Autosomal Dominant Cone and Cone-Rod Dystrophy
With Mutations in the Guanylate Cyclase
Activator 1A Gene-Encoding Guanylate Cyclase
Activating Protein-1

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Objective: To describe the phenotype in 3 families with dominantly inherited cone and cone-rod dystrophy with mutations in guanylate cyclase activator 1A (GUCA1A), the gene-encoding guanylate cyclase activator protein-1 (GCAP-1).

Methods: Phenotypic characterization with psychophysical and electrophysiological evaluation and confocal laser scanning ophthalmoscopy was performed in 2 families with a Tyr99Cys mutation and 1 family with a Pro50Leu mutation. Haplotype analysis was performed in the families with Tyr99Cys mutation.

Results: The families with a Y99C mutation were shown to be ancestrally related. Decreased visual acuity and loss of color vision occurred after the age of 20 years, followed by progressive atrophy of the central 5° to 10°. Electrophysiological testing revealed generalized loss of cone function, with preservation of rod function. Abnormal rod and cone sensitivities were confined to the central 5° to 10°. Confocal laser scanning ophthalmoscopy imaging showed abnormalities of autofluorescence in early disease. Subjects with a Pro50Leu mutation demonstrated marked variability in expressivity from minimal abnormalities of macular function to cone-rod dystrophy.

Conclusions: The phenotype associated with the Y99C mutation in GUCA1A is distinctive, with little variation in expression. By contrast, that associated with the P50L mutation demonstrates variable expressivity.

Clinical Relevance: Phenotype-genotype correlation in these 2 mutations demonstrates 2 different phenotypes.

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CONE DYSTROPHIES are characterized by progressive dysfunction of the photopic system, with preservation of scotopic function. Autosomal dominant cone dystrophies have been calculated to occur in approximately 1 in 10000 live births, with an age-dependent penetrance. In cone-rod dystrophy, abnormal rod function may be part of the initial presentation, but rod involvement may be less severe, or occur later than the cone dysfunction. The diagnosis is established by electrophysiological evaluation; functional results depend on the stage of the disease and the age of the individual.

Common symptoms in cone dystrophy include photophobia and loss of visual acuity, color vision, and central visual fields. The retinal appearance may be normal early in disease. With progression, the retinal pigment epithelium (RPE) may take on a granular appearance and finally central atrophy. In some cases, temporal atrophy of the optic nerve is present. Nystagmus is associated with early-onset severe cone dystrophy. Psychophysical evaluation in cone dystrophy demonstrates loss of central visual fields; recovery from bleach is monophasic, with a normal final-rod threshold. Color vision is usually abnormal early in disease with elevation of protan, deutan, or tritan thresholds or any combination of these. In cone-rod dystrophy, function subserved by rods, including visual fields and night vision, will be variably affected depending on the degree of involvement. Varying degrees of intraretinal pigment and vessel attenuation occur.

Seven loci have been identified in autosomal dominant cone and cone-rod dystrophies. Those associated with known genes include chromosome 6p12, with mutations in peripherin/human retinal degeneration slow (RDS) gene; chromosome 6p21, with mutations in guanylate cyclase...
SUBJECTS AND METHODS

MOLECULAR ANALYSIS

The methods performed for linkage studies, haplotype analysis, mutation screening, heteroduplex electrophoresis, and direct genomic sequencing have been previously described.11,19

SUBJECTS

Twenty-seven subjects from one 4-generation pedigree (7 affected and 20 unaffected) were recruited to the study (family A). Two further families were recruited, with 2 members from family B and 3 from family C (Figure 1). Autosomal dominant inheritance was evident, with affected individuals in each generation and male-to-male transmission. This research was in accordance with the Declaration of Helsinki and was approved by the Moorfields Hospital Ethics Committee. Informed consent was obtained from all participants.

CLINICAL AND FUNCTIONAL INVESTIGATIONS

Phenotype characterization included an ophthalmic history and fundus examination. In addition, fundus photography, confocal laser scanning ophthalmoscopy (cLSO), and psychophysical and electrophysiological evaluations were performed.

