Shared Mutations in NR2E3 in Enhanced S-cone Syndrome, Goldmann-Favre Syndrome, and Many Cases of Clumped Pigmentary Retinal Degeneration

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Objectives: To determine if enhanced s-cone syndrome (ESCS), Goldmann-Favre syndrome (GFS), and clumped pigmentary retinal degeneration (CPRD) are caused by mutations in the NR2E3 gene and to characterize the clinical findings in patients with NR2E3 mutations.

Patients: One patient with ESCS, one with GFS, and 20 with CPRD.

Methods: The coding regions of the NR2E3 and NRL genes and part of the THRB1 coding region were scanned for mutations using single-strand conformation and direct sequencing methods. We evaluated visual acuity, refractive error, visual fields, fundi, final dark-adaptation thresholds, and electroretinograms (ERGs).

Results: The patients with ESCS and GFS and 9 of the 20 unrelated patients with CPRD had mutations in the NR2E3 gene. Six mutations were found in these 11 patients, including 2 novel mutations: the missense mutation Ala256Glu and the frameshift mutation Pro276del17 (the first obviously null allele reported). Three patients were mutant homozygotes, and 8 had 2 mutations. All but one of the mutations in the patients with ESCS and GFS were also found in patients with CPRD. All NR2E3 cases were hyperopes and had retinal vascular attenuation and reduced and delayed full-field ERGs. Clumped pigment deposits were recognized in the patients with ESCS and GFS. The CPRD patients without NR2E3 mutations had no detected mutations in NRL or THRB1.

Conclusions: We found that ESCS, GFS, and CPRD can all have the same genetic basis.

Clinical Relevance: The combination of night blindness, hyperopia, and clumped retinal pigment deposits should raise the suspicion that a patient has NR2E3 disease.

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N ESTIMATED 0.5% of patients with retinitis pigmentosa (RP) have a clumped or nummular pattern of pigmentation in the mid-peripheral fundus referred to as “clumped pigmentation.” This pattern has been described in Bardet-Biedl syndrome, in RP with preserved para-arteriolar retinal pigment epithelium (RPE), in Goldmann-Favre syndrome (GFS), in enhanced s-cone syndrome (ESCS), and in nonsyndromic autosomal recessive RP. Different primary mutations that cause RP can result in clumped pigmentation, because, for example, the gene that causes RP with preserved para-arteriolar RPE in chimpanzee 1 is distinct from all of the known genes that cause Bardet-Biedl syndrome. However, the gene or genes responsible for nonsyndromic, recessive RP with clumped pigmentation have remained unidentified. To et al reviewed the clinical and pathological findings in patients with non-syndromic RP and clumped pigmentation and found that they have signs and symptoms of RP, such as night blindness and reduced and delayed full-field electroretinograms (ERGs); the severity of retinal degeneration as measured by ERG amplitudes could vary at a given age by more than 10-fold. Histopathologic examination of 1 case revealed that the clumped pigment deposits seen by funduscopy corresponded to RPE cells that were packed with melanin granules.

Patients with either ESCS or GFS have psychophysical hypersensitivity to blue light. In addition, their ERGs have greater amplitudes to short-wavelength (eg, blue) light flashes than to intensity-matched, long-wavelength (eg, orange) light flashes. Although rods and s-cones are maximally sensitive to blue light and might hypothetically mediate the patient’s hypersensitivity to it, the similar ERG amplitudes under scotopic and photopic conditions to single flashes of bright white...
light indicate that the hypersensitivity to blue light is mediated predominantly by s-cones.6,9-11 Evidence from the shape of the ERG a-wave and from psychophysical studies of color sensitivity indicates that the affected retinas have an overabundance of s-cone photoreceptors at birth, a reduced number of l-cones and m-cones, and, if any, functional rod photoreceptors.9,12 The relative abundance of s-cone photoreceptors persists even late in the disease, when visual function is severely reduced, as determined by histopathologic examination at autopsy of the eyes of a patient with ESCS.7

The NR2E3 gene, formerly called photoreceptor-specific nuclear receptor or PNR,13 is thought to encode a ligand-dependent transcription factor. It was originally reported to have a retina-specific expression, exclusively in photoreceptor cells,13 but was later reported to be expressed in RPE and possibly in Muller cells.14 However, findings from recent studies support the original observation of photoreceptor-specific expression in human15 and mouse16 retinas. Sharon et al17 studied levels of gene expression, and, although the gene accounts for approximately 0.06% of the messenger RNA transcripts in the retina, there was no detected expression in RPE.

