Clinical Findings in a Multigeneration Family
With Autosomal Dominant Central Areolar Choroidal
Dystrophy Associated With an Arg195Leu Mutation
in the Peripherin/RDS Gene

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Objective: To characterize clinical findings associated with a mutation in codon 195 (Arg195Leu) of the peripherin/RDS gene in a large multigeneration family of European decent.

Methods: Sixteen members from 2 generations underwent ophthalmologic examination, including best-corrected visual acuity, examination of the anterior segments, and inspection of the ocular fundus after pharmacologic mydriasis. All affected family members underwent Farnsworth Panel-D15 color testing. Five selected family members with early stages of the disease underwent multifocal electroretinography. Full-field electroretinography was performed in 2 family members with more advanced fundus changes. Finally, former patients’ records and fundus images were analyzed to determine the course of the disease in affected individuals.

Results: Nine family members in 2 generations were diagnosed as having autosomal dominant central areolar choroidal dystrophy. The family demonstrated an age-dependent increase of central granular fundus abnormalities with progressive development of geographic atrophy. Interindividual phenotypic variability was apparent and ranged from predominantly drusenlike depositions to single perifoveal pigment clumps. Age of onset of visual disturbances varied between 27 and 48 years. All individuals who manifested signs of disease were found to carry an Arg195Leu mutation in the peripherin/RDS gene.

Conclusions: Age of onset, progression of the disease, and characteristic fundus abnormalities share similarities to previous reports on families with central areolar choroidal dystrophy associated with peripherin/RDS gene mutations in codons 172, 142, and 195, respectively. However, striking variability in individual phenotypic findings and age of onset in our family suggests that additional factors that modify the defined peripherin/RDS gene mutation Arg195Leu likely influence the severity of the disease.

Clinical Relevance: Caution should be advised in predicting the clinical course and severity of the disease based solely on a specific mutation in the peripherin/RDS gene.

Arch Ophthalmol. 2006;124:1020-1027

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ages (HRA 1; Heidelberg Engineering, Heidelberg, Germany) were obtained in all individuals. Autofluorescence images were recorded according to a standard protocol described previously. All affected family members underwent Farnsworth Panel-D15 color testing. Five selected family members with early stages of the disease underwent multifocal electrophoretinography (mFERG). This method identifies localized dysfunction of the retina (eg, maculopathy) where the full-field electroretinogram is only mildly affected. The mFERG recording procedures adhered to the corresponding International Society for Clinical Electrophysiology of Vision guidelines. The mFERGs were recorded binocularly with dilated pupils and DTL (Dawson-Trick-Litzkow) electrodes using a VERIS system (version 4.16; Electro-Diagnostic Imaging, Inc, San Mateo, Calif). Full-field electroretinography was performed in 2 family members with more advanced fundus changes. The method was performed in concordance with the International Society for Clinical Electrophysiology of Vision standard protocol. Finally, former patients’ records and fundus images were analyzed to determine the course of the disease in affected individuals.

Mutational analysis of the 3 coding exons of the peripherin/RDS gene, including at least 20 base pairs of intervening sequences representing the splice consensus motifs, was performed with the following primer combinations: exon 1: rds1c.f (5’-CCG GAC TAC TGT GAA G-3’)/rds1b.r (5’-ATA GCT CTT ACC CCA GGA CTA-3’); exon 2: rds2a.f (5’-AGG CCC ATC TCC AGC TGT CTG-3’)/rds2b.r (5’-CTT ACC CTC TAC CCC CAG CTG-3’); and exon 3: ex3F (5’-CCA GGG ATT CTC CCA GAT T-3’)/ex3R (5’-GAG TTG GAT GAG GGG GAG AT-3’). Polymerase chain reaction fragments were directly sequenced with the Big-Dye Terminator Cycle Sequencing Ready Reaction Kit (Perkin Elmer, Weiterstadt, Germany) and analyzed on an ABI 310 automated sequencer (Applied Biosystems, Weiterstadt, Germany).

