A Novel Locus for Autosomal Dominant Cone and Cone–Rod Dystrophies Maps to the 6p Gene Cluster of Retinal Dystrophies

Marco Castori,[1,2] *Enza Maria Valente,*[1] *Maurizio Clementi,*[3] *Alma Patrizia Tormene,*[4] *Francesco Brancati,*[1,2,5] *Viviana Caputo,*[1,2] *and Bruno Dallapiccola*[1,2]

Purpose. To characterize clinically and genetically a four-generation Italian family with autosomal dominant retinal dystrophy.

Methods. Thirty-seven family members underwent a detailed ophthalmologic investigation, comprising visual acuity determination, fundoscopy, electroretinogram, and electrooculogram. A genome-wide scan was performed, and three candidate genes mapping to the linked region were screened for mutations by direct sequencing.

Results. Nineteen individuals were affected by cone–rod dystrophy and four by cone dystrophy, whereas, in another subject, the diagnosis was compatible with central areolar choroidal dystrophy. The genome-wide search allowed mapping the disease locus to chromosome 6, region p12.2-p21.1, with a maximum lod score of 6.71. Analysis of key recombinants in affected individuals placed the locus to a 12-Mb region flanked by newly generated markers 6-41025 and 6-52969. Assuming complete penetrance, recombinations in two healthy individuals defined a smaller critical region of 3.7 Mb between markers 6-42153 and D6S459. Three genes mapping within the linked interval (*RDS*, *GUCA1A*, and *GUCA1B*) were considered excellent candidates because of their involvement in distinct forms of retinal dystrophies. However, mutation analyses of these genes failed to identify pathogenetic mutations.

Conclusions. The significant lod scores obtained and the absence of mutations in *RDS*, *GUCA1A*, and *GUCA1B* support the existence of a novel, yet unidentified gene responsible for retinal dystrophy within the chromosome 6 cluster. (*Invest Ophthalmol Vis Sci.* 2005;46:3539–3544) DOI:10.1167/iovs.05-0331

Cone–rod dystrophies (CORDs) are pigmentary retinopathies characterized by the primary degeneration of cone photoreceptors, followed by loss of rod photoreceptors. Unlike in retinitis pigmentosa, rod involvement is usually less severe and occurs later than cone dysfunction. Clinically, CORDs lead to an early reduction in visual acuity and color vision, photophobia, sometimes fine nystagmus, and central or paracentral scotomas. In the second stage, owing to secondary rod involvement, night blindness becomes apparent, and loss of the visual field extends to the periphery. The progressive loss of visual acuity can lead to a profound visual deficit and blindness. Ophthalmoscopic examination usually reveals atrophic patches in the pigmented epithelium or extensive areas of atrophy of the macula, with pigmentary deposits in the macular area, occasionally extending to the periphery, and pallor of the optic disc. The electroretinogram (ERG) is altered in both cone and rod response, with predominant involvement of the photopic over the scotopic system. In cone dystrophies (CODs), degeneration affects the cone photoreceptors only, whereas rods remain normal or only mildly affected in the late stages.[1–3]

Genetic heterogeneity of CORDs and CODs is wide, including autosomal dominant, autosomal recessive, and X-linked inheritance. To date, seven genes (*AIPL1*, *CRX*, *GUCA1A*, *GUCY2D*, *RDS*, *RIMS1*, and *UNC119*) and two additional loci (*CORD1* and *CORD4*) have been identified as responsible for autosomal dominant CODs and CORDs.[4–12] Three of these loci/genes (*RDS*, *GUCA1A*, and *RIMS1*) cluster on chromosome 6, and four (*GUCY2D*, *UNC119*, *AIPL1*, and *CORD4*) on chromosome 17. These two chromosomes also contain several additional loci/genes responsible for other dominant and recessive retinal disorders, such as retinitis pigmentosa, Leber congenital amaurosis, Stargardt disease, and central areolar choroidal dystrophy (CACD; Retinal Information Network at: http://www.sph.uth.tmc.edu/Retnet/home.htm/provided in the public domain by the University of Texas Houston Health Science Center, Houston, TX).