Mutations in the NR2E3 gene have recently been reported18 in patients with ESCS. That study included patients with GFS, but it is unclear how many patients with that diagnosis were evaluated and whether they also had similar mutations in NR2E3. A subsequent study18 found an NR2E3 mutation that caused nonsyndromic, recessive RP in a genetically isolated Jewish community in Portugal, but the relationship between RP in those patients and ESCS and GFS was not investigated. The fundus photographs of patients in that study18 showed clumped pigment deposits. We conducted this investigation to more fully explore the genetic relationships among ESCS, GFS, and nonsyndromic, recessive RP with clumped pigmentation (CPRD).

This study conformed to the tenets of the Declaration of Helsinki. All index cases in this study were diagnosed by ophthalmologic examination, including ERG. All but 1 patient resided in the United States and Canada. Most patients with CPRD in-
Table 1. Mutations Found in the NR2E3 Gene

<table>
<thead>
<tr>
<th>DNA Change*</th>
<th>Sequence Change</th>
<th>Protein Change</th>
<th>Exon</th>
<th>Patient No.</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>del199-207</td>
<td>delTGCAAGCGGC</td>
<td>del67-69</td>
<td>2</td>
<td>121-324 and 072-006</td>
<td>Haider et al,15 2000</td>
</tr>
<tr>
<td>C290A</td>
<td>CGG&gt;CAC</td>
<td>Arg97His</td>
<td>3</td>
<td>160-014</td>
<td>Haider et al,15 2000</td>
</tr>
<tr>
<td>C767A</td>
<td>GCA&gt;GAG</td>
<td>Ala256Glu</td>
<td>6</td>
<td>112-020 and 112-018</td>
<td>This study</td>
</tr>
<tr>
<td>del1827-843</td>
<td>del17bp</td>
<td>Pro276; 334Ter</td>
<td>6</td>
<td>112-003</td>
<td>This study</td>
</tr>
</tbody>
</table>

Abbreviations: IVS, intervening sequence (intronic); ND, not determined.

*The base numbers are the distance from the first base of the first codon (ATG).

