma, and loss of color discrimination with the appearance of atrophic retinal changes in the macula. The photopic electroretinograms (ERGs) are reduced more than the scotopic ERGs. To our knowledge, all of the reported cases of FA associated with CD and molecular degeneration were in men older than 40 years. Thus, we believed that some patients with FA will develop CD, and that these patients will be mainly men.

In this report, we describe the characteristics of 23-year-old, monozygotic twin sisters who had FA and CD. One twin had bilateral macular degeneration with unilateral reduction of corrected visual acuity, whereas the other twin had normal maculae with good visual acuity in both eyes. The discordant findings indicate that the severity of CD in FA is related to factors other than genetics.
The sisters were examined in the Department of Ophthalmology, Nagoya University, Nagoya, Japan. A complete ophthalmologic examination was performed, including best-corrected visual acuity, slit-lamp and fundus examinations, fundus photography, fluorescein angiography, and ERG.

Genomic DNA was extracted from leukocytes of peripheral blood, and exons 2, 3, 4, and 5 of the $RDH5$ gene were amplified by polymerase chain reaction. The polymerase chain reaction conditions and the procedures for direct sequencing have been described in detail elsewhere. To search for polymorphisms, 100 alleles from normal, unrelated Japanese individuals were also directly sequenced.

Standardized full-field ERGs, elicited by Ganzfeld stimulation, were recorded after pupillary dilation with 0.5% tropicamide and 0.5% phenylephrine hydrochloride. The rod (scotopic) ERGs were recorded with a blue stimulus of a luminance of $5.2 \times 10^{-3}$ candela-seconds per square meter (cd-s/m²). The mixed rod-cone, single-flash (bright white) ERGs were elicited by a white stimulus of $44.2$ cd-s/m². They were recorded after 20 minutes and also after 3 hours of dark adaptation. The photopic (cone) single-flash ERGs and 30-Hz flicker ERGs were elicited by white stimuli at an intensity of $4$ cd-s/m² and $0.9$ cd-s/m², respectively, on a white background of $68$ cd/m².

*Figure 1.* Pedigree of a family with fundus albipunctatus showing affected (solid symbols) and unaffected (open symbols) members. Individuals whose DNA was tested are indicated by X’s. Squares indicate men; circles, women; and slash through symbol, deceased. The parents of the affected twin sisters are consanguineous.

*Figure 2.* Fundus photographs (A, B) and fluorescein angiograms (C, D) of the patients with a mutation of the 11-cis retinol dehydrogenase gene. A. Left eye of patient IV:3 showing multiple yellow-white lesions excluding the macula, as well as high myopic changes and retinal degeneration in the macula. B. Left eye of patient IV:2 showing multiple yellow-white punctate lesions and high myopic changes. No degenerative changes are seen in the macula area. C. Fluorescein angiogram of the left eye of patient IV:3 showing hyperfluorescence in the macula. D. Fluorescein angiogram of the left eye of patient IV:2 showing no abnormality in the macular area.
The 23-year-old twin sisters were referred to our hospital for a diagnosis for their visual difficulties. They were considered to be monozygotic because they bore a close resemblance to each other. Both patients had noticed night blindness from childhood, while only twin 1 (IV:3, Figure 1) had noticed a gradual reduction of vision during the previous 5 years. Their paternal grandmother and maternal great-grandfather were siblings (Figure 1). The corrected visual acuity of twin 1 was 1.2 OD and 0.2 OS with refractive errors of $-12.50 \pm 2.25 \times 110^\circ$ OD and $-13.00 \pm 1.25 \times 115^\circ$ OS, and that of twin 2 (IV:2, Figure 1) was 1.2 OU with refractive errors of $-12.00 \pm 2.50 \times 175^\circ$ OD and $-13.00 \pm 3.00 \times 5^\circ$ OS. They stated that their healthy mother was also highly myopic.

In both patients, numerous small, discrete yellow-white dots were observed at the level of retinal pigment epithelium with scarring of the macula in both eyes (Figure 2A and B). Both maculae of twin 1 (IV:3) demonstrated macular degeneration (Figure 2A), and fluorescein angiography showed hyperfluorescence in the corresponding areas (Figure 2C). Twin 2 (IV:2) did not show any abnormality in the macula by either indirect ophthalmoscopy (Figure 2B) or fluorescein angiography (Figure 2D) in both eyes. The intraocular pressures and anterior segments were normal. Neither nystagmus nor strabismus was found in either patient.

The full-field rod ERGs elicited by Ganzfeld stimulation were significantly reduced after 20 minutes of dark adaptation, and they improved but remained subnormal after prolonged dark adaptation in both patients (Figure 3). The amplitudes of the a and b waves of the bright-flash, mixed rod-cone ERG were reduced in both sisters (Figure 3). Although a bright-flash negative-type ERG (b wave < a wave) after 20 to 30 minutes of dark adaptation is a distinct characteristic in FA, it was not possible to use this diagnostic feature because of blink artifacts (Figure 3).

The photopic a and b waves and 30-Hz flicker ERGs were significantly reduced in both patients, indicating the presence of CD (Figure 3). Molecular genetic examination disclosed a compound heterozygous mutation of G to A at nucleotide 394 (Val132Met) and G to A at nucleotide 539 (Arg280His) in the RDH5 gene (Figure 4). Their healthy mother was...
heterozygous, with a mutation at nucleotide 394 but normal findings at nucleotide 539. The same mutations in the gene have been detected in other Japanese patients with FA. No such base substitutions were found in 100 alleles from healthy individuals. In addition to the genotype of the RHDS gene, the monozygosity of the twin indicated that the sex is not a critical condition for the presence of CD because all of the patients with FA associated with CD were men. However, the patients in the present report were women, suggesting that other genetic or environmental factors might have induced the CD in the twins.

The clinical phenotype of patients with FA is heterogeneous. Recently, we examined the RHDS gene in a number of patients with FA with or without macular dystrophy; however, we observed no clear correlation between genotype and phenotype. The details of the factors affecting the progress of CD are still unknown, and additional data must be gathered to help make this clear.

Submitted for publication May 28, 2003; final revision received January 15, 2004; accepted January 15, 2004.

This study was supported in part by Grants-in-Aid for Scientific Research B14370556 (Dr Nakamura) and A13307048 (Dr Miyake) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and by the Ministry of Health, Labor, and Welfare of Japan, Tokyo, Japan.

Correspondence: Makoto Nakamura, MD, Department of Ophthalmology, Nagoya University Graduate School of Medicine, 65 Tsuruma-cho, Showa-ku, Nagoya 466-8550, Japan (makonaka@med.nagoya-u.ac.jp).
REFERENCES