**RESULTS**

The pattern of disease inheritance in 4 generations was consistent with an autosomal dominant trait of CACD in this family (Figure 1). After obtaining informed consent, 9 siblings (III-1 through III-3, III-5, III-6, and III-8 through III-11) (aged 43-61 years) were examined clinically. Five of them revealed signs of the disease. In addition, 7 children (IV-1 through IV-7) aged 14 to 36 years of 2 affected siblings (III-5 and III-6) underwent close ophthalmologic examination. Affected family members reported progressive decrease in central VA, with the onset ranging from age 27 to 48 years. Three individuals (III-5, IV-3, and IV-6) aged 14 to 45 years were not aware of their disease until examination. The age-VA relationship is plotted in Figure 2. None of the affected individuals was aware of problems with night vision or side vision.

Four clinical stages were defined according to the classification established by Piguet et al8 (Table). Consistent with stage 1, two affected family members with perifoveal pigment mottling and tiny foveal, hard drusenlike deposits; preserved central VA (1.0-1.25); and normal color perception were identified (individuals IV-3 and III-5, aged 14 and 45 years). Perifoveal pigment clumps (Figure 3) revealed high autofluorescence properties indicative of abnormal accumulation of retinal pigment epithelium (RPE) lipofuscin. Adjacent spots of low autofluorescence are suggestive of incipient RPE atrophy (arrows in Figure 4). The images depicted central oval-shaped areas of fusely increased autofluorescence up to 11.0° eccentricity. This area was not assessable by conventional fundus imaging. The mFERG17 (Figure 5) showed latencies out of normal limits in rings 1 through 3, indicating photoreceptor dysfunction up to approximately 9.6° eccentricity. Reduction of amplitudes, indicating photoreceptor degeneration, was found in rings 2 and 3.

Two affected family members (IV-6 and IV-7), aged 32 and 30 years, respectively, were classified as having stage 2 disease defined by scattered pigment clumping of the central posterior pole without the presence of focal patches of geographic atrophy (GA). The VA was slightly reduced to 0.8 OU.

Farnsworth Panel-D15 color testing identified specific color disturbances that affected the blue axis. Funduscoppy revealed diffuse depigmentation of the central posterior pole, including tiny clumps of pigment and yellow, hard drusenlike deposits. Family member IV-7 had been examined at 25 years of age with VAs of 1.0 OU. During the past 5 years a change...
from a coarse-grained pigmentation of the central fundus to a more dusty aspect was observed. Autofluorescence images exhibited a speckled central oval-shaped area (Figure 6A and B) reaching eccentricities up to 14° (IV-6). Individual tiny spots of high autofluorescence intensities corresponded to larger pigment clumps in the color image. The mfERG disclosed delayed latencies and reduced amplitudes in all rings of both family members.

Their elder sister (IV-4, aged 34 years, stage 3 disease) experienced her first visual symptoms by age 27 years. Six years later she was found to have a severe decrease in central acuity to 0.05 OU. Results from a saturated Farnsworth Panel-D15 color test showed unspe-
specific dyschromatopsia with no preference of axis in both eyes. Autofluorescence images depicted characteristic speckling within the central oval area similar to the pattern observed in her younger siblings. In addition, the left eye revealed an isolated patch of sharply demarcated chorioretinal atrophy (Figure 6C). The mfERG revealed latencies outside normal limits in all rings whereas amplitudes were extinguished in rings 1 through 4 and markedly reduced in ring 5. Full-field electroretinography displayed a normal scotopic response whereas photopic responses were near the lower limit of normal.