Table 2. Visual Function in Patients With NR2E3 Mutations*

<table>
<thead>
<tr>
<th>Patient No.†</th>
<th>Original Diagnosis</th>
<th>NR2E3 Mutations</th>
<th>Age, y</th>
<th>Sex</th>
<th>DA</th>
<th>Snellen Visual Acuity, OD:OS</th>
<th>Refractive Error, D‡</th>
<th>Visual Field Area, Degree‡</th>
<th>Full-Field 30-Hz ERG, µV‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>112-009</td>
<td>CPRD</td>
<td>Arg311Gln; Arg311Gln</td>
<td>21</td>
<td>M</td>
<td>4.0</td>
<td>C5°; 20/200</td>
<td>+.62§</td>
<td>9082</td>
<td>0.58</td>
</tr>
<tr>
<td>121-324</td>
<td>CPRD</td>
<td>Arg311Gln; Cys67del9</td>
<td>61</td>
<td>F</td>
<td>7.0</td>
<td>LP; NA</td>
<td>+.62§</td>
<td>NA</td>
<td>0.10</td>
</tr>
<tr>
<td>038-038</td>
<td>CPRD</td>
<td>Arg311Gln; IVS1-2A&gt;C</td>
<td>58</td>
<td>M</td>
<td>4.0</td>
<td>20/25; 20/40</td>
<td>+.50</td>
<td>2881</td>
<td>0.20</td>
</tr>
<tr>
<td>112-007</td>
<td>CPRD</td>
<td>Arg311Gln; IVS1-2A&gt;C</td>
<td>41</td>
<td>M</td>
<td>4.0</td>
<td>20/40; CF1*</td>
<td>+.50</td>
<td>4629</td>
<td>0.12</td>
</tr>
<tr>
<td>112-003</td>
<td>CPRD</td>
<td>Pro276del17; IVS1-2A&gt;C</td>
<td>34</td>
<td>F</td>
<td>2.8</td>
<td>20/200; LP</td>
<td>+.50</td>
<td>798</td>
<td>2.93</td>
</tr>
<tr>
<td>112-020</td>
<td>CPRD</td>
<td>Ala256Glu; IVS1-2A&gt;C</td>
<td>14</td>
<td>M</td>
<td>2.5</td>
<td>20/20; 20/20</td>
<td>+.20</td>
<td>12.695</td>
<td>18.00</td>
</tr>
<tr>
<td>112-021</td>
<td>CPRD</td>
<td>Ala256Glu; IVS1-2A&gt;C</td>
<td>17</td>
<td>F</td>
<td>2.0</td>
<td>20/20; 23/30</td>
<td>+.50</td>
<td>10.425</td>
<td>NA</td>
</tr>
<tr>
<td>112-018</td>
<td>CPRD</td>
<td>Ala256Glu; IVS1-2A&gt;C</td>
<td>17</td>
<td>F</td>
<td>3.0</td>
<td>20/20; 20/70</td>
<td>+.20</td>
<td>10.822</td>
<td>NA</td>
</tr>
<tr>
<td>072-006</td>
<td>CPRD</td>
<td>IVS1-2A&gt;C; Cys67del9</td>
<td>19</td>
<td>M</td>
<td>3.8</td>
<td>CF1; CF1*</td>
<td>+.25</td>
<td>9948</td>
<td>11.00</td>
</tr>
<tr>
<td>112-015</td>
<td>CPRD</td>
<td>IVS1-2A&gt;C; IVS1-2A&gt;C</td>
<td>19</td>
<td>M</td>
<td>3.0</td>
<td>20/40; 20/60</td>
<td>+.25</td>
<td>1850</td>
<td>1.22</td>
</tr>
<tr>
<td>160-014</td>
<td>ESCS</td>
<td>Arg97His; IVS1-2A&gt;C</td>
<td>11</td>
<td>M</td>
<td>3.0</td>
<td>20/20; 20/40</td>
<td>+.60</td>
<td>7540</td>
<td>3.85</td>
</tr>
<tr>
<td>039-203</td>
<td>CPRD</td>
<td>Arg311Gln; Arg311Gln</td>
<td>8</td>
<td>M</td>
<td>2.0</td>
<td>20/20; 20/25</td>
<td>+.40</td>
<td>13416</td>
<td>3.65</td>
</tr>
</tbody>
</table>

Abbreviations: CF1*, counting fingers at 1 ft; C5°, counting fingers at 5 ft; CPRD, clumped pigmentary retinal degeneration; D, diopter; DA, elevation of final dark-adaptation threshold, given in log10 units above normal; ERG, electroretinography; ESCS, enhanced s-cone syndrome; GFS, Goldmann-Favre syndrome; IVS, intervening sequence; LP, light perception; NA, not available.

†All patients are index cases except patient 112-021, who is related to index patient 112-020.
‡Values are averages of the 2 eyes. Normal visual field area is 11 310 deg2 or greater; normal ERG 30-Hz amplitude is 50 µV or greater.
§The refractive error listed for patient 121-204 is at age 51 years, before cataract extractions.
||Clumped pigment developed between ages 9 and 11 years.