A wide clinical heterogeneity mirrors the genetic heterogeneity of these conditions, and mutations in the same gene can cause several distinct phenotypes. A notable example is the *CRX* gene, which is mutated in autosomal dominant CORD, autosomal dominant late-onset retinitis pigmentosa, and autosomal dominant and recessive Leber congenital amaurosis.[5,13,14] Despite the obvious limits in genotype-phenotype correlates, the identification of new genes responsible for these types of retinal dystrophies and the delineation of the associated phenotypes add new insights in the pathogenesis of these disorders and in the correct management of affected individuals.

Herein, we describe a large Italian family with CORD and COD phenotypes, characterized by marked variability in age at onset, progression, and clinical presentation, and we provide evidence for a novel, still unidentified gene responsible for this condition.

From the [1]Istituto di Ricovero e Cura a Carattere Scientifico Casa Sollievo della Sofferenza (IRCCS CSS), Mendel Institute, Rome, Italy; the [2]Department of Experimental Medicine and Pathology, "La Sapienza" University, Rome, Italy; [3]Clinical Genetics and Epidemiology, Department of Pediatrics, and the [4]Department of Neurosciences-Ophthalmology, University of Padua, Padua, Italy; and the [5]Department of Biological Sciences, University "G. D'Annunzio," Chieti, Italy.

Supported by grants from the Italian Ministry of Health (Ricerca Corrente 2004–2005).

Submitted for publication March 15, 2005; revised May 19, 2005; accepted August 16, 2005.

Disclosure: **M. Castori**, None; **E.M. Valente**, None; **M. Clementi**, None; **A.P. Tormene**, None; **F. Brancati**, None; **V. Caputo**, None; **B. Dallapiccola**, None

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Corresponding author: Enza Maria Valente, CSS-Mendel Institute, Viale Regina Margherita, 261, 00198 Rome, Italy; e.valente@css-mendel.it.

TABLE 1. Position on the Physical Map (in Mb), Primer Pairs, PCR Annealing Temperatures and Allele Sizes of Microsatellite Markers Spanning the Linked Region

Marker	Mb	Forward Primer Sequence (5′–3′)	Reverse Primer Sequence (5′–3′)	Annealing Temperature (°C)	Allele Size (bp)
6-41025	41.025	TGGCTGTGTCACTCTCTTGG	ATGAAGGCTGGAGAATGCAG	59	186-202
6-41483	41.483	TGGGTAATGGGAAGCTCAAG	CACTGGTGCAGTGTGGAGTC	58	163-191
6-42153	42.153	TGCGAAGATCCACATCTCTG	AGCGGGTAAATGCAAACAGT	59	230-246
D6S271	43.547	CAATTGGGAAATGGCTTAAAA	CCCGTTAACCCCTTCTTCA	56	192-220
D6S459	45.846	GCAAGTTCTCCTTATCTCACTGG	AACACACTCCCCACGCAGA	59	136-148
6-49770	49.777	GAAATCTTTTGAAAGCCAAACAC	CTTGATTTTCTGGGAAGTTCTTG	59	187-205
6-50893	50.893	TGAGCGTTTGTGTCTGTGTG	CCTTTCCTGACTGCTTGACC	61	219-231
6-51672	51.672	AACAAATTTGGCCTCTGGAA	AAAACAAGGCCAAGTTCTCC	57	169-187
6-52969	52.969	GTCTAGAATGATGCCCTGTCC	CTTCTCCGCTCTTTATGGAA	58	285-301

Newly identified markers are in bold.

PATIENTS AND METHODS

Clinical Examination

A four-generation family originating from Northern Italy was first ascertained in 1994 through the Ophthalmology Department of Padua University. Thirty-seven individuals underwent a detailed ophthalmic examination, including visual acuity determination, fundoscopy, and ERG (evaluation of maximum combined, rod, and cone responses, according to ISCEV [International Society for Clinical Electrophysiology of Vision] standard methods available at http://www.iscev.org). Electrooculogram (EOG), visual field determination, and fluorescein angiography were performed in selected patients, to gain a better definition of the diagnosis. Most patients were regularly followed up over the years. This research adhered to the tenets of the Declaration of Helsinki.