The elder 4 siblings of generation 3 (III-1 through III-3, aged 52-61 years) presented with markedly reduced central acuity (range, counting fingers to 0.1) and advanced GA consistent with stage 4. The eldest sibling (III-6, aged 61 years) was first seen at the age of 37 years when he experienced a significant loss in VA to 0.05 OD and 0.1 OS. He had not been aware of visual symptoms before that time. His eldest sister (III-1) underwent examination at the age of 43 years with a bilateral VA of 0.4. She reported gradual visual deterioration during the past 15 years, down to 0.05 in the right and counting fingers in her left eye at the age of 57 years. The 2 youngest sisters (aged 52 and 54 years) realized severe decline in VA (defined as ≤0.1) by the age of 48 years (III-2) and 32 years (III-3),
respectively. Farnsworth Panel-D15 color test findings showed unspecific dyschromatopsia with no preference of axis in all family members with stage 4 disease. Fundus examination depicted multiple areas of sharply demarcated RPE atrophy surrounded by typical tiny scattered or confluent spots of hyperpigmentation and small, hard drusenlike depositions. Family members III-2 and III-3 displayed an overall yellowish fundus, scattered or confluent spots of hyperpigmentation and demarcated RPE atrophy surrounded by typical tiny drusen examination depicted multiple areas of sharply demarcated RPE atrophy surrounded by typical tiny scattered or confluent spots of hyperpigmentation and small, hard drusenlike depositions. Family members III-2 and III-3 displayed an overall yellowish fundus, scattered or confluent spots of hyperpigmentation and demarcated RPE atrophy surrounded by typical tiny drusen.

**Figure 5.** For amplitude and latency analysis, the multifocal electoretinogram (mfERG) traces were averaged across 5 rings that contained hexagonal stimulus fields of identical eccentricity. Amplitude and latency of each ring average were evaluated by fitting template mfERG traces as derived from our database of 50 healthy individuals. The mfERG of individual III-5 (right eye) exhibits latencies above normal limits as indicated by the gray background (dark blue ±1 SD, light blue ±2 SDs) in rings 1 through 3. In the central ring, the latency delay is accompanied by a preserved amplitude, indicating a beginning dysfunction in the foveal part of the retina.

Former fundus images of individual III-6, aged 37 years, and of individual III-1, aged 43 years, confirmed progression of the disease from a pattern of central RPE mottling to advanced GA. Autofluorescence images disclosed the characteristic speckled pattern extending beyond the vessel arcades and the optic nerve head by the sixth decade of life. Sharply demarcated dark areas of RPE atrophy preferentially involved the papillomacular area in individual III-3 (Figure 6D-G). Full-field electroretinography revealed markedly reduced photopic responses, whereas scotopic responses reached the border of normal limits (individual III-6, aged 61 years). Peripheral visual fields were unremarkable.

Sequence analysis of the 3 coding exons in the peripherin/RDS gene revealed a heterozygous point mutation (nucleotide 584 G>T) in codon 195, resulting in an arginine to leucine change at this position in all 9 affected family members analyzed. Conversely, 7 unaffected relatives in generations III and IV did not harbor the Arg195Leu mutation. Thus, the molecular findings show strict cosegregation of the Arg195Leu mutation with the clinical phenotype of CACD in the family.

The clinical features associated with the Arg195Leu mutation in the peripherin/RDS gene in our family can be categorized as a progressive macular dystrophy with relative preservation of peripheral retinal function. There is a marked similarity to patients carrying the codon 172 (Arg172Trp) and codon 142 (Arg142Trp) mutation with regard to the characteristic RPE motting within a central oval macular configuration and the progression toward GA with age. The appearance of drusenlike deposits as observed in individuals III-2 and III-3 in this family has also been noted in some members of the Dutch families with the Arg142Trp mutation and in patients with the Arg172Trp mutation originating from the Zermatt area of Switzerland.

