Clinical and Molecular Characterization of Enhanced S-Cone Syndrome in Children

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**IMPORTANCE** Enhanced S-cone syndrome (ESCS) forms part of the differential diagnosis of night blindness in childhood.

**OBJECTIVE** To report in detail the clinical phenotype and molecular genetic findings in a series of children with ESCS.

**DESIGN, SETTING AND PARTICIPANTS** Nine children with ESCS from 5 families underwent full ophthalmic examination, electrophysiological testing, and retinal imaging at a genetic eye disease clinic of a tertiary referral eye hospital. Bidirectional Sanger sequencing of all exons and intron-exon boundaries of NR2E3 was performed.

**MAIN OUTCOMES AND MEASURES** Results of ophthalmic examination and sequence analysis of NR2E3.

**RESULTS** In total, 5 girls and 4 boys with a diagnosis of ESCS were included in the study. All patients had developed nyctalopia from early childhood. Visual acuity ranged from 0.00 to 1.20 logMAR (20/20 to 20/320 Snellen). All patients had hyperopia. Three patients had nummular pigmentary lesions along the arcades as typically seen in adults, 4 patients had mild pigmentary disturbance or white dots along the arcades, and 2 patients had a normal retinal appearance, although their fundus autofluorescence imaging demonstrated foci of increased autofluorescence along the arcades. Three patients had macular schisis-like changes on optical coherence tomography. Eight patients had electrophysiological testing at a mean age of 8.6 years (age range, 3-14 years), and in each patient the findings were consistent with the diagnosis of ESCS. Direct sequencing of NR2E3 identified 3 previously described mutations and 4 novel mutations. Seven patients were compound heterozygous for mutations in NR2E3, and 2 additional sibling patients were presumed to be homozygous for a missense change based on parental sequencing.

**CONCLUSIONS AND RELEVANCE** In this sample, children with ESCS had an early onset of night blindness and hyperopia but no nystagmus. Based on this study, children with ESCS may initially manifest a normal fundus appearance but later develop mottled retinal pigment epithelium change along the arcades, followed by the appearance of white dots in the same distribution. Fundus autofluorescence imaging is abnormal in children with a normal fundus appearance. The electrophysiological findings are pathognomonic and allow targeted molecular screening and a specific diagnosis.
first described in 1990, enhanced S-cone syndrome (ESCS) (OMIM 268100) is a rare, autosomal recessive retinal dystrophy. It is one of the few disorders in which the electrophysiological findings are pathognomonic. Patients typically are seen with symptoms of nyctalopia from the first decade with or without reduced vision; the visual loss may be associated with foveal schisis. The disorder is probably slowly progressive, and deterioration on electroretinography (ERG) has been demonstrated. Adults with the disorder characteristically show nummular pigmentary deposition at the level of the retinal pigment epithelium (RPE) outside of the vascular arcades with or without foveal schisis–like cystic changes. Reports of the presentation of ESCS in children are few: case reports of early findings describe a normal fundus or early changes of white dots at the level of the RPE.

In 2000, defects in a nuclear receptor gene, NR2E3, were linked to ESCS. It encodes a 410–amino acid, 8-exon, ligand-dependent transcription factor important in the determination of photoreceptor cell fate. In cell investigations and the RD7 murine model, NR2E3 acts in tandem with CRX to promote rod photoreceptor differentiation and suppress the formation of cone cells. Mutations in NR2E3 leading to loss of function of the transcription factor are theorized to be pathogenic by the abnormal differentiation of postmitotic photoreceptor precursor cells, altering their cell fate from rod to S-cone. Histopathologic and immunocytochemical analysis of a postmortem eye of an elderly patient with ESCS showed a degenerate retina with no rods and approximately twice the number of cones, 92% of which were short wavelength sensitive. To date, at least 49 mutations have been reported with resultant phenotypes of ESCS, Goldmann–Favre syndrome, and autosomal dominant and autosomal recessive retinitis pigmentosa.