Linkage Analysis

After obtaining written informed consent from each participant, we obtained a 10-mL venous blood sample from the 35 family members and one spouse. Genomic DNA was extracted according to standard methods. Despite the clustering of most COD and CORD genes/loci on chromosomes 6 and 17, we decided to perform a genome-wide search, to identify positively the linked region by excluding the remaining genome.

For the genome-wide search, 380 markers covering the 22 autosomes with an average intermarker distance of 10 cM were PCR amplified in a thermal cycler (model 9700; PerkinElmer, Wellesley, MA) using panels of fluorescently labeled primers (Prism Linkage Mapping Set ver. 2; Applied Biosystems, Inc. [ABI], Foster City, CA), according to the manufacturer's instructions. The amplified fragments were electrophoresed in a genetic analyzer (3100 Prism; ABI) and examined on computer (Genescan and Genotyper software; ABI). Two-point lod scores were generated with the Fastlink version of the MLink program (http:www.hgmp.mrc.ac.uk/ provided in the public domain by the Human Genome Mapping Project Resources Centre, Cambridge, UK), assuming an equal male–female recombination rate, autosomal dominant inheritance, equal allele frequencies for each markers, a gene frequency of 0.0001, and reduced penetrance (0.80). The four probably affected individuals (see the Results section) were considered as "unknown phenotype" for linkage calculations. Haplotypes were manually constructed and phase assigned based on the smallest number of recombinants.

To saturate the linked region, additional polymorphic markers were selected from the Human Genome Working Draft (http://genome.ucsc.edu/ provided in the public domain by UCSC Genome Bioinformatics, University of California at Santa Cruz, Santa Cruz, CA) or were newly generated using the Tandem Repeat Finder software.[15] For each marker, the forward primer was fluorescently labeled with either an FAM or an HEX dye. Polymerase chain reactions were performed in a final volume of 15 μL containing 70 ng genomic DNA; 10 picomoles of each primer; 2 mM each of dATP, dCTP, dGTP, and dTTP; 1.5 μL 10× magnesium-free PCR Gold buffer (GeneAmp; ABI), 2.5 mM magnesium chloride; and 0.5 units of DNA polymerase (AmpliTaq Gold; ABI). Initial denaturation at 95°C for 11 minutes was followed by 30 cycles of denaturation at 94°C for 30 seconds, specific annealing temperature for 30 seconds, and extension at 72°C for 30 seconds. A final extension step was performed at 72°C for 7 minutes. Primer pairs, PCR annealing temperature, allele size range and the position of each marker on the physical map of the human genome are reported in Table 1.

Candidate Genes Analysis

All exons and intron–exon junctions, 5′ and 3′ untranslated regions of selected candidate genes were entirely sequenced in two affected family members and one unrelated control, using the dye termination chemistry and a DNA sequencer (Big Dye Terminator and 3100 Prism; ABI). Primer pairs and PCR conditions are available on request.

RESULTS

Clinical Results

The pedigree of the family is depicted in Figure 1. Vertical and male-to-male transmission indicated an autosomal dominant mode of inheritance of the disease. Twenty-four family members received a definite diagnosis of retinal dystrophy based on clinical history, fundus examination, and visual electrophysiological screening. Three distinct phenotypes were identified based on the appearance of first symptoms and the clinical evolution of the disease (Table 2).

Nineteen patients (Fig. 1, filled symbols) received a diagnosis of CORD. The disease became manifest in the fourth decade of life, with slow progression to a gradual reduction of visus and chromatic sensitivity, slight photophobia, and, in the late stages, night blindness. Fundoscopy showed wide areas of atrophy of the posterior pole, converging midperipheral areas of atrophic pigmented epithelium and choriocapillaries, and/or bone-spicule–type pigment accumulations in the peripheral retina (Fig. 2a). ERG was initially affected in the cone component only, but subsequently there was a similar reduction in the rod response. EOG, which could not always be recorded because of the severely reduced visual acuity, was either normal or showed a slight reduction of the EOG index. Some individuals in their second or third decade, albeit clinically asymptomatic, presented macular alterations, and ERG subnormal responses and were judged to be affected.