ELECTROPHYSIOLOGY

Subjects underwent electrophysiological investigation using techniques in accord with the recommendations of the International Society for Clinical Electrophysiology of Vision.20-22 Electro-oculographic responses (EOG), full-field electroretinography (ERG), and pattern electroretinograms (PERG) were recorded. Depolarizing (ON) and hyperpolarizing (OFF) responses were recorded using a mini-Ganzfeld stimulator (CH Electronics, Bromley, England), based on light-emitting diode technology, using a 120-millisecond, 530-nm stimulus of 440 candelas (cd) per square meter, on a background of 612-nm and 160 cd/m², and a stimulus rate of 2 per second.

PSYCHOPHYSICAL TESTS

Static threshold perimetry in the dark- and light-adapted states was performed using a Humphrey field analyzer (Allergan Humphrey, Hertford, England). Photopic visual fields were performed using the standard protocol.23-25 For dark-adapted visual fields, the pupil was dilated with 2.5% phenylephrine hydrochloride and 1% cyclopentolate hydrochloride, and the patient was dark adapted for 45 minutes. The Humphrey field analyzer was modified for use in dark-adapted conditions.23-25 An infrared source illuminated the bowl, and an infrared monitor (Phillips, Eindhoven, Holland) was used to detect eye movements. Fields were recorded using the central 30-2, peripheral 30/60-2, and macular programs. The target size corresponded to Goldmann size V for peripheral testing and to Goldmann size III for macular programs. Each was performed with a red (dominant wavelength, 650 nm) and then blue (dominant wavelength, 450 nm) filter in the stimulus beam.

The dark-adapted blue central 30-2 fields were reviewed to determine the most informative locations of dark-adapted visual sensitivity. Two test locations were chosen at 3° and 9°. The Humphrey field analyzer was used for dark adaptometry controlled by a custom program on a computer (PS/2 model 50; International Business Machines, Armonk, NY).25,26 Fully dark-adapted rod thresholds were measured before exposure to the adapting light at the 2 coordinates with the blue filter in the stimulus beam. For fine matrix mapping, a modified Humphrey field analyzer was used to present flashes of blue stimuli under scotopic conditions with 4 red light-emitting diodes in a small diamond configuration for fixation. One hundred positions on a square 10 × 10 matrix over a 9° × 9° test field were presented with a Humphrey size III target at 1° intervals. Subsequent processing of data produced 3-dimensional representation of rod thresholds, with highest elevations from baseline representing greatest loss of sensitivity.24-26

Color vision was tested using Hardy-Rand-Rittler plates, and color contrast sensitivity was performed in 3 subjects.27

AUTOFLUORESCENCE IMAGING

Confocal scanning laser ophthalmoscope images of the central macular region were obtained using a prototype cLSO SM 30-4024, donated by Zeiss (Oberkochen, Germany). An argon laser (488 nm, 250 µW) was used for illumination. Reflectance imaging was undertaken using the Zeiss LSO with a 40° field and the argon blue laser, with the depth plane adjusted to maximize the visibility of the fundus features. A wide bandpass filter, with a cut-off at 521 nm inserted in front of the detector, was used to detect autofluorescence, which was recorded, measured, and analyzed using published techniques.26

RESULTS

DNA ANALYSIS

A GUCA1A mutation in exon 2 of the gene causing a tyrosine to a cysteine change at position 99 in the protein was identified in 7 subjects of family A11 and in 4 subjects in family B. The mutation was found to segregate with disease, and was not identified in those without the Pro50Leu mutation, shows intrafamilial variability in expression.
mutation or in 200 “control” subjects. In family C, a mutation in exon 1 of GUCA1A causing a proline to a leucine change at position 50 in the protein was identified in 3 family members. Haplotype analysis of families A and B demonstrated that these 2 families were ancestrally related. Pedigrees of the 3 families are shown in Figure 1. The clinical characteristics of subjects from these families are documented in the Table.