The present study describes the molecular genetic analysis and detailed phenotype in a series of pediatric patients with ESCS. The findings are compared with the data from affected adults.

Methods

Study Design

The study protocol adhered to the tenets of the Declaration of Helsinki and received approval from the Research Ethics Committee, Moorfields Eye Hospital, London, England. Written informed consent was obtained from all participants before their inclusion in the study, with parental written consent provided on behalf of the children involved in this study.

Nine patients (2 simplex cases, 2 sibling pairs, and 1 sibling pair and a half cousin) were ascertained from the inherited retinal disease clinics at Moorfields Eye Hospital. Each confirmed patient underwent a full clinical examination, including visual acuity and dilated ophthalmoscopic examination. One patient declined further investigations apart from molecular testing, but the sibling had undergone full investigation. All other patients had electrophysiological testing and dilated fundus imaging. Retinal fundus photographs were obtained by conventional 35° fundus color photographs (Topcon Great Britain Ltd) or ultra-wide-field confocal scanning laser imaging (Optos plc). Fundus autofluorescence (FAF) imaging encompassed 30°, 55°, or ultra-wide-field. Spectral-domain optical coherence tomography (OCT) scans (Spectralis; Heidelberg Engineering Ltd) of the macula were obtained in 8 patients, as well as through the superior arcades in 2 patients. Full-field and pattern ERG was performed using gold foil electrodes to incorporate the International Society for Clinical Electrophysiology of Vision standards; recording in 2 younger patients was performed with surface electrodes. Additional S-cone ERG was recorded, when possible, to a 5-millisecond blue stimulus (445 nm and 80 candela [cd]/m−2) on a bright orange background (620 nm and 560 cd/m−2); on-off ERG was recorded to the orange stimulus (duration, 200 milliseconds) on a green background (530 nm and 150 cd/m−2).

Molecular Biology

Patients were screened for disease-causing mutations by direct sequencing of all 8 exons and intron-exon boundaries of NR2E3; subsequently, available relatives also underwent sequencing. Genomic DNA was isolated from peripheral blood lymphocytes using a kit (Genta Puregene blood extraction kit; Qiagen). DNA was amplified using specifically designed primers by polymerase chain reaction, and the polymerase chain reaction fragments were sequenced using standard protocols (details are available from the author on request). Mutation nomenclature was assigned in accord with GenBank accession number NM_014249.3, with nucleotide position 1 corresponding to the A of the ATG initiation codon. Variants were identified as novel if not previously reported in the literature and if absent from dbSNP (http://www.ncbi.nlm.nih.gov/projects/SNP/), National, Heart, Lung, and Blood Institute Exome Sequencing Project (http://evs.gs.washington.edu/EVS/), and 1000 Genomes (http://www.1000genomes.org/). The likely pathogenicity of novel missense variants was assessed using the predictive algorithms of SIFT (http://sift.jcvi.org) and PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2) and by analysis of conservation of each residue throughout the species using HomoloGene (www.ncbi.nlm.nih.gov/homologene).

Results

Clinical Findings

Clinical findings are summarized in Table 1. Nine children (5 girls and 4 boys) from 5 families were assessed. The mean age at the last review was 10.8 years (median age, 11 years; age range, 7-15 years). Diagnostic ERG was performed in 8 patients at a mean age of 8.6 years (median age, 8 years; age range, 3-14 years). Geographic origin was white race/ethnicity British in 7 patients and the Kashmir region of Pakistan in 2 patients. Longitudinal data were available in 8 patients (mean follow-up period, 3 years; range, 1-10 years). All patients reported nyctalopia, although patient 3.1 reported this only from the age of 7 years. No patient had nystagmus. Visual acuity ranged from 0.00 to 1.20 logMAR (20/20 to 20/320 Snellen). Reduced vision in both eyes (0.30 logMAR or worse [20/40 Snellen]) was recorded in patients 1.1, 1.2, and 4, with the rest retaining good vision.
Table 1. Key Clinical Features in the Series of Children With Enhanced S-Cone Syndrome