We screened 1 patient with ESCS, 1 patient with GFS, and 20 unrelated index patients with CPRD for mutations in the NR2E3 gene. Six different mutations were found in 11 patients (Table 1). Three index patients diagnosed as having CPRD were homozygotes, 2 with the missense mutation changing amino acid residue 311 (Arg311Gln) and the other with a mutation affecting an intron splice site (IVS1-2A>C). Eight patients (1 with ESCS, 1 with GFS, and 6 with CPRD) harbored 2 likely disease-causing mutations and were presumed to be compound heterozygotes (Table 2). The family of 1 of the presumed compound heterozygotes was available for analysis (patient 112-018 with CPRD), and the 2 mutations carried by this index patient segregated in the family, thereby confirming the presumption of compound heterozygosity (Figure 1C).

Four of the 6 mutations (IVS1-2A>C, Cys67del9, Arg97His, and Arg311Gln) have been previously reported as causes of ESCS15 or RP.18 The remaining 2 mutations were novel. One was a frameshift deletion, Pro276del17, found heterozygously in 1 patient with CPRD (patient 112-003) (Figure 1A). If this allele were translated, it would alter the next 58 amino acids, followed by a premature stop at codon 334, 77 residues less than the wild-type protein of 411 residues. The second novel mutation was a missense change, Ala256Glu, found heterozygously in 2 patients with CPRD (patients 112-020 and 112-018) (Figure 1B). This amino acid is cons-
served and located within the presumed ligand-binding domain of the NR2E3 protein. We screened 94 healthy individuals and found that none carried it. The Ala256Glu allele cosegregated with the disease in the family available for segregation analysis (Figure 1C).

Direct sequence analysis of the entire coding sequence and of all intron splice donor and acceptor sites revealed no likely mutations in the NR2E3 gene in the remaining 11 patients with CPRD. An intron change, IVS2+8C>T, was found heterozygously in 1 of these 11 patients, but this change was interpreted as being non-pathogenic. This change was not predicted to destroy the nearby splice donor site or to create an intron splice donor or acceptor site based on the results of neural network software analysis (see the “Methods” section).

The 11 patients with CPRD who had no detected NR2E3 mutations were evaluated for mutations in the NR2E3 gene (coding for a retina-specific transcription factor) and in the retina-specific exon 1 of the THRB1 gene (a thyroid hormone–responsive transcription factor). No sequence anomalies were found in these patients in either of these 2 genes.

**CLINICAL RESULTS**

We clinically evaluated all 11 of the index patients with NR2E3 mutations and the affected sibling of 1 of the patients with CPRD (Table 2). At the time of their clinical evaluations, the patients ranged in age from 8 to 61 years, with an average age of 27 years. Visual acuity ranged from 20/20 to 20/60 (in both eyes of a 14-year-old patient and in the right eye of an 8-year-old patient) to light perception (in a 34-year-old and a 61-year-old patient). All patients were hyperopes, with refractive errors (average of the 2 eyes) ranging from +0.50 to +8.62 diopters (D) spherical equivalent; the average refractive error for the entire group was +3.4 D. Visual fields were constricted, and final dark-adaptation thresholds were elevated by 2 to 7 log10 units in all patients (average elevation, 3.42 log10 units). Clumped pigmentary deposits were clearly evident in the fundi of all adult patients. Some young patients had only a few, small pigmentary deposits that were not recognized as clumped pigment deposits (eg, patient 112-020 at age 5 years shown in Figure 2A); these were interpreted as the early stage of this characteristic fundus abnormality because follow-up examinations of these patients later in life showed the typical clumped pigment deposits. In addition, many patients had small subretinal white deposits (Figure 2A, C, and E). The macula appeared normal in some patients, whereas others had an atrophic scar (Figure 2E and F) or a macular hole (Figure 2G). Whereas the patient with GFS had macular schisis characteristic of that syndrome, none of the patients with CPRD had macular schisis at the time of their clinical evaluations. However, some patients had evidence suggesting previous macular schisis (eg, a macular hole, as illustrated in Figure 2G). The caliber of the retinal arterioles was attenuated. All of the patients had reduced cone ERG amplitudes in response to 30-Hz light flashes ranging from 0.10 to 18 µV (average of the 2 eyes; normal, 50 µV).