Consistency in the age of onset and progression of the disease has been reported in families segregating the Arg172Trp mutation in the peripherin/RDS gene. For example, 11 individuals of 11 ancestrally related British families were found to exhibit first visual symptoms by the age of 30 years, and a severe decrease in central acuity (≤20/200) was reported by the late 40s and early 50s in these families. Similarly, 24 affected members of the Swiss family with the same mutation had initial visual symptoms in their 30s (stage 2; VA, 0.8-1.0; mean±SD age, 33±3 years) and decreases in VA below 0.1 by their 40s to 50s. Comparably, severe visual impairment (VA ≤20/200) in 7 members of a Swedish family segregating the Arg172Trp mutation was noted in their fourth to fifth decades of life. Affected members of the Swedish family were found to develop a degeneration of more peripheral parts of the retina with advancing age, suggesting additional involvement of rods late in the disease. Age of onset of first visual symptoms was also reported in 30 affected family members of 7 Dutch families that harbored the Arg142Trp mutation.
Figure 6. Age-dependent variability in pattern of fundus autofluorescence: left eyes of 7 individuals affected by central areolar choroidal dystrophy stages 2 through 4. Individuals IV-7 (A), IV-6 (B) (stage 2 disease), and IV-4 (C) (stage 3 disease) show an abnormal speckled pattern of autofluorescence that reveals enlargement with age and encloses a single patch of geographic atrophy in individual IV-4 (C). There was a range of autofluorescence variability within individuals disclosing central areolar choroidal dystrophy stage 4: III-3 (D), III-2 (E), III-1 (F), and III-6 (G). The characteristic speckled pattern extends beyond the vessel arcades and the optic disc with more advanced age. Sharply demarcated dark areas indicate loss of lipofuscin-loaded retinal pigment epithelial cells. Note that the size of geographic atrophy is not necessarily linked to age.
mutations in retinitis pigmentosa, have been proposed. It has been shown, for example, with ROM1 and peripherin/RDS. Interactions with other gene products, as previously proposed, appear to play an essential role in the assembly, orientation, and structural stability of outer segment discs and to account for an increased turnover of unstable memranous segments. The encoded glycoprotein has been localized to the rim region of the disc membranes of both rods and cones. The functional basis of why some mutations of this gene account for predominantly rod and others for cones may be more susceptible to alterations in stability than foveal cones. Blue cones may play a role, since they are mostly absent from the foveal center, are most numerous at 0.3° to 0.5° from the foveal center, and are markedly different from red and green cones in their anatomical structure and cellular function. The ring of high blue cone density corresponds to the perifoveal region, where the disease is initially observed in our family. Two of these young family members had blue cone deficit. The involvement of blue cones, however, is not supported by the facts that they are relatively sparse (compared with red and green cones) and that the disease spreads into neighboring areas that affect other types of photoreceptors. Finally, we cannot rule out the presence of thus far unknown protective factors for foveal photoreceptors or segment stability factors at the site of the fovea, which could account for the preservation of central acuity up to the age of 45 years, such as in family member IIIa.

In summary, we observed a striking variability in age of onset and macular phenotype in our relatively large family with an Arg195Leu mutation in the peripherin/RDS gene. Also, a single mutation in this gene has been recently noted to cause various phenotypic features, including retinitis pigmentosa, fundus flavimaculatus, and pattern dystrophy in affected members of a single family.23 Thus, a wide phenotypic range associated with an identical mutation in the peripherin/RDS gene is not uncommon. Further investigations may identify whether additional genetic factors may exert an influence on individual phenotype expression and/or whether environmental influences are responsible for the wide range of pathologic changes.

Submitted for Publication: July 1, 2005; final revision received November 7, 2005; accepted November 14, 2005. Correspondence: Claudia N. Keilhauer, MD, Department of Ophthalmology, University Hospital Würzburg, Josef-Schneider-Str 11, D-97080 Würzburg, Germany (ckeilhauer@yahoo.com).

Funding/Support: This study was supported by grant 01KS9603 (IZKF Würzburg) from the Bundesministerium für Bildung und Forschung.

Financial Disclosure: None reported.

Acknowledgment: We thank the family members for their participation.

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