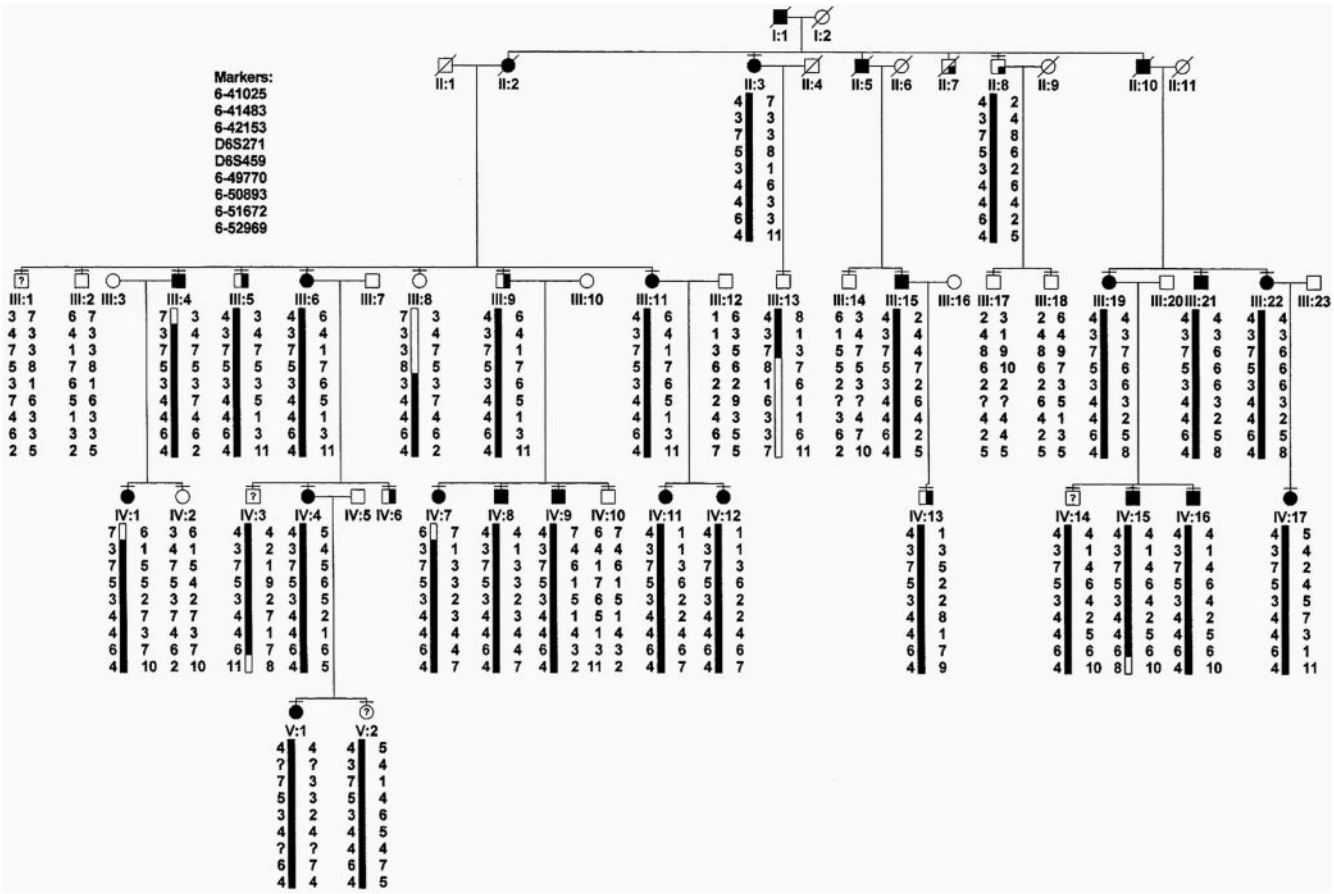

FIGURE 1. Family tree with haplotypes spanning the linked interval on chromosome 6p12.2-p21.1. *Filled symbols*: patients with CORD; *half-filled symbols*: individuals affected by COD; *one-quarter-filled symbols*: individuals with selective macular atrophy; *symbols with diagonal slash*: deceased members. *question mark*: probably affected family members; *thin horizontal line above symbol*: individuals who were clinically examined; *black vertical bars*: haplotype segregating with the disease in the family.

Four individuals (Fig. 1, half-filled symbols) received a diagnosis of COD, characterized by reduction in visual acuity and changes in chromatic sensitivity at a much earlier age (III:5, at birth; III:9, IV:6, and IV:13, in the second to third decade). Subject III:9 was also affected by nystagmus. In these subjects, the retina showed signs of atrophy in the macular area (Fig. 2b), whereas the ERG was reduced in the cone response. This reduction progressed with time but did not involve the rod function, with the only exception being subject III:5, who showed a mild reduction of rod response after more than 30 years of disease progression.

The remaining affected individual (Fig. 1, one-quarter-filled symbol) presented a much milder phenotype, characterized by isolated visus reduction appearing at a more advanced age (>60 years). Ophthalmoscopic examination revealed an area of atrophy limited to the macular region (Fig. 2c), whereas ERG showed a marked reduction of cone response with minimal abnormalities in rod response. Fluorescein angiography showed chorioretinal atrophy restricted to the macular area. This patient received a diagnosis of CACD.

