Arrestin Gene Mutations in Autosomal Recessive Retinitis Pigmentosa

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Objective: To assess the clinical and molecular genetic studies of patients with autosomal recessive retinitis pigmentosa associated with a mutation in the arrestin gene.

Design: Results of molecular genetic screening and case reports with DNA analysis and clinical features.

Setting: University medical center.

Patients: One hundred twenty anamnestically unrelated patients with autosomal recessive retinitis pigmentosa.

Methods: DNA analysis was performed by single strand conformation polymorphism followed by nucleotide sequencing to search for a mutation in exon 11 of the arrestin gene. Clinical features were characterized by visual acuity slitlamp biomicroscopy, fundus examinations, fluorescein angiography, kinetic visual field testing, and electroretinography.

Results: We identified 3 unrelated patients with retinitis pigmentosa associated with a homozygous 1-base-pair deletion mutation in codon 309 of the arrestin gene designated as 1147delA. All 3 patients showed pigmentary retinal degeneration in the midperipheral area with or without macular involvement. Patient 1 had a sibling with Oguchi disease associated with the same mutation. Patient 2 demonstrated pigmentary retinal degeneration associated with a golden-yellow reflex in the peripheral fundus. Patients 1 and 3 showed features of retinitis pigmentosa without the golden-yellow fundus reflex.

Conclusions: Although the arrestin 1147delA has been known as a frequent cause of Oguchi disease, this mutation also may be related to the pathogenesis of autosomal recessive retinitis pigmentosa. This phenomenon may provide evidence of variable expressivity of the mutation in the arrestin gene.


Recent molecular genetic analyses of autosomal recessive retinitis pigmentosa (RP) have revealed that mutations in the rhodopsin, the α- or β-subunit of rod cyclic guanosine-monophosphate phosphodiesterase, and rod cyclic guanosine monophosphate–gated channel genes can cause autosomal recessive RP in some families. These mutations have been identified in only a few families with autosomal recessive RP, however, and genetic causes are still largely unknown in most patients. Oguchi disease is a form of congenital stationary night blindness inherited as an autosomal recessive trait, and most Japanese patients with Oguchi disease have had homozygous 1-base-pair deletion of the arrestin gene designated as 1147delA mutation. Oguchi disease has also been reported in other members of families with RP, and partial chorioretinal degeneration is sometimes associated with Oguchi disease. These findings have suggested the possibility that mutations in the arrestin gene are related to not only Oguchi disease but also RP. We, therefore, screened 120 anamnestically unrelated patients with autosomal recessive RP for search for mutations in exon 11 of the arrestin gene by the method previously described and detected the 1147delA mutation in 3 patients. We describe in this report these 3 patients with autosomal recessive RP associated with a homozygous 1147delA mutation in the arrestin gene.

REPORT OF CASES

CASE 1

A 58-year-old man had initially noticed night blindness during his early teens, when he had been diagnosed by a local
ophthalmologist as having RP. After that, he had a gradual progression of visual impairment, including constriction of his visual field and night blindness. His parents were first cousins. His 55-year-old sister (Figure 1, OG12) had Oguchi disease associated with the arrestin 1147delA mutation. Fundus examination showed atrophic macular lesions in both eyes associated with pigmentary retinal degeneration in midpe-

peripheral and peripheral retina bilaterally (Figure 2, A). Fluorescein angiography revealed hypofluorescent areas, indicating chorioretinal atrophy in the macular and pericentral regions, and hyperfluorescent areas in the central and midperipheral regions bilaterally (Figure 3, A). A dark-adapted standard flash electroretinogram (ERG) disclosed decreased amplitudes of the a waves and extinguished amplitudes of the b waves. The amplitudes of the 30-Hz flicker ERG were reduced bilaterally. The scotopic ERG was not recordable (Figure 4).

