Molecular Vision 2005; 11:143-51 <http://www.molvis.org/molvis/v11/a16>
Received 29 November 2004 | Accepted 18 January 2005 | Published 19 February 2005

Autosomal dominant cone dystrophy caused by a novel mutation in the GCAP1 gene (*GUCA1A*)

Li Jiang,[1,2,3] Bradley J. Katz,[1,2] Zhenglin Yang,[1,2,4] Yu Zhao,[1,2] Nathan Faulkner,[1,2] Jianbin Hu,[1,2,4] Jennifer Baird,[1] Wolfgang Baehr,[1,3,5] Donnell J. Creel,[1] Kang Zhang[1,2,5]

Departments of [1]Ophthalmology and Visual Sciences, [3]Biology, and [5]Neurobiology and Anatomy, and the [2]Program in Human Molecular Biology and Genetics, University of Utah Health Sciences Center, Salt Lake City, UT; [4]Sichuan Provincial Medical Academy & Sichuan Provincial People's Hospital, Sichuan, People's Republic of China

Purpose: To describe the clinical features and genetic analysis of a family with an autosomal dominant cone dystrophy (adCD).

Methods: Selected members of a family with an autosomal dominant cone dystrophy underwent ophthalmic evaluation. Blood samples were obtained, genomic DNA was isolated, and genomic fragments were amplified by PCR. Linkage to locus D6S1017 was established. DHPLC mutational analysis and direct sequencing were used to identify a mutation in *GUCA1A*, the gene encoding the guanylate cyclase activating protein 1 (GCAP1).

Results: Of 24 individuals who are at risk of the disease in a five generation family, 11 members were affected. Clinical presentations included photophobia, color vision defects, central acuity loss, and legal blindness with advanced age. The disease phenotype was observed in the second and third decades of life and segregated in an autosomal dominant fashion. An electroretinogram performed on one proband revealed profoundly subnormal and prolonged photopic and flicker responses, but preserved scotopic ERGs, consistent with a cone dystrophy. Mutational analysis and direct sequencing revealed a C451T transition in *GUCA1A*, corresponding to a novel L151F mutation in GCAP1. Like the E155G mutation, this mutation occurs in the EF4 hand domain, a region of GCAP1 critical in conferring calcium sensitivity to the protein. The leucine at this position is highly conserved among vertebrate guanylate cyclase activating proteins.

Conclusions: A novel L151F missense mutation in the EF4 high affinity Ca^{2+} binding site of GCAP1 is linked to adCD in a large pedigree. The cone dystrophy in this family shares clinical and electrophysiologic characteristics with other previously described adCD caused by mutations in *GUCA1A*.

The cone dystrophies are a phenotypically heterogeneous group of hereditary retinal degenerations characterized by progressive dysfunction of the photopic (cone mediated) system, presenting with hemeralopia (day blindness), loss of color vision, reduced central visual acuity, and preserved peripheral vision [1]. Cone dystrophies may be contrasted to rod dystrophies, such as retinitis pigmentosa, which are characterized by abnormalities in scotopic (rod mediated) functions, manifesting as night blindness, preserved central visual acuity early in the disease process, and constricted peripheral vision. Early in the disease process, the fundus appearance of a patient with a cone dystrophy may be normal. The disease is then diagnosed based on characteristic changes in the electroretinogram. Later in the disease process, the retinal pigment epithelium may take on a granular appearance that may progress to central atrophy.

Like retinis pigmentosa (RP), the cone dystrophies are genetically heterogeneous and may present as a sporadic, autosomal dominant, autosomal recessive, or X-linked recessive trait (RetNet). Identified genes linked to autosomal dominant cone dystrophies include *GUCY2D*, encoding photoreceptor guanylate cyclase 1 (retGC-1, or GC1) and *GUCA1A*, encoding the photoreceptor specific Ca^{2+} binding protein termed guanylate cyclase activating protein 1 (GCAP1). GC1 and GCAP1 are key components in the phototransduction cascade in rod and cone photoreceptors. In the dark adapted state, photoreceptors have high levels of cGMP and this molecule holds photoreceptor plasma membrane cation channels open. Exposure to light initiates the phototransduction cascade in photoreceptors, resulting in the hydrolysis of cGMP and closure of the cGMP-gated cation channels [2-4]. The concentration of free intracellular Ca^{2+} decreases as a consequence of continued activity of the Na^{+}/Ca^{2+}-K^{+} exchanger (NCKX) exchanger also located in the plasma membrane, an event that in turn activates guanylate cyclases [4]. The stimulation of the guanylate cyclases by decreased levels of calcium occurs indirectly via GCAPs [5-7]. The GCAP-stimulated GC activity eventually returns cGMP to levels that are sufficient to reopen the cGMP-gated cation channels, establishing the dark adapted state.

The GCAPs are neuron specific calcium binding proteins (NCBPs), a subgroup of the large calmodulin supergene family with four EF hand [8] motifs [9]. NCBPs include recoverins, another set of photoreceptor specific Ca^{2+} binding proteins, frequenins, hippocalcins and hippocalcin-like proteins, neu-

Correspondence to: Dr. Kang Zhang, Eccles Institute of Human Genetics, 15 North 2030 East, Building 533, Room 3060A, University of Utah Health Science Center, Salt Lake City, UT, 84132; Phone: (801) 585-6797; FAX: (801) 585-3501; email: kang.zhang@hmbg.utah.edu

ronal Ca^{2+} sensors and many others [10]. Unlike calmodulin and other NCBPs, the GCAPs activate their target proteins, the guanylate cyclases, when the concentration of free intracellular Ca^{2+} is low [11], while other NCBPs activate their targets when the concentration of free Ca^{2+} is high. Up to eight GCAPs have been identified in vertebrates [12], but in human retina there are only three (GCAP1, GCAP2, and GCAP3). The mouse appears to express only GCAP1 and GCAP2, but not GCAP3 [11,13]. The human and mouse GCAP1 and GCAP2 genes reside in a tail-to-tail array on chromosome 6p21.1 and chromosome 17, respectively, and share a four-exon/three-intron arrangement [14,15]. GCAP3 has the same exon/intron arrangement, but has been localized to 3q13.1 [11]. Thus, it appears that these three GCAP genes arose as a result of the duplication and translocation of a common ancestral gene.