<table>
<thead>
<tr>
<th>Patient No./Sex (Genetic Database No.)</th>
<th>Age at Last Examination, Y</th>
<th>Fundus Appearance</th>
<th>FAF Imaging</th>
<th>OCT</th>
<th>Other Findings</th>
<th>Visual Acuity at Last Examination, LogMAR (Snellen)</th>
<th>Refraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1/F (GC19824)</td>
<td>9</td>
<td>White dots and nummular pigmentation along the arcades</td>
<td>Diffuse paracentral hyperfluorescence, multiple small high-density foci along the arcades, hypofluorescence outside of the arcades</td>
<td>Normal</td>
<td>Left eye small exotropia</td>
<td>OD: 0.80 (20/125) OS: 0.90 (20/160)</td>
<td>+8.60/ -3.50 × 5° −3.50 × 160°</td>
</tr>
<tr>
<td>1.2/F</td>
<td>9</td>
<td>White dots and nummular pigmentation along the arcades</td>
<td>Diffuse paracentral hyperfluorescence, multiple small high-density foci along the arcades, hypofluorescence outside of the arcades</td>
<td>Foveal sparing, intraretinal cysts BE</td>
<td>Right eye small esotropia</td>
<td>OD: 0.50 (20/63) OS: 0.36 (20/50)</td>
<td>+10.50/ -1.00 × 70° +10.00/ -1.00 × 80°</td>
</tr>
<tr>
<td>1.3/M</td>
<td>12</td>
<td>Few white dots and RPE mottling along the arcades</td>
<td>Diffuse paracentral hyperfluorescence with multiple small high-density foci along the arcades</td>
<td>Normal</td>
<td>Left eye small esotropia, left eye amblyopia</td>
<td>OD: 0.14 (20/25) OS: 0.74 (20/100)</td>
<td>+3.00/ -0.50 × 10° +4.50 DS</td>
</tr>
<tr>
<td>2.1/F (GC15494)</td>
<td>15</td>
<td>Subtle RPE mottling along the arcades</td>
<td>Small foci of high density along the arcades</td>
<td>Foveal sparing, intraretinal cysts NA</td>
<td>NA</td>
<td>OD: 0.10 (20/25) OS: 0.10 (20/25)</td>
<td>+2.50/ -1.25 × 180° +2.25/ -1.25 × 180°</td>
</tr>
<tr>
<td>2.2/M</td>
<td>11</td>
<td>Normal</td>
<td>Small foci of high density along the arcades</td>
<td>Normal</td>
<td>NA</td>
<td>OD: 0.00 (20/20) OS: 0.08 (20/25)</td>
<td>+1.00/ -1.00 × 15° +2.50/ -2.25 × 170°</td>
</tr>
<tr>
<td>3.1/M (GC19784)</td>
<td>7</td>
<td>Few white dots along the superior arcades</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>OD: 0.05 (20/25) OS: 0.10 (20/25)</td>
<td>+2.25/ -1.00 × 180° +3.00/ -1.00 × 180°</td>
</tr>
<tr>
<td>3.2/M</td>
<td>9</td>
<td>RPE mottling along the arcades</td>
<td>Diffuse paracentral hyperfluorescence with multiple small high-density foci along the arcades</td>
<td>Normal</td>
<td>NA</td>
<td>OD: 0.14 (20/25) OS: 0.00 (20/20)</td>
<td>+3.50 DS +2.50 DS</td>
</tr>
<tr>
<td>4/F (GC19940)</td>
<td>14</td>
<td>White dots and nummular pigmentation along the arcades</td>
<td>Diffuse paracentral hyperfluorescence, multiple small high-density foci along the arcades, hypofluorescence outside of the arcades</td>
<td>Foveal involving, intra-retinal cysts BE</td>
<td>NA</td>
<td>OD: 0.86 (20/160) OS: 1.20 (20/320)</td>
<td>+3.50/ -0.50 × 21° +3.50/ -1.00 × 145°</td>
</tr>
<tr>
<td>5/F (GC16/15)</td>
<td>11</td>
<td>Normal</td>
<td>Small foci of high density along the arcades</td>
<td>Normal</td>
<td>NA</td>
<td>OD: 0.10 (20/25) OS: 0.13 (20/25)</td>
<td>+3.50/ -1.50 × 20° +4.00/ -1.50 × 165°</td>
</tr>
</tbody>
</table>