CLINICAL FINDINGS

Clinical evaluation, including electrophysiology, psychophysics, and autofluorescence imaging, was performed in family A before the results of the genetic analysis were known. Affected members of family A became symptomatic in their late 20s with very minimal photophobia and reduced central vision. The visual deficit, even in the oldest subject (age 88 years), was confined to the central vision, with no peripheral field loss, and visual acuities of counting fingers. Mild RPE granular changes were seen in the presymptomatic 16-year-old subject A IV/2 (Figure 2A-B), and white deposits were noted in at the maculae of subjects A III/2 and A II/11 (Figure 2C-D). Finer, less obvious, white deposits were also noted in A III/4 and A II/9. Central atrophy was noted in all subjects, apart from subject A IV/2 (Figure 2A, B, D, and E). This became more pronounced with age, apart from subject A II/9, in whom a milder phenotype was observed. No abnormalities were observed outside the macular region in any member. In family B, subject B IV/1 (aged 32 years), with visual acuity of 20/200 OU, had been symptomatic since her early 20s, with mild photophobia and poor central vision. Fundus examination revealed symmetrical parafoveal RPE granular abnormalities distributed in a limited bull’s eye–type pattern (Figure 2G). Fluorescein angiography findings corresponded to the bull’s eye–type appearance seen on fundus examination (Figure 2G-I). Her father was diagnosed as affected with a central dystrophy in late childhood with similar symptoms. Both her brothers were reported by the family to have similar difficulties and were found to have the mutation.

In family C, variability of expression was seen. Subject C III/2 had onset of his symptoms in his late 30s, with photophobia and reduced central vision but normal peripheral visual fields and visual acuity of 20/40 OU by the age of 43 years. Central RPE granular changes were noted (Figure 2J-I). Subject C II/3, his aunt, only began to be symptomatic in her mid-50s, with mild photophobia and poor central vision. Fundus examination revealed symmetrical parafoveal RPE granular abnormalities distributed in a limited bull’s eye–type pattern (Figure 2G). Fluorescein angiography findings corresponded to the bull’s eye–type appearance seen on fundus examination (Figure 2G-I). Her father was diagnosed as affected with a central dystrophy in late childhood with similar symptoms. Both her brothers were reported by the family to have similar difficulties and were found to have the mutation.

![Pedigree of families A, B, and C showing generations (roman numerals) of affected (solid symbols) and unaffected (open symbols) family members. Only relevant members of family A are shown, as in the genetic article.](image)

**Patient Characteristics**

*ON indicates depolarizing; OFF: hyperpolarizing; NP: not performed; and Ext, extinguished light rise.*

*Non–International Society for Clinical Electrophysiology of Vision standards.*

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Figure 2. A, Macula of right eye of subject A IV/2, showing no obvious abnormality. B, Increased autofluorescence signal parafoveally, with an annulus of decreased autofluorescence in same eye of same subject. C, Macular atrophy in right eye of subject A II/11, with white deposits surrounding the atrophic area. D, Increased autofluorescent signal surrounding the central area of decreased autofluorescence in area of atrophy in same subject. E, Atrophic macula and surrounding normal retinal appearance in subject A II/1. F, Same area showing markedly decreased levels of autofluorescence in the area of atrophy and high autofluorescence at edge of atrophy. G, Right macula of subject B III/1 showing central retinal thinning. H, Fluorescein angiogram in same subject showing central masking, presumed to be caused by lipofuscin deposition (corresponding to bright signal of increased autofluorescence), and hyperfluorescence caused by loss of retinal pigment epithelium of central retina (corresponding to decreased autofluorescent signal on confocal laser scanning ophthalmoscopy). I, Confocal laser scanning ophthalmoscopy imaging showing increased autofluorescence at right macula. J, Right macula of subject C III/2 showing early atrophy and abnormalities of the retinal pigment epithelium. K, Autofluorescence imaging of same eye of same subject C III/2, showing band of autofluorescence surrounding the area of early atrophy seen on funduscopy. L, Showing similar findings in the left eye of the same subject. M, Right macula of subject C III/10, showing atrophy and intraretinal bone-spicule pigmentation. N, Showing peripheral view of right eye with intraretinal bone spicule pigmentation. O, Autofluorescence imaging of same eye of same subject showing massive deposition of autofluorescent material within the macula.
central vision since his late 20s, with visual acuities of 20/60 OD and 20/40 OS by the age of 35 years. His visual fields were constricted to a central 5°, and typical peripheral intraretinal bone-spicule pigmentation was observed. (Figure 2M-O). Clinical characteristics are documented in the Table.

**ELECTROPHYSIOLOGY**

Electrophysiological tests were performed in 7 affected subjects from family A, 2 from family B, and 3 from family C.