Four different mutations linked to retina disease have been previously described in GCAP1 (Y99C, P50L, E155G, and I143NT) [16-20]. All are missense mutations, one (I143NT) has an insertion of an additional amino acid residue. Loss of Ca^{2+} sensitivity is associated with the Y99C, E155G, and I143NT mutations. Common to these is that the mutation affects one of the three functional EF hand motifs in GCAP1 (EF3 or EF4). The biochemical effect of the mutations consists of the inability of the mutant GCAPs to inhibit photoreceptor GC in the dark, when Ca^{2+} is elevated [21,22]. The result is that cGMP levels are elevated in mutant photoreceptors, and a larger number of cation channels remain open, which eventually leads to elevated Ca^{2+} concentration and to photoreceptor cell death [23]. In this manuscript, we describe the clinical features of and the genetic mutations in a family with an autosomal dominant cone dystrophy carrying a novel missense mutation in the GUCA1 gene.

METHODS

Patients: This study was approved by the Institutional Review Board of the University of Utah Hospitals and Clinics and all subjects provided informed consent prior to participation. Some subjects underwent complete ophthalmologic ex-

Table 1. Oligonucleotide primers used for amplification and sequencing of exons 1-4 of the human GUCA1A (GCAP1) gene

Exon	Primer sequence
GCAP1_1F	5'-GGCCTGTCCATCTCAGACGT-3'
GCAP1_1R	5'-CCCCAGCTGGTCAGGCTTCCAG-3'
GCAP1_2F	5'-GCCTGAGGCTGGAGTGAGCG-3'
GCAP1_2R	5'-CTAACCCTGGGCTCTCAGTTCC-3'
GCAP1_3F	5'-CCTGAGATAGGATAAGGATGG-3'
GCAP1_3R	5'-ACCCCACATCCATGGTGACC-3'
GCAP1_4F	5'-CTGGACTGCAGAAATGAACACCCTC-3'
GCAP1_4R	5'-GGCGAGCTAAGCCTCTGAGTTC-3'

Primers marked with "F" are forward (sense) primers, while those marked with "R" are reverse (antisense) primers. Amplicons generated with F/R pairs were directly sequenced to identify mutations in the GCAP1 gene.

Table 2. Accession numbers or references for GCAP sequences used in the alignment of Figure Figure 3B

Name	Species	Source
bGCAP1	Bos taurus	AAB31698
hGCAP1	Homo sapiens	NP_000400
mGCAP1	Mus musculus	NP_032215
rGCAP1	Rattus norvegicus	27681847
cGCAP1	Gallus gallus	P79880
fGCAP1	Rana pipiens	O73761
zGCAP1	Danio reric	AAK95947
fuGCAP1	Fugu rubripes	CAD12779
siluGCAP1	Xenopus (Silurana) tropicalis	AL874865
oryGCAP1	Oryzias latipes	BAB83093
bGCAP2	Bos taurus	L43001
hGCAP2	Homo sapiens	8928106
mGCAP2	Mus musculus	NP_666191
sbGCAP2	Morone saxatilis	unpublished data
cGCAP2	Gallus gallus	P79881
fGCAP2	Rana pipiens	O73762
siluGCAP2	Xenopus (Silurana) tropicalis	AL797721
oryGCAP2	Oryzias latipes	BAB83094
fuGCAP2	Fugu rubripes	CAD12780
zGCAP2	Danio reric	AAK95948
hGCAP3	Homo sapiens	AAD19944
zGCAP3	Danio reric	AAK95949
zGCAP4	Danio reric	AY850384
zGCAP5	Danio reric	AY850385
zGCAP7	Danio reric	AY850386
fGCIP	Rana pipiens	O73763
fuguGCIP	Fugu rubripes	[12]

Up to eight GCAP genes have been identified in vertebrates (mammals, fishes, and amphibia). One sequence (sbGCAP2, from M. saxatiolis) is unpublished, and one sequence (fuguGCIP), derived from genomic contigs as described in [12], is not available from Genbank.