Four additional individuals (aged 68, 30, 29, and 19 years) had suspected retinal dystrophy, due to the presence of visual impairment and mild fundus abnormalities but with normal results in functional investigations such as ERG and EOG. Five deceased family members were deemed affected according to their histories, based on the anamnestic report of progressive visual loss leading to blindness or evaluation of available clinical records and functional examinations.

Genetic Results

The genome-wide search generated negative or nonsignificant lod scores for all genotyped loci, except for 11 markers on chromosomes 2, 6, 11, 17, and 22. The regions surrounding these loci were saturated with densely spaced additional markers, and haplotypes were manually constructed. The segregation of different haplotypes in affected individuals, and the negative lod scores obtained allowed exclusion of all regions but a 12-Mb interval in region 6p12.2-p21.1. All genotyped markers within this interval generated lod scores above 3, with a maximum lod score of 6.71 for marker 6-49770 (recombination fraction $\theta = 0.0$). The boundaries of the region were determined by recombination events that occurred in affected individuals III:4 and IV:7 (upper flanking marker: 6-41025) and individual IV:15 (lower flanking marker: 6-52969). Under the assumption of complete penetrance, recombinations in the healthy individuals III:8 and III:13 defined a smaller critical region of 3.7 Mb between markers 6-42153 and D6S459 (Fig. 1). This region contains two COD/CORD genes, *GUCA1A* and *RDS* (the latter being responsible also for a form of autosomal dominant CACD), and the gene *GUCA1B*, recently identified as responsible for retinitis pigmentosa or isolated macular degeneration.[16,17] Also, the larger identified region overlaps with a locus for benign concentric annular macular dystrophy spanning the pericentromeric region of chromosome 6 (Fig. 3).[18]

The three candidate genes *RDS* (retinal degeneration slow, RefSeq NM_000322), *GUCA1A* (guanylate cyclase activator 1A,