We also reviewed the clinical findings of the 11 patients with CPRD who had no detected mutations in NR2E3. These patients ranged in age from 16 to 59 years (mean age, 39.5 years). This group had an average refractive error of +0.09 D spherical equivalent (Table 3). Although the difference in average refractive error between the groups of patients with vs without NR2E3 mutations was not statistically significant (P = .09), the frequency of hyperopia was statistically significantly higher in patients with NR2E3 mutations (12 of 12 cases) vs those without NR2E3 mutations (4 of 10 cases) (P = .003, 2-tailed Fisher exact test). The visual function of the 2 groups of patients was also compared. After correcting for age, sex, and refractive error, there was no statistically significant difference in visual acuity, visual field area, or 30-Hz (cone) ERG amplitude between patients with vs without detected NR2E3 mutations, and this was true whether we included patients diagnosed as having ESCS and GFS before the molecular genetic analysis. The group of patients with NR2E3 mutations had on average a higher elevation of their final dark-adaptation threshold (mean, 3.44 log10.

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**Figure 1.** A and B. The DNA sequences of novel NR2E3 mutations in patients and the corresponding normal DNA sequences in control individuals. Part A shows the DNA sequence around codon 276 in patient 112-003, who is heterozygous for a deletion of 17 base pairs starting in this codon (arrow). This mutation causes a frameshift and a premature termination stop at codon 334 (data not shown). Part B shows the DNA sequence around codon 256 in patient 112-018, who is heterozygous for the missense mutation Ala256Glu (arrow). C, The segregation of NR2E3 alleles in the relatives of index patient 112-018 (family 3480). Note that only the index patient is affected and that she is the only compound heterozygote, with the mutation IVS1-2A (previously reported) and the novel mutation Ala256Glu (A). The cosegregation analysis also revealed a nonpathogenic missense change, Val302Ile (c), which was previously reported.15
units) compared with the group without detected mutations (mean, 1.94 log₁₀ units), but this difference was of borderline statistical significance ($P = .04$ if all patients were included; $P = .06$ if patients with a previous diagnosis of ESC5 and GFS were excluded) (Table 3). The fundus changes in both groups seemed comparable.

Figure 2. Fundus photographs of patients with clumped pigmentary retinal degeneration showing the range of pigment deposits and subretinal white spots in patients of different ages (A-D) and the range of macular pathologic findings in this disease (E-G). A, Right eye of patient 112-020 at age 5 years, at an early stage of the disease. Very few clumped pigment deposits are seen at the 1- and 2-o'clock positions in the photograph. There are also small, tadpole-shaped white deposits in the macula. B, Right eye of patient 112-021 at age 19 years (the sister of patient 112-020 with the same mutations). The fundus had white deposits at age 13 years (described by To et al³), which disappeared by age 19 years. The macula shows no abnormality. C, Right eye of patient 112-015 at age 18 years. The predominant feature is numerous small white deposits of variable shapes, reminiscent of those seen in the fundi of the mouse model with mutations in the murine NR2E3 gene.²⁵ D, Right eye of patient 038-038 at age 62 years. The pigment deposits extend close to the macula. E, Left eye of patient 112-009 at age 20 years. The clumped pigment deposits involve the macula, which has an atrophic scar. F, Left eye of patient 121-324 at age 54 years. The fundus shows a macular scar with dense pigment deposits. There are also clumped pigment deposits and bone-spicule pigment deposits in the periphery. G, Left eye of patient 112-003 at age 37 years. Clumped pigment deposits and subretinal white deposits are seen in the nasal periphery. A macular hole is also present.
Table 3. Ocular Findings in Patients With Clumped Pigmentary Retinal Degeneration*