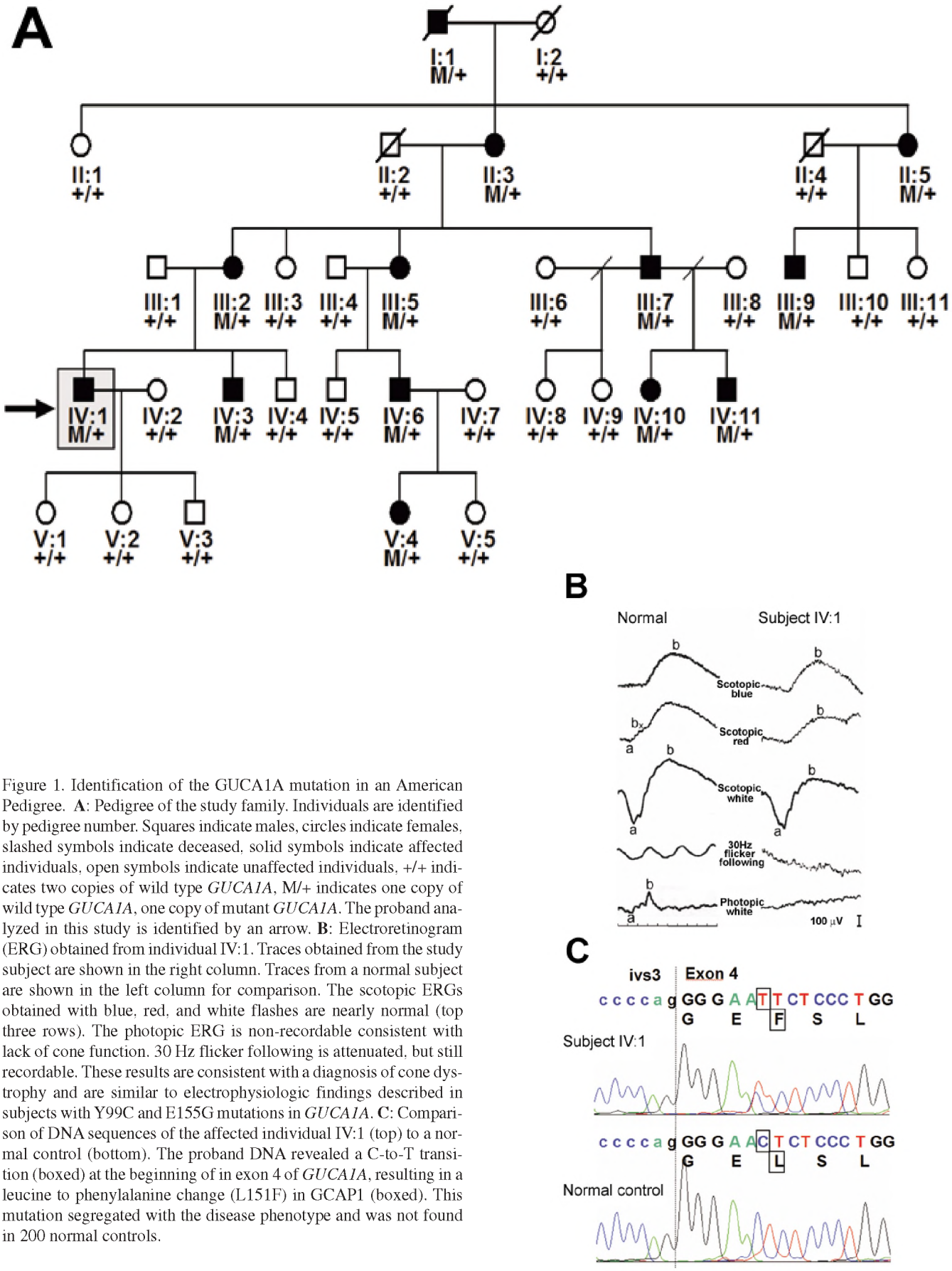

Figure 1. Identification of the GUCA1A mutation in an American Pedigree. **A**: Pedigree of the study family. Individuals are identified by pedigree number. Squares indicate males, circles indicate females, slashed symbols indicate deceased, solid symbols indicate affected individuals, open symbols indicate unaffected individuals, +/+ indicates two copies of wild type *GUCA1A*, M/+ indicates one copy of wild type *GUCA1A*, one copy of mutant *GUCA1A*. The proband analyzed in this study is identified by an arrow. **B**: Electroretinogram (ERG) obtained from individual IV:1. Traces obtained from the study subject are shown in the right column. Traces from a normal subject are shown in the left column for comparison. The scotopic ERGs obtained with blue, red, and white flashes are nearly normal (top three rows). The photopic ERG is non-recordable consistent with lack of cone function. 30 Hz flicker following is attenuated, but still recordable. These results are consistent with a diagnosis of cone dystrophy and are similar to electrophysiologic findings described in subjects with Y99C and E155G mutations in *GUCA1A*. **C**: Comparison of DNA sequences of the affected individual IV:1 (top) to a normal control (bottom). The proband DNA revealed a C-to-T transition (boxed) at the beginning of in exon 4 of *GUCA1A*, resulting in a leucine to phenylalanine change (L151F) in GCAP1 (boxed). This mutation segregated with the disease phenotype and was not found in 200 normal controls.

amination including visually acuity measurements and fundus examinations. Other subjects were interviewed by telephone. Blood samples were obtained by venipuncture. Patients were diagnosed with cone dystrophy if they showed the classic triad of photophobia, decreased color vision, and decreased visual acuity.

Electroretinography: One patient underwent electroretinography. Electroretinograms (ERGs) were recorded using standard electrophysiologic methods (D. Creel, Clinical Electrophysiology, Webvision). The subject was dark adapted for 30 min. Reference and ground electrodes were each attached to an earlobe. Using an indirect headlamp with several Wratten 26 red filters simulating a mobile dark room "safe" light, a Burian-Lawwill speculum contact lenses was inserted to record ERGs from the cornea. Responses were obtained using a Nicolet ganzfeld bowl, amplifier, and computer. Responses were differentially amplified (band pass 0.1-1000 Hz), averaged, and stored. Amplitude band pass sensitivity was one millivolt. ERGs were recorded using single scotopically balanced dim blue and red flashes, and bright white flashes. Patients were then light adapted with background illumination of $3.18x10^4$ cd/m^2 for 10 min and photopic ERGs were recorded using 30 Hz flicker following and the same bright white flash.

Genetic linkage and mutation screening: Genomic DNA was extracted from blood samples using a Qiagen DNA isolation kit according to the manufacturer's specifications (QIAGEN, Valencia, CA). Linkage to microsatellite marker D6S1017, linked to the GCAP1 locus was assessed using established methods [24]. Each of the four exons of GCAP1 were then amplified by PCR using flanking intron specific primers (Table 1) and screened for mutations by denaturing high performance liquid chromatography (DHPLC; WAVE® System, Transgenomic, Omaha, NE). Sequence alterations were identified by direct sequencing with a CEQ Dye Terminator Cycle Sequencing Kit on Beckman-Coulter CEQ 8000 Genetic Analysis System, according to the manufacturer's instructions and using established methods [25,26].

Fundus photography: Fundus photographs and fluorescein angiography were performed using a TOPCON digital fundus camera according to the manufacturer's specification (TOPCON America Corporation, Pleasanton, CA).

Sequence alignments: The alignments of FastA versions of GCAP amino acid sequences were generated by Clustal W (version 1.82). The GenBank accession numbers for the amino acid sequences are in Table 2.