**Family A**

The EOG light rise was normal in each subject; in 2 affected subjects, the rises were particularly high (>370% in 4 eyes, with 3 being ≥400%). Pattern electroretinograms were recorded in all subjects (Figure 3A). In subject A IV/2, the P50 component was normal in the right eye, but significantly lower than the left. In subject A II/9 it was still recordable, although markedly reduced in amplitude, but her son, subject A III/2, showed only minimal residual PERG activity. In the remaining subjects, the PERG was extinguished. Scotopic ERGs, including the rod-specific response and the bright white–flash ERG, were normal in 6 of 7 members in family A (Figure 3B-C). The oldest member, A I/1, aged 88 years, had a low rod ERG b-wave amplitude, but this was within normal limits for age. The rod ERG b-wave of his son, A II/1, was of borderline amplitude, but normal implicit time (Figure 3B). The photopic ERG showed decreased b-wave amplitude, with no increase in implicit time in 6 symptomatic subjects, but a normal response in the asymptomatic A IV/2 (Figure 3D). The 30-Hz flicker ERG was reduced in symptomatic subjects, but, however small, showed no shift in implicit time (Figure 3E). Both ON and OFF responses were reduced in 6 of 6 patients in whom the test was abnormal. No abnormality was present in the asymptomatic A IV/2 (Figure 3F). The findings in A II/1 differ in that the ON response was delayed, and the OFF response was markedly reduced.

**Family B**

In subject B IV/1, aged 32 years, the PERG was extinguished. The EOG was normal, and full-field ERGs were normal to all stimuli. In particular, photopic and flicker were of normal amplitudes and normal implicit times. Her father had had an ERG in 1980 that showed significantly reduced cone activity.

**Family C**

The electrophysiology of the proband C III/2 was not performed according to International Society for Clinical Electrophysiology of Vision standards, but a normal EOG light rise and normal rod electrophysiology were obtained. His PERG was extinguished bilaterally, and just as in family A, photopic and flicker ERG responses showed reduced amplitudes but no increase in implicit times. In his aunt, C II/3, the PERG was reduced bilaterally and there was a very slight increase in the implicit time of the 30-Hz flicker ERG; however, the scotopic ERG and EOG were normal. In her son, C III/10, the PERG was extinguished bilaterally, there was no EOG light rise, full-field ERGs showed severe reduction in rod-specific b-wave amplitude, and there was marked reduction in both a- and b-wave amplitudes in the bright white–flash responses. His 30-Hz response was markedly delayed with moderately severe amplitude reduction. The photopic ERG was markedly reduced and delayed (Figure 3G).

**PSYCHOPHYSICS**

**Families A and B**

In family A, loss of sensitivity confined to the central 5° to 10° was seen, particularly in subjects A II/1, A II/11, and A III/4. In these 3 subjects, severe sensitivity loss of 10 to 20 dB with an absolute scotoma was identified. Subjects A II/9 and A III/2 (mother and son) and subjects A IV/2 and B III/1 had minimal loss of sensitivity. Dark-adapted red and blue perimetry also demonstrated decreased sensitivity to cone and rod stimuli (Figure 4A). Similar findings were seen in subjects B III/2 and B IV/1.

Fine matrix mapping was performed in family A and demonstrated areas of elevated thresholds even in subject A IV/2, in whom nearly normal sensitivity was observed. The central threshold elevation was primarily due to the normal rod-free zone of the fovea (Figure 4B-D). The older subjects had greater losses of sensitivity, although once again subject A II/9 exhibited a milder phenotype. Dark adaptation was recorded in A II/11, A III/2, A III/4, and A IV/2. In these subjects, the cone plateau, the rod-cone break, and the rate of recovery of the rod portion of the dark-adaptation curve fell within the normal range (Figure 5). Hardy-Rand-Ritler color plate testing was abnormal in all affected subjects, apart from A IV/2, and color-contrast sensitivity, performed in subjects A III/4, A IV/2, and B IV/1, demonstrated marked elevation of threshold in all 3 axes in A III/4 and thresholds at the upper limit of normal in his 16-year-old daughter (subject A IV/2); thresholds for all 3 axes were elevated in both eyes of subject B IV/1.