TABLE 2. Clinical Details of Definitely Affected Family Members

No.	Age at Latest Examination (y)	Diagnosis	VOD	VOS	ERG				EOG	
					Sco OS	Sco OD	Pho OD	Pho OS	OD	OS
II:3	80	CORD	HM	HM	SN	SN	SN	SN	NP	NP
II:8	70	CACD	HM	HM	SN	SN	NR	NR	NP	NP
III:4	58	CORD	0.1	0.2	SN	SN	SN	SN	NP	NP
III:5	70	COD	CF	CF	SN	SN	NR	NR	NP	NP
III:6	66	CORD	CF	CF	SN	SN	NR	NR	NP	NP
III:9	60	COD	0.02	0.02	N	N	NR	NR	NP	NP
III:11	53	CORD	0.1	0.1	SN	SN	SN	SN	NP	NP
III:15	60	CORD	0.02	0.01	SN	SN	NR	NR	NP	NP
III:19	59	CORD	0.1	0.04	SN	SN	SN	SN	140	146
III:21	57	CORD	CF	CF	SN	SN	SN	SN	NP	NP
III:22	50	CORD	0.02	0.02	SN	SN	SN	SN	NP	NP
IV:1	30	CORD	0.9	0.9	SN	SN	SN	SN	NP	NP
IV:4	44	CORD	0.1	0.1	SN	SN	SN	SN	NP	NP
IV:6	48	COD	0.8	0.8	N	N	SN	SN	155	160
IV:7	26	CORD	0.8	0.8	N	N	SN	SN	NP	NP
IV:8	29	CORD	0.8	0.8	SN	SN	SN	SN	181	179
IV:9	32	CORD	0.02	1.0	SN	SN	SN	SN	NP	NP
IV:11	24	CORD	1.0	1.0	SN	SN	SN	SN	178	180
IV:12	19	CORD	0.6	0.6	SN	SN	SN	SN	177	180
IV:13	30	COD	0.8	0.8	N	N	SN	SN	179	178
IV:15	35	CORD	0.7	1.0	SN	SN	SN	SN	177	167
IV:16	29	CORD	1.0	1.0	N	N	SN	SN	173	165
IV:17	25	CORD	1.0	1.0	SN	SN	SN	SN	170	173
V:1	21	CORD	0.8	0.8	SN	SN	SN	SN	183	179

CACD, central areolar choroidal dystrophy; CF, count fingers; COD, cone dystrophy; CORD, cone–rod dystrophy; EOG, electrooculography (normal, ≥180); ERG, electroretinogram; HM, hand motion; N, normal; NP, not performed; NR, nonrecordable; Pho, photopic; Sco, scotopic; SN, subnormal; VOD, VOS, visual acuity right and left eye, respectively.

RefSeq NM_000409) and *GUCA1B* (guanylate cyclase activator 1B, RefSeq NM_002098) were screened for mutations. Sequencing of the entire coding region, splice site junctions, and 5′ and 3′ untranslated regions did not reveal any pathogenetic change. Several polymorphisms were found in the sequences of the three genes, all previously reported.