Abbreviations: BE, both eyes; DS, dipter sphere; F, female; FAF, fundus autofluorescence; M, male; NA, not applicable; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

visual acuity with appropriate refractive correction. Deterioration of visual acuity over time was recorded in these 3 patients, with only 1 having evidence of intraretinal cysts involving the fovea. This patient was intolerant of topical and oral carbonic anhydrase inhibitors. All patients had a hyperopic refractive error, with a mean spherical equivalent at presentation of +4.40 diopter (D) (range, +1.40 to +11.75 D) and at the last review a mean of +4.00 D (range, +0.50 to +10.00 D).

Retinal fundus imaging results from representative patients are shown in Figure 1 and Figure 2. Two patients had a normal biomicroscopic fundus appearance, although their FAF imaging demonstrated foci of high density around the arcades (Figure 1A-C). Two patients had RPE motting only (Figure 1E), and 2 patients had RPE motting with white dots. The typical adult ESCS feature of nummular pigmentary deposits along the arcades was present in only 3 patients (Figure 1I). Within family 1, phenotypic variability existed that was independent of age; one girl and her female half cousin (patients 1.1 and 1.2) had extensive nummular pigmentation not present in her older male half cousin (patient 1.3) (Figure 1G-J).

Progression of ophthalmoscopic changes was recorded in 4 patients. Patient 2.1, who was first seen at age 6 years with a normal fundus appearance, showed subtle RPE motting along the arcades at age 11 years (Figure 1D and E). Patient 3.1 had subtle RPE motting on presentation at age 4 years and subsequently developed white dots along the arcades from age 6 years. In patients 1.1 and 1.2, nummular pigmentary lesions along the arcades increased during follow-up periods of 2 and 3 years, respectively.

Fundus autofluorescence imaging was abnormal in 8 of 8 patients. Three patients had multiple fine foci of increased autofluorescence associated with the arcades. Two of these patients had a normal fundus appearance; the third had subtle RPE motting only (Figure 1E and F). Diffuse paracentral hyperfluorescence associated with the arcades. Two of these patients had a normal fundus appearance; the third had subtle RPE motting only (Figure 1E and F). Diffuse paracentral hyperfluorescence associated with the arcades. Two of these patients had a normal fundus appearance; the third had subtle RPE motting only (Figure 1E and F). Diffuse paracentral hyperfluorescence associated with the arcades. Two of these patients had a normal fundus appearance; the third had subtle RPE motting only (Figure 1E and F).
perfluorescence within the arcades in conjunction with multiple fine high-density foci alongside the arcades (Figure 1J) was present in 5 patients; in 3 of these patients with more severe disease, reduced autofluorescence was noted outside of the arcades in the midperipheral retina.

Eight patients underwent OCT: 5 had normal OCT findings (Figure 2A), 2 had evidence of macular intraretinal cysts without foveal involvement (Figure 2B), and 1 had fovea-involving cysts. Extended OCT to include the superior arcades was performed in a sibling pair. Loss of normal retinal architecture and small hyperreflective lesions throughout the outer nuclear layer were noted (Figure 2C).