RESULTS

Clinical evaluation of the family with adCORD: The pedigree consisted of 30 living members of a five generation family (Figure 1A) in which the disease was inherited in an autosomal dominant pattern. Clinical characteristics of the family (Table 3) included photophobia, color vision defects and central acuity loss. Most subjects within the family noted symptoms in the second and third decades of life. Visual acuity ranged from younger individuals with normal or nearly normal visual function to older individuals with legal blindness. Representative fundus photos from two individuals from this pedigree are presented in Figure 2. The proband IV:1 at age 36 is mildly affected. Fundus examinations revealed only subtle pigmentary changes in the macula (Figure 2A,B). However, the fundus fluorescent angiogram of this individual (Figure 2C,D) revealed more marked atrophic changes in the macula than can be seen on fundus examination. The mother of the proband at age 64 is more severely affected and has geographic atrophy of the retina and retinal pigment epithelium (Figure

Table 3. Clinical characteristics of individuals from study family

Individual	Gender	Current age	Current acuity OD	Current acuity OS	Age at onset of symptoms	Age at time of correct diagnosis
II:3	F		<20/200	<20/200	3	
II:5	F	88	<20/200	<20/200	5	40
III:2	F	64	20/400	20/400	20	16*
III:5	F	60	<20/300	<20/300	28	32
III:7	M	64	20/200	20/400	11	32
III:9	M	52	20/400	20/400	8	16
IV:1	M	38	20/40	20/50	24	24*
IV:4	M	24	20/40	20/40	8-13	24
IV:6	M	33	20/40	20/40	26	32
IV:10	F	36	20/400	20/200	14	25
IV:11	M	39	20/30	20/30	27	27
V:4	F	8	20/20	20/20	**	6

In the "Age at time of correct diagnosis" column, the two individuals having a single asterisk were originally diagnosed with juvenile macular dystrophy. In the "Age at onset of symptoms" column, the symptoms include photophobia, decreased color vision, and decreased visual acuity. In this same column, the double asterisk indicates that this individual is asymptomatic, most likely due to her youth, though she has inherited an L151F mutation.

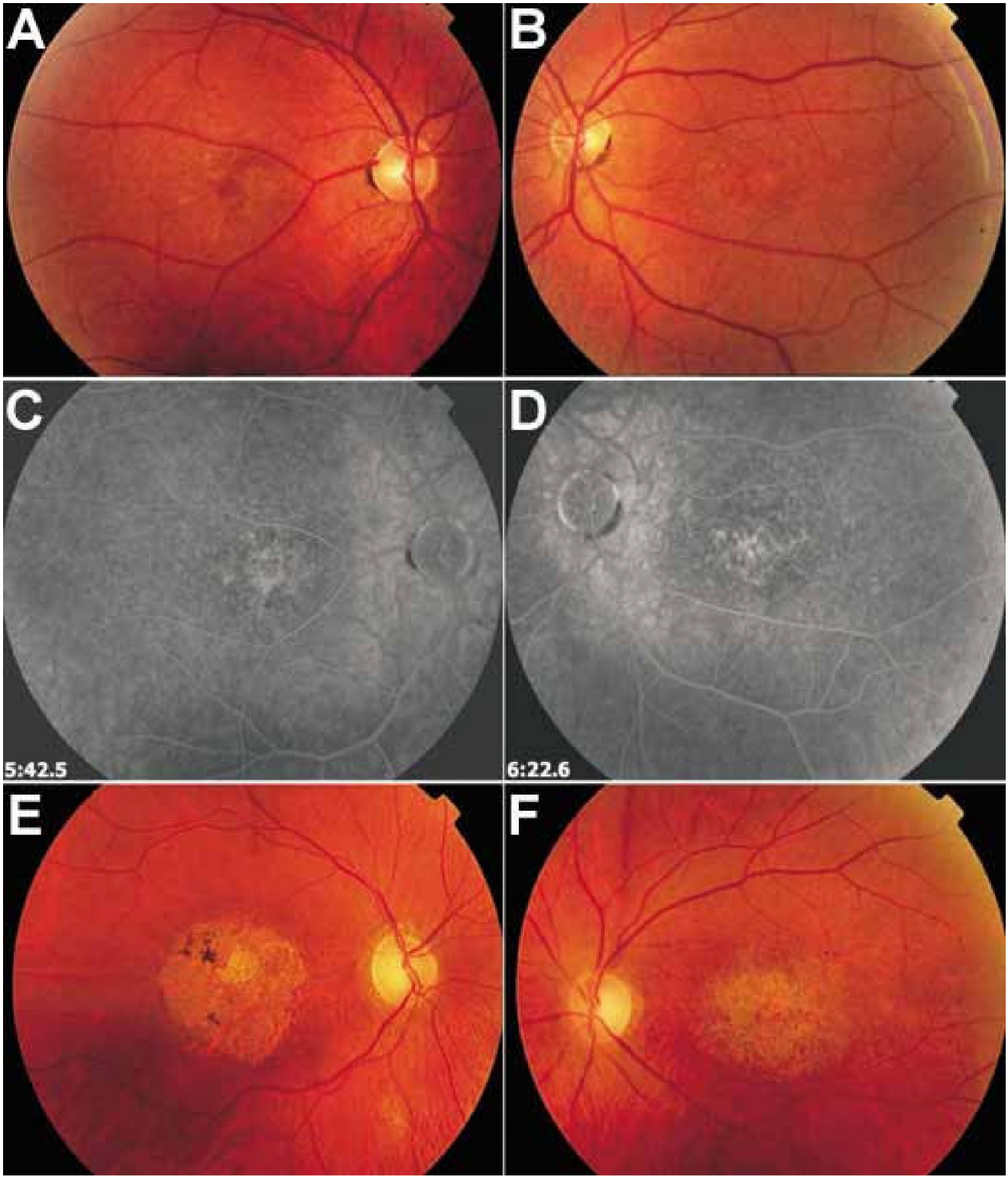

Figure 2. Fundus photographs of affected subjects from the study family. **A**: Individual IV:1, age 36, with visual acuities of 20/40 in the right eye and 20/50 in the left eye. Color fundus photograph of the right eye. Subtle pigmentary changes are evident in the macula. **B**: Color fundus photograph of the left eye show similar changes. **C**: Fundus fluorescein angiogram of the right eye. Taken at 5:42 min after injection of sodium fluorescein, this photographic method reveals more marked changes in the retina that are not immediately evident in the color photographs. Areas of brightness within the macula (arrows) are referred to as "window defects" and represent areas of retinal and retinal pigment epithelium atrophy. **D**: Fundus fluorescein angiogram of the left eye taken at 6:22 min after injection shows similar changes. **E**,**F**: Color fundus photographs from the more severely affected mother of the subject depicted in Figure 2. Individual III:2, age 64, has visual acuities of 20/400 in the right eye and 20/400 in the left eye. **E**: Color fundus photograph of the right eye reveals atrophy of the macula. **F**: Color fundus photographs of the left eye reveal similar changes. The peripheral retina looks normal.