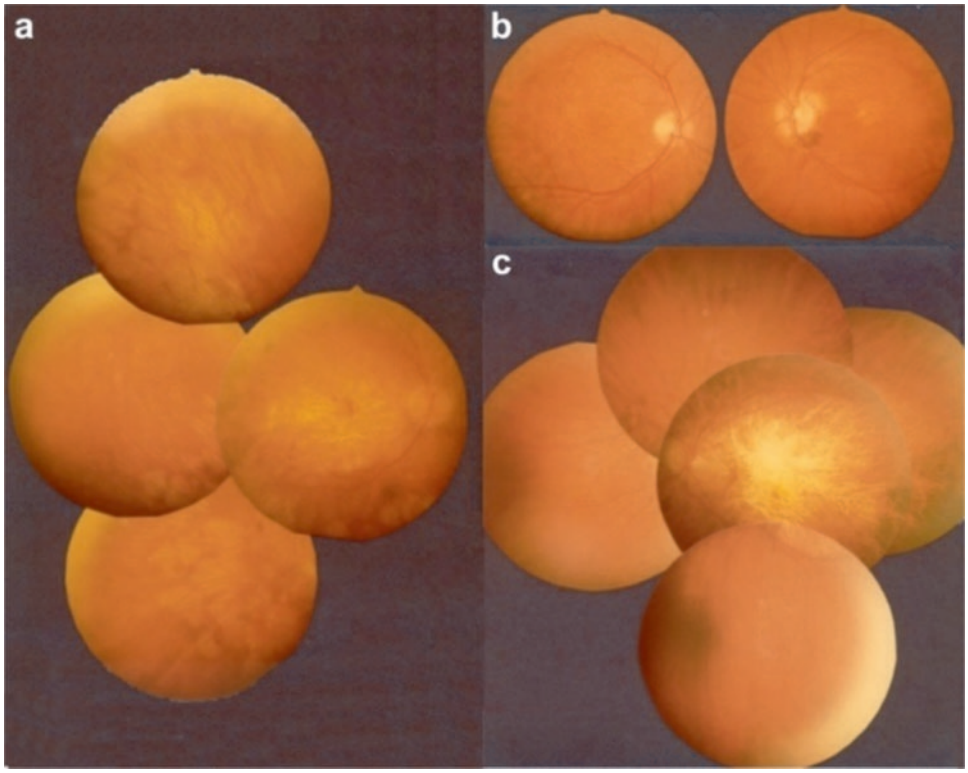

FIGURE 2. Fundoscopy of the three phenotypes observed in this family. (**a**) Patient III:15 (CORD): normal optic disc, attenuation of retinal vessels, area of atrophy of retinal pigmented epithelium (RPE) in the macula, confluent patches of atrophy of RPE, and pigment deposits in midperiphery. (**b**) Patient IV:13 (COD): slight pallor of the temporal optic disc in the right eye, peripapillary chorioretinal atrophy with pigment deposits (myopic) in the left eye, normal vessels, and slight alterations of RPE in the macula (fine granular pigmentation and depigmentation). (**c**) Patient II:8 (CACD): normal optic disc and vessels, RPE, and choriocapillaris atrophy with indistinct limits in the macula.

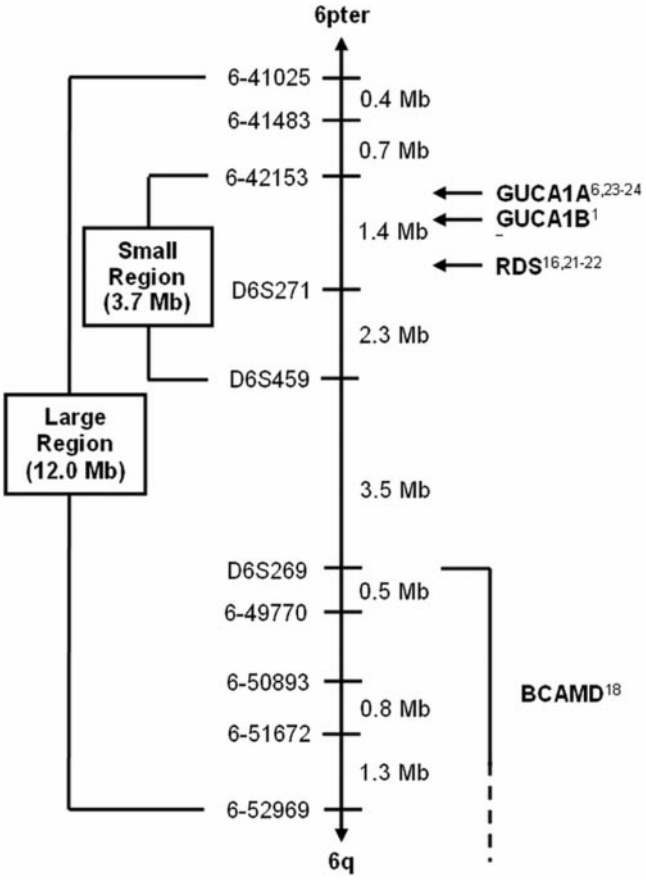

FIGURE 3. Physical map of the linked region. The large region (flanking markers: 6-41025 and 6-52969) is defined by recombinations in the affected individuals III:4, IV:7, and IV:15, whereas the small region (flanking markers: 6-42153 and D6S459) is defined by recombinations in the healthy individuals III:8 and III:13. The physical distances and relative position of markers and candidate genes (*GUCA1A*, *GUCA1B*, and *RDS*) are taken from the University of California at Santa Cruz human genome mapping project (at http://genome.ucsc.edu/; May 2004 assembly). The benign central areolar macular dystrophy (*BCAMD*) locus partly overlaps the large but not the small linked region identified in this study.