Electroretinography demonstrated the characteristic features of ESCS. The rod-specific dark-adapted 0.01 response was undetectable; brighter flash dark-adapted ERG (dark-adapted 3.0 and dark-adapted 11.0) was of simplified, delayed waveform (Figure 3A). The responses to the same stimuli under scotopic adaptation (dark-adapted 3.0) and photopic adaptation (light-adapted 3.0) were of similar waveform; the 30-Hz flicker ERG was profoundly delayed and was of lower amplitude than the single-flash light-adapted 3.0 ERG a-wave. S-cone–specific testing was performed in 5 children and showed high-amplitude, delayed, and simplified responses, in keeping with the origins in short wavelength–sensitive cones, and of similar waveform to those obtained with white light stimulation. Extended S-cone ERG from patient 2.1 is shown in Figure 3B. The 200-millisecond blue stimulus response shows some off activity, as occurs in some but not all patients with ESCS. The photopic on-off response in the patient (200-millisecond orange flash) is markedly reduced, demonstrates a simplified waveform, and shows delay in all components.
The pattern ERG P50 component, used to assess macular function, was within normal amplitude limits in 2 patients, was subnormal without delay in 2 patients, was delayed without amplitude reduction in one patient, and was delayed and subnormal in one patient. Pattern ERG data from one patient were excluded because of high levels of physiological noise. One patient did not have electrodiagnostic testing owing to parental preference, but his brother had typical electrophysiological findings; both have genetically confirmed disease.

**Molecular Genetic Analysis**

DNA was available for molecular analysis in 7 individuals from 4 families, all of whom had compound heterozygous mutations in NR2E3 (Table 2 and eFigure in the Supplement). Members of family 1, a brother and sister pair and their cousin, all have the same compound heterozygous change (c.119-2A>C), predicted to cause aberrant splicing and the most common mutation reported in ESCS, and a novel frameshift mutation (c.1194delT; p.Pro399Glnfs*44). Segregation analysis demonstrated that both mothers harbored the c.1194delT mutation in the heterozygous state, while the father of the siblings was negative for the c.119-2A>C mutation. DNA from the cousin’s father was unavailable for analysis. The mothers are half-sisters, with no known geographic or family links between the fathers. Two siblings from family 2 declined molecular genetic testing, but parental DNA analysis identified the same c.310C>T; p.Arg104Trp mutation, homozygous in the father, who has Goldmann-Favre syndrome, and heterozygous in the unaffected mother. Therefore, it is likely that the 2 children are homozygous for this change. This consanguineous family demonstrating pseudodominant inheritance has been previously reported.3-4-44 The 2 siblings from family 3 are compound heterozygous for c.119-2A>C and c.1025T>C; p.Val342Ala, a novel mutation, with the father carrying c.119-2A>C and the mother carrying c.1025T>C. The affected child from family 4 had a novel mutation, c.305C>A; p.Ala102Asp, as well as a previously reported mutation, c.767C>A; p.Ala256Glu.43 Sequencing results of the affected individual from family 5 demonstrated the previously reported mutation c.767C>A; p.Ala256Glu and c.994G>A; p.Glu332Lys, the latter being novel to this study. All novel missense mutations are predicted to have a pathogenic effect on protein function based on SIFT and PolyPhen-2 analysis (Table 2). They all occur in amino acids highly conserved throughout evolution as confirmed by HomoloGene. The novel mutations have not been previously reported in the literature or in dbSNP, Exome Sequencing Project, or 1000 Genomes.

**Figure 2. Spectral-Domain Optical Coherence Tomography Scans (Infrared Images Are on the Left, and Tomographic Images Are on the Right)**

A. Patient 5 has left eye normal macular optical coherence tomography. B. Patient 2.1 has right eye abnormal macular optical coherence tomography with intraretinal cysts. C. Patient 1.2 has right eye abnormal superior arcade optical coherence tomography demonstrating disorganized architecture and multiple hyperreflective lesions in the outer nuclear layer (white arrowhead).
Discussion

This article describes the characteristic retinal features of ESCS in children, compares the features with those of adults having the disorder, provides details of evolution, and reports 4 novel mutations in the NR2E3 gene. The diagnostic importance of the appropriate investigations, particularly the pathognomonic ERG findings and FAF imaging, is emphasized.