2E,F).

The dim blue scotopic ERG response (mostly rod response) of the proband is essentially normal. The dim red scotopic ERG predominantly reflects rod activity, but also reflects some cone activity. Thus the normal subject's dim red ERG has an a-wave, an early, small b-wave labeled bx, and oscillatory potentials on the ascending limb of the b-wave. The early a-wave, b_x-wave, and oscillatory potentials reflect cone activity, and these responses are absent in the proband's ERG. The scotopic bright white ERG is minimally abnormal with an attenuated b-wave amplitude and slow implicit time. The 30 Hz flicker response and the photopic white ERG were profoundly subnormal and prolonged. Electrophysiologically, the manifestations of the L151F phenotype closely resemble that of the Y99C, E155G, and I143NT mutations where photopic responses and flickers were non-recordable [16,19,20]. Rod responses and maximal dark adapted single white flash responses were only mildly subnormal in amplitude.

Genetic analysis: An initial genotype analysis with marker D6S1017 yielded a LOD score of 3.3 at θ=0.00, consistent with linkage to *GUCA1A*. Subsequently, DHPLC mutation screening and direct sequencing identified a C451T transition resulting in a novel L151F change in the GCAP1 amino acid sequences in all affected individuals (Figure 1C). This mutation segregated with the disease phenotype and was not found in 200 normal controls. Like the E155G [16] and the I143NT [20] mutation, the L151F mutation occurs within the fourth EF-hand domain of GCAP1.

DISCUSSION

Progressive cone dystrophies are inherited in an autosomal recessive, autosomal dominant, or X-linked fashion, and are caused by a heterogeneous set of genes (Table 4) [1]. These genes include phototransduction genes like *GNAT2*, which encodes the cone transducin α subunit, the *CNGA3* and *CNGB3* genes, which encode subunits of the cGMP-gated cation channel, and the genes *GUC2D* and *GUC1A*, which encode GC1 and GCAP1. Also contained in this group are transcription factors (CRX), genes involved in the retinoid cycle (ABCA4, RDH5), and genes involved in protein transport through the cilium (RPGR and RPGRIP). A number of loci are known for which the corresponding gene has yet to be identified (RetNet).

We have described the clinical features of twelve subjects in a five generation family with an autosomal dominant cone dystrophy (Table 3). This disease was found to be caused by a novel mutation in *GUCA1A* affecting the EF4 high affinity Ca^{2+} binding site of GCAP1. The phenotype of affected family members carrying the L151F mutation is clinically very similar to three of the four previously described mutations in *GUCA1A*. Initial symptoms of reduced central acuity and loss of color vision became apparent in the second and third decades. It appears that all affected individuals eventually progress to legal blindness, with visual acuities between 20/200 and 20/400. Funduscopic changes were initially subtle, but progressed to central atrophy over time. The L151F phenotype resembles the Y99C mutation in severity, but the age of onset of clinical symptoms is somewhat earlier in patients with the L151F mutation.

EF hands represent high affinity Ca^{2+} binding sites and are responsible for the calcium sensitivity of the GCAP/GC system. Not surprisingly, mutations within these domains were shown to alter calcium sensitivity [16,21,22]. Some of the amino acids within the domain contain oxygen in their side chains that facilitate calcium coordination [27,28]. Although the L151 residue does not directly participate in calcium binding, the L151F mutation affects the structure of the EF-hand

Table 4. Genetic loci associated with progressive cone dystrophies

Inheritance	Locus	Symbol	OMIM	Gene	Reference
AR	1p13.3		139340	GNAT2	[33]
AR	1p22.1	CORD3	604116	ABCA4	[34]
AR	1q12-q24	CORD8	605549		[35]
AR	2q11.2		600053	CNGA3	[36]
AD	6p21.1	COD3	602093	GUCA1A	[19]
AD	6q13	CORD7	603649	RIMS1	[37]
AD	6q25-26		180020	RCD1	[38]
AR	8q21.3		605080	CNGB3	[39]
AR	12q13.3		601617	RDH5	[40]
AD	17p13.1	CORD6	601777	GUCY2D	[41]
	18q21.1-q21.3	CORD1	600624		[42]
AD	19q13.3	CORD2	120970	CRX	[43]
XR	Xp11.4	CORDX1	304020	RPGR	[25]
XR	Xp11.4-q13.1	CORDX3	300476		[44]
XR	Xq27	CORDX2	300085		[45]

The table lists the inheritance mode (AR represents autosomal recessive; AD represents autosomal dominant; XR represents X-linked recessive), the chromosomal localization ("Locus"), the disease nomenclature from RetNet, the Online Mendelian Inheritance in Man (OMIM) accession number, a gene symbol, and a reference.