**Family C**

Subject C III/2 had losses in sensitivity confined to the central 5° to 9°, with no peripheral abnormalities on photopic testing. Subject C II/3 showed relatively normal photopic function throughout the central 30°, with gradual increasing cone sensitivity losses in the periphery (Figure 6A). Rod sensitivity was within 1.0 log unit of normal throughout the central retina, with no clear-rod sensitivity loss for most of the visual field. Her son (subject C IV/10) showed profound photopic sensitivity losses of more than 3.0 log units throughout most of the central 30° with a small foveal region of spared function. Extensive regions of reduced but abnormal cone sensitivity were observed peripheral to 30° (Figure 6B). Rod function showed a similar pattern of midperipheral
Figure 3. A. Pattern electroretinograms (PERGs) of family A. In subject II/9, the P50 component is grossly reduced. Her son, subject III/2, shows only residual activity. In all subjects, other than A IV/2, the PERG is extinguished. B. Scotopic-rod electroretinograms (ERGs) show no definite abnormality for age. C. Maximal ERGs (bright white–flash, dark-adapted) show no definite abnormality. D. 30-Hz flicker ERGs are normal in II/2, II/4, and IV/2, but markedly reduced in the other subjects. No increase in implicit time is present. E. Photopic ERGs showing decreased b-wave amplitude in all subjects, apart from subject IV/2, in whom there is no abnormality. No subject shows implicit time increase. F. Depolarization (ON) and hyperpolarization (OFF) responses. No abnormality was present in the asymptomatic A IV/2. The other subjects show reduction in both ON and OFF responses. Subject A II/11 differs in that the ON response is delayed and the OFF response is more markedly reduced. G. Electrophysiology of mother (C III/3) and son (C III/10) of family C. Showing reduction of the PERG in C III/3, mild increase in 30-Hz flicker implicit time, but otherwise normal evaluation. The son has, by contrast, extinguished PERGs, gross reduction in the rod-specific b-wave amplitude, marked reduction of both a- and b-wave amplitudes in the bright white-flash responses, and grossly delayed and reduced amplitudes of his 30-Hz flicker and photopic ERG.
sensitivity loss, with profound losses of more than 4.0 log units in the central region and relatively good rod function within 2.0 log units of normal extending from about 30° out to the far periphery in the inferior nasal field (Figure 6C).

Figure 4. A. Photopic and dark adapted scotopic red and blue 30° static perimetry showing central loss of both cone and rod sensitivities centrally in subject A II/1, aged 58 years. B. Fine matrix mapping to show marked sensitivity losses superior to fixation with nearly normal measurements below fixation in subject A II/1 (aged 58 years). C. Fine matrix mapping in subject A III/4 (aged 42 years) showing less marked sensitivity losses. D. Fine matrix mapping in subject A IV/2 (aged 16 years) showing minimal sensitivity loss.

AUTOFLUORESCENCE IMAGING

In family A, localized increased autofluorescence was observed centrally with a surrounding annulus of decreased autofluorescence. Asymptomatic subject A IV/2


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showed increased levels of autofluorescence at the fovea, with little to see on funduscopy (Figure 2B). In the older subjects, the area of decreased autofluorescence was more extensive, but still localized to the central area. A high level of autofluorescence surrounded the area of atrophy (Figure 2I). In subject A III/2, discrete areas of high autofluorescence corresponded to white deposits seen in the fundus. This was also seen to a lesser extent in subject A II/11 (Figure 2D). In family B, only subject B IV/1 had imaging performed. The fluorescein angiogram showed hyperfluorescence corresponding very closely to the area where decreased levels of autofluorescence were observed, presumably in this case because of loss of RPE pigment and early atrophy (Figure 2I). There is again an increased fringe of autofluorescence around the perimeter of the lesion (Figure 2J). In family C, subject C III/2 showed a clear annulus of autofluorescence similar to that seen in family A in older subjects, but broader in width (Figures 2K and L). His aunt, subject C II/3, showed no abnormality, but her son (subject C II/10) had a massive increase in autofluorescence at both maculae, but none peripherally (Figure 2O).

