Autosomal Dominant Central Areolar Choroidal Dystrophy and a Novel Arg195Leu Mutation in the Peripherin/RDS Gene

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Increased numbers of mutations in the peripherin/RDS (retinal degeneration slow) gene have been identified in families with autosomal dominant retinitis pigmentosa¹ and several kinds of macular dystrophy.² In this study, we identified a novel heterozygous transversion mutation in codon 195 of the peripherin/RDS gene that results in an amino acid substitution of leucine for arginine (Arg195Leu) in a Japanese family (Figure 1) with autosomal dominant central areolar choroidal dystrophy (CACD). The mutation showed complete cosegregation with the disease in the family and was not found in 100 normal control chromosomes. We describe herein the phenotypic features of patients with autosomal dominant CACD associated with the Arg195Leu of the peripherin/RDS gene, as well as results of a comparative study of the relationship between clinical severity and alteration of putative secondary structures of the mutant Arg195Leu peripherin/RDS protein.

REPORT OF CASES

CASE 1
A 59-year-old man was referred to our clinic because of abnormal macular findings. He had had impaired visual acuity since his fifth decade of life, but he had not experienced night blindness. His right eye had been previously enucleated because of a perforating eye injury. The best-corrected visual acuity was 20/40 OS. Visual field testing of the left eye revealed a ring-shaped parafoveal scotoma with a preserved central region. Slit-lamp microscopy disclosed normal anterior segments and ocular media. Fundus examination showed sharply demarcated areas of chorioretinal atrophy in the macular and peripapillary regions, associated with small patchy areas of granular changes in the retinal pigment epithelial layer around the fovea (Figure 2A). Electoretinogram (ERG) recordings showed subnormal responses of a and b waves (Figure 3).

CASE 2
A 70-year-old man (a first cousin of case 1) had noticed impaired visual acuity in his fifth decade of life but no night blindness. His best-corrected visual acuity was 20/200 OD and 20/250 OS. Visual field testing revealed large central scotomas in both eyes. The anterior segments appeared normal in both eyes. Slight cataracts were seen bilaterally. Fundus examination showed well-circumscribed chorioretinal atrophy that included the macular area and a peripapillary region (Figure 2B). Fluorescein angiography revealed an absence of choriocapillaris in the atrophic area; large choroidal vessels were clearly outlined by fluorescein angiography (Figure 2C). Dark choroid was not observed. The ERG recordings displayed a

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subnormal pattern of cone responses, whereas rod function was within normal range (Figure 3).

CASE 3

A 45-year-old man (a half brother of case 1) had noticed gradual impairment of visual acuity in both eyes since his fourth decade of life. His best-corrected visual acuity was 20/30 OD and 20/50 OS. Fundus examination showed atrophic macular lesions in both eyes (Figure 2D). Fluorescein angiography revealed transmitted hyperfluorescence, suggesting atrophy of retinal pigment epithelium bilaterally (Figure 2E). No area of dark choroid was found.
Figure 3. Electroretinograms (ERGs) of cases 1 and 2. Rod severity was estimated by the pattern of the dark-adapted single white-flash ERG, and cone severity was based on that of the 30-Hz flicker ERG. White-flash ERGs demonstrate slightly reduced (case 1) and normal (case 2) responses of both a and b waves, and 30-Hz flicker ERGs show reduced (subnormal) amplitudes of cone responses in both patients. R indicates right eye; L, left eye; and on, flicker stimulation following the 30-Hz flicker ERG.

Figure 4. Correlation between rod severity and changes in secondary structure scores (A) and between cone severity and changes in secondary structure scores (B). Black squares indicate Arg195Leu (R195L), Arg172Gln (R172Q), and Arg172Trp (R172W) mutations; open squares indicate previously reported missense mutations.2

PREDICTED SECONDARY STRUCTURE CHANGES AND CLINICAL SEVERITY SCORE

Putative secondary structure of a mutant protein was predicted by a method previously described3 using the computer software Gene Works (Teijin, Tokyo, Japan). The protein secondary structure analysis of the Arg195Leu mutation revealed that the secondary structure could be changed at the residues of 2 amino acids, namely, Ser198 (from coil to β structure) and Val200 (from turn to coil), in the Arg195Leu protein compared with wild-type protein. Therefore, the protein structure score was counted as 2. Clinical severity was graded as a score based on each patient’s ERG response by a method previously described.3 Rod severity was estimated by the pattern of the dark-adapted single white-flash ERG, and cone severity was based on that of the 30-Hz flicker ERG. The mean severity of rods and cones estimated by the ERG findings of cases 1 and 2 gave rise to a score of 1 for rods and 2 for cones, respectively. These scores were plotted on the previously described correlation between these 2 scores of other missense mutations (Figure 4).

Based on the clinical features exhibited by these patients, clinical phenotypes of the novel Arg195Leu mutation of the peripherin/RDS gene were characterized as sharply demarcated progressive chorioretinal atrophy in the macular area, which is compatible with findings in CACD.

Central areolar choroidal dystrophy is a heterogeneous disease that has been reportedly associated with the peripherin/RDS locus and some other loci. Among mutations in the peripherin/RDS gene, Arg172Trp,2,4 Arg172Gln,2 and Arg142Trp5 have been previously reported to cause autosomal dominant CACD. It is of particular interest that all of these mutations affect an arginine residue. Although the precise molecular mechanisms are still unknown, it is possible that a substitution of a highly charged amino acid such as arginine to another amino acid residue in the large loop of peripherin/RDS protein may be related to the formation of this focal chorioretinal atrophy.

The natural course of CACD associated with Arg172Trp has been well documented. In particular, a study6 of a large number of Swiss patients with Arg172Trp mutation revealed that most patients become legally blind after age 60 years. Conversely, the clinical course of patients with Arg172Gln has been less severe than that associated with Arg172Trp.2 Based on the phenotypic features described, it is suggested that the clinical course of CACD with Arg195Leu mutation is less severe than that with Arg172Trp.

Previously, Nakazawa et al3 described the relationship between clinical severity and alteration of the secondary structure of putative mutant peripherin/RDS protein and found that the more the secondary structure changed the more severe was the deterioration of ERG responses. In their study, the scores of changes in secondary structure of Arg172Trp and Arg172Gln were 3 and 1, respectively (Figure 4). Also, the scores of clinical severity in these mutations were 2 and 0.5 for rods and cones, respectively (Figure 4). In the present study, the scores of secondary structure changes and clinical severity for rods and cones with Arg195Leu were estimated as 2, 1, and 2, respectively (Figure 4). Therefore, these scores for secondary structures suggest that the severity of disease associated with Arg195Leu as measured by ERG findings lies somewhere between that associated with Arg172Trp and Arg172Gln. As Nakazawa et al reported, information regarding the degree of alteration in the secondary structure may partly predict the clinical severity of phenotypes associated with mutations in the peripherin/RDS gene.
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REFERENCES


ARCHIVES Web Quiz Winner

Congratulations to the winner of our June quiz, Ching Lin Ho, MD, Massachusetts Eye & Ear Infirmary, Boston. The correct answer to our June challenge was nasolacrimal duct mucocele. For a complete discussion of this case, see the Clinicopathologic Reports, Case Reports, and Small Case Series section in the July ARCHIVES (Yip CC, McCulley TJ, Kersten RC, Bowen AT, Alam S, Kulwin DR. Adult nasolacrimal duct mucocele. Arch Ophthalmol. 2003;121:1065-1066).

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