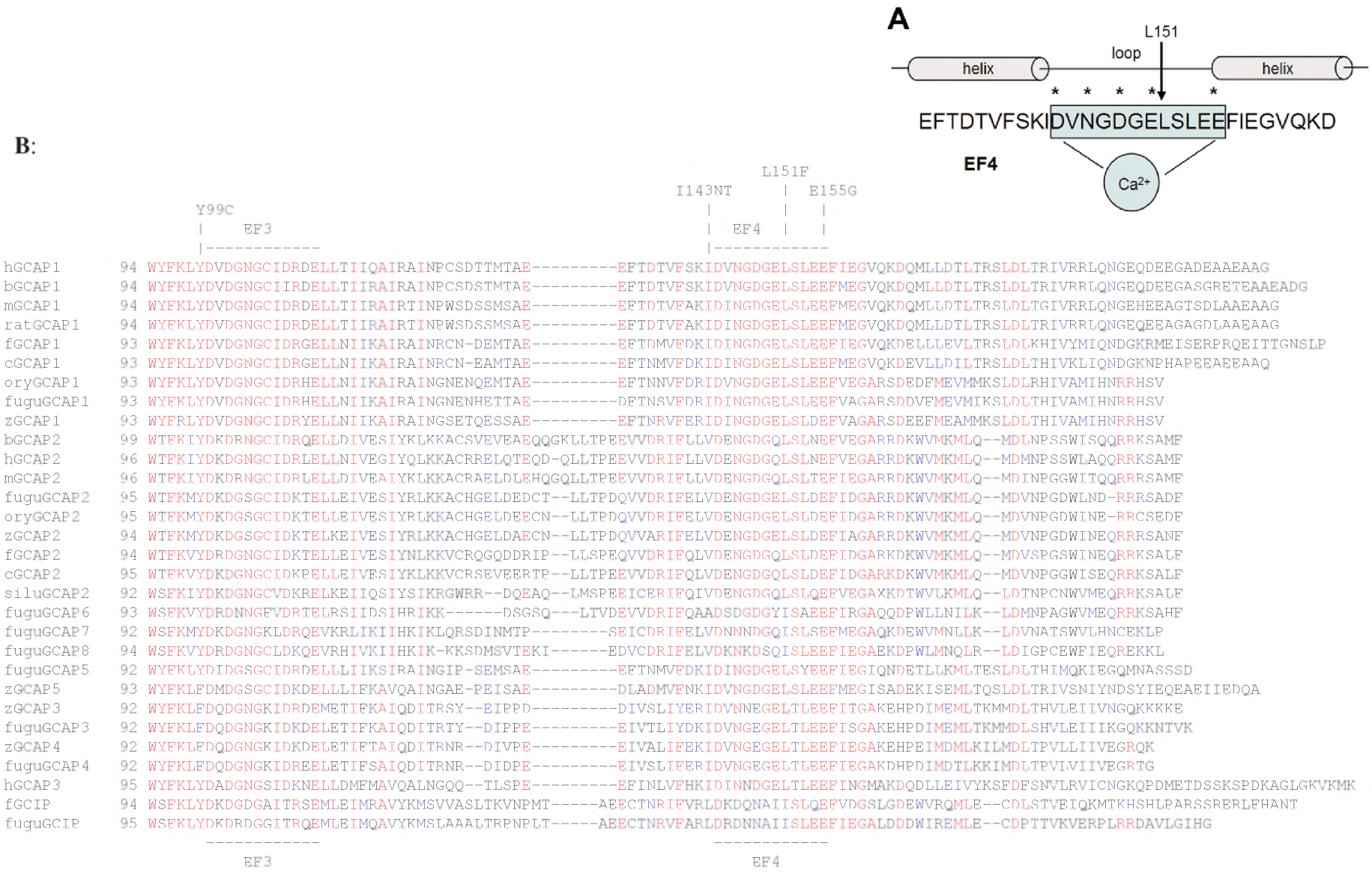

Figure 3. The EF4 Ca^{2+} binding site and sequence alignment of vertebrate GCAPs. **A**: The Ca^{2+} binding loop consisting of 12 amino acids is flanked by two a-helical regions. Residues in the loop that coordinate the Ca^{2+} ion are marked with an asterisk. Although the 151 position amino acid (arrow) does not directly coordinate the Ca^{2+} ion, it is highly conserved throughout the GCAPs (leucine or isoleucine) suggesting it is essential for structure and function of this loop. **B**: The known vertebrate guanylate cyclase activating proteins (vertebrate GCAP1-8) have been aligned (only the C-terminal halves containing EF3 and EF 4 are shown). Residues conserved in more than 50% of the sequences shown are red. Conservative substitutions are blue (for origin of sequences and accession numbers, see Methods).

domain and thereby affects calcium sensitivity [29]. Review of the sequences of 30 GCAPs in 8 vertebrate species (Figure 3) revealed that the L151 residue is highly conserved. Only the more distantly related GCAP6-8 of pufferfish and the guanylate cyclase-inhibitory proteins (GCIPs) carry a chemically similar isoleucine at this position. The presence of isoleucine is not considered to interfere with Ca^{2+} binding to EF4 since it conforms with the EF hand consensus sequence [30]. Replacement of L151 by phenylalanine is also considered a conservative substitution since both Leu and Phe are hydrophobic and not much different in size [29]. However, even conservative substitutions can alter binding of Ca^{2+} to EF hand loops significantly. For example, An E155D mutant of GCAP1 (replacement of an acidic Glu by another acidic residue, Asp), drastically reduced Ca^{2+} sensitivity of E155D-GCAP1 [31].

We conclude that the L151F mutation is pathogenic for the following reasons. First, the mutation segregates with disease in a large five generation pedigree with 30 family members. Second, this mutation was not found in over 200 controls. Third, the mutation affects the high affinity Ca^{2+} binding site EF4, which has been shown to be key for Ca^{2+} sensitivity of GCAP1 in vitro [31,32]. Fourth, two other mutations in EF4 have been linked to dominant cone dystrophy [16,20]. Fifth, the L151F mutations was found to be pathogenic in an autosomal dominant cone/rod dystrophy in an unrelated pedigree [29].

ACKNOWLEDGEMENTS

Supported by NIH K23 RR16427 (BJK), NIH R01 EY14428 (KZ), NIH R01 EY14448 (KZ), EY08123 (WB); RCL Foundation (KZ), the American Health Assistance Foundation (KZ); the Karl Kirchgessner Foundation (KZ); the Ruth and Milton Steinbach Fund (KZ); Ronald McDonald House Charities (KZ); The Macular Vision Research Foundation, Val and Edith Green Foundation (KZ); an unrestricted grant to the Department of Ophthalmology and Visual Sciences from Research to Prevent Blindness, Inc., New York, NY, and a Center Grant from the Foundation Fighting Blindness, Inc.