DISCUSSION

The clinical and genetic heterogeneity of CODs and CORDs is well known, and intrafamilial variability has been reported frequently. The large family described in the current study represents yet another example of this marked variability, with a retinal phenotype ranging from CACD, to cone dystrophy, to cone–rod dystrophy. Four individuals showed visual impairment and mild fundus abnormalities, but ERG and EOG examinations were normal. Three of them (individuals IV:3, IV:14, and V:2) carried the disease haplotype. These three patients were young at the time of examination (aged 30, 29, and 19 years). Thus, their visual impairment could represent a very mild presentation of the disease, with possible evolution into a more severe phenotype over time. Conversely, the individual who did not carry the disease haplotype (III:1) was 68 years of age at the time of examination. As the onset of the disease is usually in the fourth to fifth decades, it is less likely that this individual will have progressive retinal dystrophy in the future. In this family, it was not possible to estimate penetrance accurately, as only two definitely healthy family members (III:8 and III:13) carried distinct parts of the at-risk haplotype (Fig. 1), and one of them may indeed be carrying a nonpenetrant mutation. For this reason, a conservative estimate of the linked region was made on the basis of recombinations in affected individuals only. However, as reported for other CORDs,[19,20] the disease gene could be fully penetrant in the present family. In this case, recombinations in the two healthy individuals partly carrying the disease haplotype would significantly refine the critical region from 12 to 3.7 Mb. This smaller region still contains the three candidate genes analyzed in this study, but does not overlap with the locus for benign concentric annular macular dystrophy (Fig. 3).

There is no clear genotype–phenotype correlation within the distinct genetic forms of CODs and CORDs, with very similar clinical presentation and functional results.

Within our candidate region, three genes (*RDS*, *GUCA1A*, and *GUCA1B*) have been shown to be involved in various forms of hereditary retinal dystrophy: the first two being also responsible for phenotypes clinically indistinguishable from the cases described herein. More than 30 distinct mutations of the *RDS* gene have been reported in a wide spectrum of retinal dystrophies, including CORD, adult vitelliform macular dystrophy, classic retinitis pigmentosa, and CACD—occasionally with extreme intrafamilial phenotypic variability.[16,21,22] Three missense mutations in the *GUCA1A* gene have been found in autosomal dominant COD families, although one of these (the P50L mutation) segregated in a family with both COD and CORD.[6,23,24] Recently, a single missense mutation (G157R) in *GUCA1B*, an orthologous gene of *GUCA1A*, has been identified in three unrelated Japanese families with retinitis pigmentosa or isolated macular degeneration.[17] However, a previous screening of 400 British probands who had with a range of autosomal dominant retinal dystrophies yielded negative results.[25] Mutation screening in our family failed to reveal pathogenetic mutations in any of these three genes, supporting the existence of an additional, still unidentified gene responsible for a retinal phenotype on chromosome 6.

Outside the linked region defined herein, seven additional genes or loci responsible for various types of dominant and recessive retinal dystrophies have been mapped to chromosome 6 (Retinal Information Network). The existence of such a cluster of genes on the same chromosome is not exceptional, and clusters of genes causing similar phenotypes and mapping in close proximity to each other have been described previously. For instance, the long arm of human chromosome 8 harbors five epilepsy genes and loci that give rise to different epilepsy syndromes.[26–28]

The human genome working draft reports more than 100 genes within the 12-Mb region identified in this study. However, no other striking candidate genes were identified through a bioinformatic analysis of the region based on tissue expression pattern and putative function of gene products. The ascertainment of other families with retinal dystrophy showing linkage to this locus but without mutations in the *RDS*, *GUCA1A*, and *GUCA1B* genes will greatly help refine the critical interval and ease the identification of a novel gene.

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