**COMMENT**

This study is, to our knowledge, the first to document the phenotype associated with 2 mutations in a gene only recently described as disease-causing. The phenotype seen in the Y99C mutation is highly distinctive, with detectable abnormal function and autofluorescence occurring before either symptoms or obvious ophthalmoscopic changes, and only mild variation in phenotype. Although the fundus features evolving from granular RPE changes at the macula to frank atrophy in the older individuals is fairly typical for a cone dystrophy, the electrophysiology seen in this mutation is distinctive. Cone dystrophies are associated with increased implicit times and decreased amplitudes in the cone-specific responses. However, in this family, no increase in implicit time was seen, despite reduced amplitudes in the 30-Hz flicker and photopic ERG responses. The electro-physiology is not well described by using the classification of Szylek et al, as this distinguishing feature is lost. However, according to this classification, the Y99C dystrophy would be categorized as a type 1a. The lack of preferential loss of color vision is unlike the cone degenerations described by Weleber and Eisner, in which the most common color defect was shown to be the green-red type. Other clinical studies have highlighted particular color deficits, as in a 4-generation family with autosomal dominant cone dystrophy described by Went et al, in which the characteristic features are a decline in vision after the age of 20 years, with a near complete absence of blue-cone function before any ophthalmological abnormality.

Fishman et al describe a cone dystrophy in a family with S27F mutation in peripherin/RDS. The electrophysiology described in their family with 3 affected members is very similar to that seen in the Y99C GUCA1A family. Specifically, their family has normal rod responses, and reduction in the cone-specific ERG amplitudes, but no increase in implicit times. However, the cone degeneration described in this study seems to be milder regarding visual acuity and psychophysics testing than the families with a Y99C mutation. In addition, the 77-year-old in their study with a codon S27F mutation has...
no central atrophy, unlike the marked central atrophy noted in the Y99C GCAP-1 mutation at a comparable age. It is also of note that 2 other members of this same family had a different sequence change in peripherin/RDS and did not have disease. On the basis of the electrophysiology, it would be interesting perform mutational analysis for a Y99C mutation in GUCA1A in this family.

The phenotype in the family with the P50L mutation in GUCA1A is quite different, with marked variation in expressivity. In this family, all 3 affected subjects manifested a different phenotype with minimal maculopathy and involvement with mild symptoms, a cone dystrophy, with the same phenotype as seen in the Y99C mutation, and a moderately severe cone-rod dystrophy classifiable under the Szylek system as a type 2b. This marked variation in expression is not so extreme as that seen in the peripherin/RDS codon 153/4 mutation. Variable expressivity has been reported in autosomal dominant RP associated with loci 7p and 19q.33,34 There is also a precedent for a members of a family to demonstrate a more severe phenotype, despite having the same mutation.35 Secondary factors, such as deleterious or protective alleles or environmental influences, may be influencing the phenotype, and epigenetic or stochastic effects will probably prove to be the most likely explanations.

It is predictable that the disorder would affect cones more than rods. Immunohistochemical staining for GCAP-1 in human retinas has demonstrated that there is intense staining of cone outer and inner segments, the cell body from axon to pedicle, but weaker immunoreactivity in rod inner segments, and very minimal immunostaining of rod outer segments.36-37

The GCAP-1 activates retinal guanylate cyclase (retGC-1), and has been considered to restore levels of cyclic guanine monophosphate (cGMP) after transduction38 (Figure 7). The GCAP-1 is inhibited by intracellular calcium, which rises in the dark-adapted state.38,39 These experimental observations support the inference that the cone degeneration associated with the Y99C mutation in GCAP-1 is a result of constitutive activation of cGMP synthesis.

These results are consistent with a model in which enhanced retGC-1 activity in dark-adapted cones leads to elevated levels of cytoplasmic cGMP. Evidence exists that continuously high levels of cGMP can cause photoreceptor cell death.40 Retinal degeneration, with either excess levels of cGMP, as in the case of mutations in phosphodiesterase β, or disease associated with insufficient cGMP, as in Leber congenital amaurosis, exists.

It is difficult to predict what effect constant elevation of cGMP may have on transduction kinetics, and the relationship between the phenotype and the putative metabolic abnormality consequent on the mutation is not clear. However, there is ample evidence that continuously high levels of cGMP may cause photoreceptor cell death.41 The abnormalities of the ON and OFF responses seen in family A may reflect abnormal transduction kinetics. Alternatively, they may imply a posttransduction disturbance caused by either abnormalities of the cones themselves and/or their synapses.42 There is no evidence to suggest consistent selective involvement of either depolarizing (ON) or hyperpolarizing (OFF) pathways.

References