Most children initially lack the deep nummular pigmentation typically seen in adults with ESCS, and fundus examination findings may be normal at presentation, in keeping with prior studies\(^{5,6}\) of the pediatric phenotype in ESCS. Patient 2.1 in this series, previously reported to have a normal fundus...
appearance.3,4 has developed subtle RPE mottling. Isolated, subtle RPE changes along the arcades are a finding not previously noted in ESCS but are apparent in this series of pediatric patients. Subretinal white dots without nummular pigmentation in children have been previously reported in a series of 3 patients.6 While the white dots are characteristic of ESCS, they are not diagnostic and have also been reported in autosomal recessive retinitis pigmentosa with clumped pigmentation due to NR2E3 mutations.43 Choroidal neovascular membrane or subretinal fibrosis complications were previously reported in children with ESCS47 but were not evident in the present series.

The present series suggests a sequence of change from a normal fundus appearance, followed by RPE mottling along the arcades, and then the development of white dots, followed by deep nummular pigmented deposition. Fundus autofluorescence imaging is particularly useful in highlighting subtle abnormalities along the arcades in children with a normal fundus appearance. High-density foci along the arcades on FAF imaging with a normal fundus appearance have previously been reported in an 8-year-old child.47 A practical application is determining whether other (younger) family members are affected. The high-density foci on FAF imaging do not always correspond to white dots seen ophthalmoscopically.7 Four patients in the present series demonstrated high-density foci on FAF imaging, without white dots. These foci have been shown in a murine model to originate from accumulations of microglial cells between the outer nuclear layer and the RPE.46 Microglial cells are known to have a central role in chronic degenerative conditions of the central nervous system. In adults, FAF imaging may demonstrate a ring of increased hyperfluorescence within the arcades (as seen in 5 patients in this series), a spoke-like hyperfluorescence in the macula in the presence of foveal schisis, or a reduction in autofluorescence anterior to the arcades in the midperiphery of the retina.4 This latter sign was found in 3 patients in this series, all of whom have more severe disease, and is thought to represent loss of photoreceptor cells. It corresponds well to reported histologic findings in advanced ESCS, which demonstrated relative preservation of photoreceptors in the macula and the far periphery of the retina, with loss of photoreceptors in the midperiphery.5 Therefore, monitoring of disease progression with FAF imaging, in particular loss of autofluorescence in the midperiphery, can be used as a marker of photoreceptor loss.

Intraretinal cysts in the macula similar to those in adult ESCS can occur in children and lead to loss of vision.3,4 Most patients in the present series maintained good visual acuity, in keeping with other reported ESCS cases,3,47 but vision deteriorated in 3 patients. One patient had intraretinal cysts involving the fovea that could explain the reduction in visual acuity, and one patient had parafoveal cysts. However, these 3 patients also had more advanced ophthalmoscopic changes with nummular pigmentation.

Two patients in the present series underwent extended OCT outside of the macula. Intraretinal, hyperreflective lesions were noted in the outer nuclear layer, with a disorganized retinal architecture and loss of normal laminar. This has been previously described in a child with ESCS and may be a useful adjunct in diagnosis and monitoring.7,48 The OCT findings are consistent with previously reported histologic data that demonstrated loss of normal retinal lamination and disorganization of the retina.5

Electrophysiological testing remains the most useful investigation in ESCS because of the pathognomonic ERG abnormalities. Additional nonstandard ERG testing provides further evidence of the disorder with S-cone–specific ERG several times the magnitude of normal, as well as showing a waveform similar to that of conventional Ganzfeld ERG.2 Pattern ERG was abnormal in 4 of 6 patients herein but was generally better preserved than that in affected adults; a previous study4 revealed abnormal pattern ERG in 16 of 16 adults with ESCS, including 5 with undetectable responses. Atypical ESCS has been reported in which S-cone responses are enhanced, but, unusually, variable degrees of preserved rod responses were evident on ERG.23,27,49 In 2 of these families, compound heterozygous NR2E3 mutations were found in association with a milder phenotype, but molecular screening was negative in a third family.