<table>
<thead>
<tr>
<th>Finding</th>
<th>With NR2E3 Mutations</th>
<th>Without NR2E3 Mutations</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snellen visual acuity†</td>
<td>-2.55 ± 0.59 (20/251)</td>
<td>-1.11 ± 0.66 (20/61)</td>
<td>.18</td>
</tr>
<tr>
<td>Refractive error, dipters</td>
<td>+3.45 ± 0.75</td>
<td>-0.09 ± 1.75</td>
<td>.09</td>
</tr>
<tr>
<td>Final dark-adaptation threshold</td>
<td>3.44 ± 0.42</td>
<td>1.94 ± 0.48</td>
<td>.04</td>
</tr>
<tr>
<td>Total visual field area‡</td>
<td>8.66 ± 0.40 (5767 degree²)</td>
<td>7.63 ± 0.42 (2059 degree²)</td>
<td>.12</td>
</tr>
<tr>
<td>30-Hz ERG amplitude§</td>
<td>+0.03 ± 0.71 (1.03 µV)</td>
<td>1.66 ± 0.73 (5.26 µV)</td>
<td>.15</td>
</tr>
</tbody>
</table>

Abbreviation: ERG, electroretinogram.

*These data were corrected for age, sex, and refractive error, except refractive error itself. Data are given as mean ± SE. The mean visual acuity, visual field area, and 30-Hz ERG amplitude are listed in parentheses without the logarithmic conversion.
†Snellen visual acuity is expressed as log, decimal; normal is 20/20 or greater.
‡Visual field area is expressed as log, to a V-4e white test light; normal is 11 310 deg² or greater.
§30-Hz ERG expressed as loge amplitude; normal is 50 µV or greater.

It is typical for patients with ESCS to have dark- and light-adapted ERGs of similar amplitude and with prolonged implicit times to single flashes of white light; this feature has been used to distinguish these patients from those with typical RP, who have light-adapted ERGs (if detectable at all) with substantially lower amplitudes than dark-adapted ERGs. Thirteen of our patients with CPRD had dark- and light-adapted ERGs that were recorded in response to single flashes of the same intensity; 8 of these patients had sufficiently high amplitudes so that a comparison could be made. In 5 of these 8 patients, the dark- and light-adapted responses were comparable in amplitude, and in the remaining 3 patients, the light-adapted responses were substantially lower than the dark-adapted responses (Figure 3). All 5 patients with similar dark- and light-adapted responses had identified NR2E3 mutations, including the patient previously diagnosed as having GFS and the patient previously diagnosed as having ESCS; none of the 3 patients with substantially lower light-adapted responses had identified mutations. Thus, patients with NR2E3 mutations had ERG features that were consistent with those observed in ESCS, whereas those without NR2E3 mutations did not.

COMMENT

In 1991, Jacobson et al6 reported that patients with GFS had psychophysical and electrophysiologic findings that were similar to those in patients with ESCS and that the 2 diseases were likely to be identical.6 Although clumped pigment deposits were often observed in patients with either GFS6,20,21 or ESCS,11,29 the association between these 2 synonymous diseases and the clumped pigmenary form of RP went unrecognized. To et al6 also did not recognize the connection between these diseases during their clinical and histopathologic study of a series of patients with CPRD. The shared pattern of pigment deposits in the fundus was not mentioned by the researchers who first reported the NR2E3 gene as the cause of ESCS.13 We found mutations in the NR2E3 gene in patients clinically diagnosed as having each of these 3 diseases. One of the mutations, IVS1-2A>C, was found in a patient with ESCS, a patient with GFS, and 6 index patients with CPRD. We found another mutation, Cys67(9-bp del), previously reported as causing ESCS,15 in a patient with GFS and a patient with CPRD. These shared mutations suggest that the range of clinical findings in patients with NR2E3 mutations is not due to different mutations in this gene.