CASE 2

A 35-year-old man (Figure 1) had had impaired visual acuity in his teens. In addition to a gradual progression of visual impairment, he noticed disturbance of his night vision. Fundus examination demonstrated bilateral pigmentary retinal degeneration in the posterior portion that extended from the macular area to the midperipheral retina (Figure 2, B) and an abnormal golden-yellow fundus reflex in the peripheral area (Figure 2, C) that showed the Mizuo-Nakamura phenomenon. Fluorescein angiography disclosed a diffuse hyperfluorescent area in the posterior portion associated with hypofluorescent areas in the pericentral region bilaterally (Figure 3, C). A dark-adapted standard ERG (Figure 4) showed severely reduced amplitudes of the a waves and extinguished responses of the b waves. The amplitudes of the 30-Hz flicker ERG were reduced bilaterally.
CASE 3

A 72-year-old woman was referred to our clinic because of RP. She had had night blindness and constriction of her visual field for 20 years. She noticed a gradual progression of visual impairment. Her parents were first cousins (Figure 1). Fundus examination showed diffuse pigmentary retinal degeneration in the midperipheral retina associated with attenuated retinal vessels (Figure 2, D). The macular area was relatively spared. Fluorescein angiography disclosed diffuse hyperfluorescence in the posterior and midperipheral regions associated with patchy hypofluorescent areas along the vascular arcade (Figure 3, C). The scotopic ERG showed extinguished amplitudes bilaterally. A dark-adapted standard ERG (Figure 4) disclosed reduced amplitudes of the a waves and extinguished amplitudes of the b waves bilaterally. The amplitudes of the 30-Hz flicker ERG were reduced bilaterally.

COMMENT

Arrestin is a photoreceptor-specific soluble protein that normally plays an important role in quenching the phototransduction cascade by inactivating phosphorylated-activated rhodopsin. The 1147delA mutation in the arrestin gene has been found as a frequent cause of Oguchi disease in the Japanese population. In this study, we found the same mutation in patients with autosomal recessive RP. No other possible disease-causing mutation was found in the rhodopsin, peripherin/RDS, and ROM1 genes in these patients. The results suggest that variable expressivity is produced by the mutation in the arrestin gene.

In our previous study on phenotypic characteristics of patients with Oguchi disease, we also found slight variability in clinical features in patients with the arrestin 1147delA mutation. In particular, the presence of partial chorioretinal degeneration in a patient with Oguchi disease led us to speculate that the arrestin gene might also be a candidate gene of RP. We therefore extended our study and found that a previously unexamined sibling (patient 1) of the patient with Oguchi disease (OG12) had RP that was associated with the same mutation as Oguchi disease. Further screening revealed the homozygous 1147delA mutation in the arrestin gene in 2 additional patients with RP. Phenotypic characteristics of
these 3 patients with the 1147delA mutation were also variable in visual acuity, the distribution of pigmentary retinal degeneration, and the presence or absence of the golden-yellow fundus reflex. The patients commonly showed partial chorioretinal atrophy, however, particularly along the vascular arcade, which was demonstrated by fluorescein angiography (Figure 3). This region is also the location in which partial chorioretinal atrophy preferentially occurs in patients with Oguchi disease. Electrophysiologically, a pattern of rod-predominant impairment was observed in these patients. Although the degree of impairment in rods and cones was more severe in patients with RP than in those with Oguchi disease, the pattern of impairment was similar among patients with the arrestin 1147delA mutation (Figure 4 and Nakazawa et al). As was found in our previous study, clinical expressions associated with the arrestin 1147delA mutation were distributed in Oguchi disease, Oguchi disease with partial chorioretinal degeneration, and RP with or without the golden-yellow fundus reflex. It has been suggested that this variability may be a spectrum of phenotypes caused by a mutation in the arrestin gene. This could also explain the coexistence of patients with Oguchi disease and RP in the same family, although the exact mechanism of such a wide range of clinical features is unknown.

Accepted for publication October 29, 1997.

This study was supported in part by a grant from the Research Committee on Chorioretinal Degenerations and Optic Atrophy, the Ministry of Health and Welfare of the Japanese Government (Dr Nakazawa), Tokyo, and a grant-in-aid for scientific research from the Ministry of Education, Science, and Culture of the Japanese Government (Dr Nakazawa, C-2-09671782), Tokyo.

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