The NR2E3 protein constitutes a DNA-binding domain (DBD) (amino acid residues 45-131) and a ligand-binding domain (LBD) (amino acid residues 222-410).50 The DBD is a highly conserved region comprising 2 zinc finger–like structures that specifically bind to consensus sites in the promoter regions of target genes.50 Interaction of the DBD with the homeodomain of CRX enables Nr2E3 transactivation of target genes.50 Mutations in the DBD have been shown to abolish DNA binding.50 Reported mutations in NR2E3 are evenly split be-

Table 2. NR2E3 Mutations in the Series

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Family</th>
<th>SIFT Score</th>
<th>Polyphen-2 Score</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>c.119-2A&gt;C, aberrant splicing</td>
<td>1, 3</td>
<td>NA</td>
<td>NA</td>
<td>Haider et al, 9</td>
</tr>
<tr>
<td>c.1194delT; p.Pro399Glnfs*4+4</td>
<td>1</td>
<td>NA</td>
<td>NA</td>
<td>Present study</td>
</tr>
<tr>
<td>c.310C&gt;T; p.Arg104Trp, homozygous</td>
<td>2</td>
<td>0.00, Predicted to affect protein function</td>
<td>1.00, Probably damaging</td>
<td>Present study</td>
</tr>
<tr>
<td>c.310C&gt;T; p.Val342Ala</td>
<td>3</td>
<td>0.00, Predicted to affect protein function</td>
<td>0.996, Probably damaging</td>
<td>Present study</td>
</tr>
<tr>
<td>c.305C&gt;A; p.Ala102Asp</td>
<td>4</td>
<td>0.00, Predicted to affect protein function</td>
<td>0.998, Probably damaging</td>
<td>2003</td>
</tr>
<tr>
<td>c.767C&gt;A; p.Ala256Glu</td>
<td>5, 4</td>
<td>0.02, Predicted to affect protein function</td>
<td>0.912, Possibly damaging</td>
<td>Present study</td>
</tr>
<tr>
<td>c.994G&gt;A; p.Glu332Lys</td>
<td>5</td>
<td>0.04, Predicted to affect protein function</td>
<td>0.912, Possibly damaging</td>
<td>Present study</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.
tween the DBD and the LBD, without any obvious clustering. Four novel mutations are reported in the present study, 3 of which are missense mutations predicted to be damaging based on SIFT and PolyPhen-2 analysis, including p.Ala102Asp located within the DBD and p.Glu332Lys and p.Val342Ala located within the LBD. The novel deletion c.1194delT; p.Pro399Glnfs*4, also located in the LBD, is a frameshift mutation that creates an alternative reading frame predicted to result in a new 43–amino acid chain, followed by a stop codon.

All but 1 family in this series were found to be compound heterozygous for mutations in NR2E3, limiting the possible phenotype-genotype correlations that could be made based on a specific type or location of mutation. Molecular diagnosis enables genetic counseling of affected families, specifically with regard to the diagnosis of other family members and for prenatal planning. At present, the prognosis related to a specific genotype is unknown, and the molecular diagnosis does not alter patient management.

Conclusions

This study details novel aspects of ESCS in children, in whom the physical signs can differ notably from those usually associated with affected adults. New observations of the evolution of ophthalmoscopic changes are described. Pathomonic ERGs facilitates targeted molecular diagnosis, and FAF imaging and OCT also have a role in the diagnosis and in monitoring progression. Variability of presentation and visual disability across and within families is demonstrated.


33. Bouayed-Tiab L, Delarive T, Agosti C, Bornut F-X, Munier FL, Schorderet DF. A heterozygous mutation in the NR2E3 Gene is associated with an autosomal dominant Retinitis Pigmentosa. Presented at the Annual meeting of the Association for Research in Vision and Ophthalmology; May 1st 2006; Fort Lauderdale, USA.