REFERENCES

1. Simunovic MP, Moore AT. The cone dystrophies. Eye 1998; 12:553-65.
2. Yau KW. Phototransduction mechanism in retinal rods and cones. The Friedenwald Lecture. Invest Ophthalmol Vis Sci 1994; 35:9-32.
3. Jindrova H. Vertebrate phototransduction: activation, recovery, and adaptation. Physiol Res 1998; 47:155-68.
4. Polans A, Baehr W, Palczewski K. Turned on by Ca2+! The physiology and pathology of Ca(2+)-binding proteins in the retina. Trends Neurosci 1996; 19:547-54.
5. Gorczyca WA, Polans AS, Surgucheva IG, Subbaraya I, Baehr W, Palczewski K. Guanylyl cyclase activating protein. A calcium-sensitive regulator of phototransduction. J Biol Chem 1995; 270:22029-36.
6. Pugh EN Jr, Duda T, Sitaramayya A, Sharma RK. Photoreceptor guanylate cyclases: a review. Biosci Rep 1997; 17:429-73.
7. Dizhoor AM, Olshevskaya EV, Henzel WJ, Wong SC, Stults JT, Ankoudinova I, Hurley JB. Cloning, sequencing, and expression of a 24-kDa Ca(2+)-binding protein activating photoreceptor guanylyl cyclase. J Biol Chem 1995; 270:25200-6.
8. Kretsinger RH, Barry CD. The predicted structure of the calcium-binding component of troponin. Biochim Biophys Acta 1975; 405:40-52.
9. Palczewski K, Polans AS, Baehr W, Ames JB. Ca(2+)-binding proteins in the retina: structure, function, and the etiology of human visual diseases. Bioessays 2000; 22:337-50.
10. Burgoyne RD, Weiss JL. The neuronal calcium sensor family of Ca2+-binding proteins. Biochem J 2001; 353:1-12. Erratum in: Biochem J 2001; 354:727.
11. Haeseleer F, Sokal I, Li N, Pettenati M, Rao N, Bronson D, Wechter R, Baehr W, Palczewski K. Molecular characterization of a third member of the guanylyl cyclase-activating protein subfamily. J Biol Chem 1999; 274:6526-35.
12. Imanishi Y, Yang L, Sokal I, Filipek S, Palczewski K, Baehr W. Diversity of guanylate cyclase-activating proteins (GCAPs) in teleost fish: characterization of three novel GCAPs (GCAP4, GCAP5, GCAP7) from zebrafish (Danio rerio) and prediction of eight GCAPs (GCAP1-8) in pufferfish (Fugu rubripes). J Mol Evol 2004; 59:204-17.
13. Imanishi Y, Li N, Sokal I, Sowa ME, Lichtarge O, Wensel TG, Saperstein DA, Baehr W, Palczewski K. Characterization of retinal guanylate cyclase-activating protein 3 (GCAP3) from zebrafish to man. Eur J Neurosci 2002; 15:63-78.
14. Surguchov A, Bronson JD, Banerjee P, Knowles JA, Ruiz C, Subbaraya I, Palczewski K, Baehr W. The human GCAP1 and GCAP2 genes are arranged in a tail-to-tail array on the short arm of chromosome 6 (p21.1). Genomics 1997; 39:312-22.
15. Howes K, Bronson JD, Dang YL, Li N, Zhang K, Ruiz C, Helekar B, Lee M, Subbaraya I, Kolb H, Chen J, Baehr W. Gene array and expression of mouse retina guanylate cyclase activating proteins 1 and 2. Invest Ophthalmol Vis Sci 1998; 39:867-75.
16. Wilkie SE, Li Y, Deery EC, Newbold RJ, Garibaldi D, Bateman JB, Zhang H, Lin W, Zack DJ, Bhattacharya SS, Warren MJ, Hunt DM, Zhang K. Identification and functional consequences of a new mutation (E155G) in the gene for GCAP1 that causes autosomal dominant cone dystrophy. Am J Hum Genet 2001; 69:471-80.
17. Newbold RJ, Deery EC, Walker CE, Wilkie SE, Srinivasan N, Hunt DM, Bhattacharya SS, Warren MJ. The destabilization of human GCAP1 by a proline to leucine mutation might cause cone-rod dystrophy. Hum Mol Genet 2001; 10:47-54.
18. Downes SM, Holder GE, Fitzke FW, Payne AM, Warren MJ, Bhattacharya SS, Bird AC. Autosomal dominant cone and cone-rod dystrophy with mutations in the guanylate cyclase activator 1A gene-encoding guanylate cyclase activating protein-1. Arch Ophthalmol 2001; 119:96-105.
19. Payne AM, Downes SM, Bessant DA, Taylor R, Holder GE, Warren MJ, Bird AC, Bhattacharya SS. A mutation in guanylate cyclase activator 1A (GUCA1A) in an autosomal dominant cone dystrophy pedigree mapping to a new locus on chromosome 6p21.1. Hum Mol Genet 1998; 7:273-7.
20. Nishiguchi KM, Sokal I, Yang L, Roychowdhury N, Palczewski K, Berson EL, Dryja TP, Baehr W. A novel mutation (I143NT) in guanylate cyclase-activating protein 1 (GCAP1) associated with autosomal dominant cone degeneration. Invest Ophthalmol Vis Sci 2004; 45:3863-70.
21. Sokal I, Li N, Surgucheva I, Warren MJ, Payne AM, Bhattacharya SS, Baehr W, Palczewski K. GCAP1 (Y99C) mutant is constitutively active in autosomal dominant cone dystrophy. Mol Cell 1998; 2:129-33.
22. Dizhoor AM, Boikov SG, Olshevskaya EV. Constitutive activa-

tion of photoreceptor guanylate cyclase by Y99C mutant of GCAP-1. Possible role in causing human autosomal dominant cone degeneration. J Biol Chem 1998; 273:17311-4.