We also gathered evidence that at least 1 other gene can cause CPRD. First, no mutations in NR2E3 were found in 11 of the 20 index patients that we surveyed. Second, the patients with NR2E3 mutations were all hyperopes; hyperopia was not a shared feature among those without detected mutations. Third, the patients with NR2E3 mutations had dark- and light-adapted single-flash ERG amplitudes of similar amplitude (as expected for patients with ESCS),11 whereas the patients without NR2E3 mutations had light-adapted amplitudes lower than dark-adapted amplitudes. Fourth, patients with NR2E3 mutations invariably had final dark-adaptation thresholds elevated at least 100-fold (ie, 2 log units), suggesting little or no residual rod function, a finding previously reported8,20 as a consistent finding among patients with ESCS and GFS. However, of the 11 patients without NR2E3 mutations, 6 had dark-adaptation thresholds elevated by less than 2 log units, indicating some residual rod function. Additional evidence for a form of CPRD distinct from ESCS comes from a previously reported study20 of 2 affected siblings, 1 living and 1 dead, presumably with the same disease. Clumped pigment was present in both siblings, but psychophysical and electrophysiologic findings did not support the diagnosis of ESCS. The histologic findings from the eye of the dead sibling were similar to those found in an autopsy case of CPRD from our group.1 We did not have DNA samples from the autopsy case to evaluate for mutations in NR2E3.

Although some of our patients without NR2E3 mutations have clinical features suggesting a diagnosis other than ESCS, others have advanced disease with poorly detectable ERGs, making it difficult to know whether they had an s-cone disease. We thus evaluated all patients without NR2E3 mutations for mutations in 2 other candidate genes, NRL and THRB1, because mutations in these genes in transgenic mice result in retinal disease similar to that...
found in mice that are nullizygous for NR2E3. Specifically, the NRL nullizygous mice have a complete loss of rod function and super-normal s-cone function, and mice lacking the retina-specific exon of THRB1 have an excess of s-cones. We found no mutations in either of these genes in patients with CPRD who did not have detected NR2E3

Figure 3. Full-field, 0.5-Hz, single-flash, dark-adapted (A) and light-adapted (B) electroretinograms (ERGs) in patients with clumped pigmentary retinal degeneration. The 5 patients at the top of the figure had dark- and light-adapted ERGs that were similar in amplitude; all of these 5 patients were compound heterozygotes with NR2E3 mutations (see Table 2). The 3 patients at the bottom of the figure had dark-adapted ERGs (after 45 minutes of dark adaptation) with greater amplitudes than light-adapted ERGs (in the presence of a steady white background light, 17 candela/m²); none of these patients had detected NR2E3 mutations. These full-field ERGs were elicited in response to 10-microsecond flashes of white light as described previously. Two to 4 consecutive responses are illustrated. All patients were tested under the same set of conditions. Only the first 100 milliseconds of some light-adapted ERGs were recorded, as indicated by the responses followed by dotted lines.
Hyperopic refractive errors in patients with ESCS and GFS have been previously reported but not recognized as a common feature of the syndrome. Fishman, Peyman, and Marmor and their colleagues recorded refractive errors in a total of 12 patients: 7 were hyperopic (range, +1.50 to +9.75 D spherical equivalent), 4 were myopic (range, –0.50 to –2.06 D), and 1 was reported as emmetropic. The average refractive error overall for these 12 patients was +2.38 D spherical equivalent. This may be an underestimate of the actual hyperopic refractive error because some cases might not have been refracted after cycloplegia. This could explain why the average hyperopic refractive error found among our group of patients with NR2E3 mutations (+3.4 D) is greater; all refractive errors were measured after cycloplegia in the present study. Another possibility is that the more consistent hyperopia found in this study may be related to the ascertainment of patients as cases of RP with clumped pigmentation in their fundi; cases ascertained as ESCS or GFS might have qualitative differences in their ocular findings, including less frequent or less severe hyperopia. Hyperopic refractive errors have also been described among patients with RP with preserved para-arteriolar RPE, a form of RP caused by the gene on chromosome band 15q23.

Clumped pigment deposits in the fundus have also been reported in Bardet-Biedl syndrome, and a locus responsible for Bardet-Biedl syndrome (BBBS) is closely linked to the NR2E3 gene on chromosome band 15q23. However, no mutations in the NR2E3 gene were found during a study of more than 50 unrelated patients with Bardet-Biedl syndrome. The BBBS locus has been identified recently; this locus is separated from NR2E3 by less than 1 million base pairs of DNA. It is not known which loci causing Bardet-Biedl syndrome are associated with the clumped pigmentation sometimes found in this syndrome.

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REFERENCES


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