23. Olshevskaya EV, Calvert PD, Woodruff ML, Peshenko IV, Savchenko AB, Makino CL, Ho YS, Fain GL, Dizhoor AM. The Y99C mutation in guanylyl cyclase-activating protein 1 increases intracellular Ca2+ and causes photoreceptor degeneration in transgenic mice. J Neurosci 2004; 24:6078-85.
24. Kniazeva M, Chiang MF, Morgan B, Anduze AL, Zack DJ, Han M, Zhang K. A new locus for autosomal dominant stargardt-like disease maps to chromosome 4. Am J Hum Genet 1999; 64:1394-9.
25. Yang Z, Peachey NS, Moshfeghi DM, Thirumalaichary S, Chorich L, Shugart YY, Fan K, Zhang K. Mutations in the RPGR gene cause X-linked cone dystrophy. Hum Mol Genet 2002; 11:605-11.
26. Zhang K, Garibaldi DC, Kniazeva M, Albini T, Chiang MF, Kerrigan M, Sunness JS, Han M, Allikmets R. A novel mutation in the ABCR gene in four patients with autosomal recessive Stargardt disease. Am J Ophthalmol 1999; 128:720-4.
27. Kawasaki H, Kretsinger RH. Calcium-binding proteins 1: EF-hands. Protein Profile 1995; 2:297-490.
28. Persechini A, Moncrief ND, Kretsinger RH. The EF-hand family of calcium-modulated proteins. Trends Neurosci 1989; 12:462-7.
29. Sokal I, Dupps WJ, Grassi MA, Brown Jr. J, Affatigato LM, Roychowdhury N, Yang L, Filipek S, Palczewski K, Stone EM, and Baehr W. A novel GCAP1 missense mutation (L151F) in a large family with autosomal dominant cone-rod dystrophy. Invest Ophthalmol Vis Sci. In press 2005.
30. Falke JJ, Drake SK, Hazard AL, Peersen OB. Molecular tuning of ion binding to calcium signaling proteins. Q Rev Biophys 1994; 27:219-90.
31. Rudnicka-Nawrot M, Surgucheva I, Hulmes JD, Haeseleer F, Sokal I, Crabb JW, Baehr W, Palczewski K. Changes in biological activity and folding of guanylate cyclase-activating protein 1 as a function of calcium. Biochemistry 1998; 37:248-57.
32. Otto-Bruc A, Buczylko J, Surgucheva I, Subbaraya I, Rudnicka-Nawrot M, Crabb JW, Arendt A, Hargrave PA, Baehr W, Palczewski K. Functional reconstitution of photoreceptor guanylate cyclase with native and mutant forms of guanylate cyclase-activating protein 1. Biochemistry 1997; 36:4295-302.
33. Michaelides M, Aligianis IA, Holder GE, Simunovic M, Mollon JD, Maher ER, Hunt DM, Moore AT. Cone dystrophy phenotype associated with a frameshift mutation (M280fsX291) in the alpha-subunit of cone specific transducin (GNAT2). Br J Ophthalmol 2003; 87:1317-20. Erratum in: Br J Ophthalmol 2004; 88:314.
34. Cremers FP, van de Pol DJ, van Driel M, den Hollander AI, van Haren FJ, Knoers NV, Tijmes N, Bergen AA, Rohrschneider K, Blankenagel A, Pinckers AJ, Deutman AF, Hoyng CB. Autosomal recessive retinitis pigmentosa and cone-rod dystrophy caused by splice site mutations in the Stargardt's disease gene ABCR. Hum Mol Genet 1998; 7:355-62.
35. Khaliq S, Hameed A, Ismail M, Anwar K, Leroy BP, Mehdi SQ, Payne AM, Bhattacharya SS. Novel locus for autosomal recessive cone-rod dystrophy CORD8 mapping to chromosome 1q12-Q24. Invest Ophthalmol Vis Sci 2000; 41:3709-12.
36. Wissinger B, Gamer D, Jagle H, Giorda R, Marx T, Mayer S, Tippmann S, Broghammer M, Jurklies B, Rosenberg T, Jacobson SG, Sener EC, Tatlipinar S, Hoyng CB, Castellan C, Bitoun P, Andreasson S, Rudolph G, Kellner U, Lorenz B, Wolff G, Verellen-Dumoulin C, Schwartz M, Cremers FP, Apfelstedt-Sylla E, Zrenner E, Salati R, Sharpe LT, Kohl S. CNGA3 mutations in hereditary cone photoreceptor disorders. Am J Hum Genet 2001; 69:722-37.
37. Johnson S, Halford S, Morris AG, Patel RJ, Wilkie SE, Hardcastle AJ, Moore AT, Zhang K, Hunt DM. Genomic organisation and alternative splicing of human RIM1, a gene implicated in autosomal dominant cone-rod dystrophy (CORD7). Genomics 2003; 81:304-14.
38. Tranebjaerg L, Sjo O, Warburg M. Retinal cone dysfunction and mental retardation associated with a de novo balanced translocation 1;6(q44;q27). Ophthalmic Paediatr Genet 1986; 7:167-73.
39. Sundin OH, Yang JM, Li Y, Zhu D, Hurd JN, Mitchell TN, Silva ED, Maumenee IH. Genetic basis of total colourblindness among the Pingelapese islanders. Nat Genet 2000; 25:289-93.
40. Nakamura M, Hotta Y, Tanikawa A, Terasaki H, Miyake Y. A high association with cone dystrophy in Fundus albipunctatus caused by mutations of the RDH5 gene. Invest Ophthalmol Vis Sci 2000; 41:3925-32.
41. Gregory-Evans K, Kelsell RE, Gregory-Evans CY, Downes SM, Fitzke FW, Holder GE, Simunovic M, Mollon JD, Taylor R, Hunt DM, Bird AC, Moore AT. Autosomal dominant cone-rod retinal dystrophy (CORD6) from heterozygous mutation of GUCY2D, which encodes retinal guanylate cyclase. Ophthalmology 2000; 107:55-61.
42. Warburg M, Sjo O, Tranebjaerg L, Fledelius HC. Deletion mapping of a retinal cone-rod dystrophy: assignment to 18q211. Am J Med Genet 1991; 39:288-93.
43. Freund CL, Gregory-Evans CY, Furukawa T, Papaioannou M, Looser J, Ploder L, Bellingham J, Ng D, Herbrick JA, Duncan A, Scherer SW, Tsui LC, Loutradis-Anagnostou A, Jacobson SG, Cepko CL, Bhattacharya SS, McInnes RR. Cone-rod dystrophy due to mutations in a novel photoreceptor-specific homeobox gene (CRX) essential for maintenance of the photoreceptor. Cell 1997; 91:543-53.
44. Meire FM, Bergen AA, De Rouck A, Leys M, Delleman JW. X linked progressive cone dystrophy. Localisation of the gene locus to Xp21-p11.1 by linkage analysis. Br J Ophthalmol 1994; 78:103-8.
45. Bergen AA, Pinckers AJ. Localization of a novel X-linked progressive cone dystrophy gene to Xq27: evidence for genetic heterogeneity. Am J Hum Genet 1997; 60:1468-73. Erratum in: Am J Hum Genet 1997; 61:471.

The print version of this article was created on 3 Mar 2005. This reflects all typographical corrections and errata to the article through that date. Details of any changes may be found in the online version of the article.