

# Bilateral Helicoid Peri-papillary Sub-retinal Fibrosis Due to a Biallelic NR2E3 Mutation: Describing Variable Expressivity of a Single Genetic Mutation

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## Research

**Keywords:** NR2E3 mutation, sub-retinal fibrosis, Helicoid, peri-papillary, inherited retinal degeneration, retinal dystrophy, enhanced S-cone syndrome, night blindness, high hyperopia, pleiotropy

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# Abstract

**Background:** To describe different clinical presentations of *NR2E3* (nuclear receptor subfamily 2, group E, member 3; OMIM 604485) recessive mutation in two families and within one family.

**Design:** Interventional family study.

**Results:** Our first case was a one-year-old male child with high hyperopia and refractive accommodative esotropia. In retinal examination, peri-papillary sub-retinal fibrosis with a helicoid configuration was observed in both eyes. Parents and the only sibling had no pathologic finding in the eyes. The child showed to have severely reduced responses in both photopic and scotopic electroretinogram components. In genetic investigation, a homozygous autosomal recessive mutation in *NR2E3* gene was discovered in the affected child, while the other family members were heterozygous for this mutation. We followed up the patient for 3 years and no new lesion developed during this time period.

The second case was a 13-year-old male child who was referred to retina clinic for decreased vision in the right eye. In retina examination, there were nummular pigmentary changes at the level of retinal pigment epithelium and along the vascular arcades with foveo-schitic changes in both eyes. A choroidal neovascularization (CNV) was noticed in macula of his right eye. Genetic evaluation proved the same mutation in *NR2E3* gene. Family history was remarkable for an uncle, an aunt and two cousins with night blindness. In retina examination, asymptomatic father of proband showed to have slight pallor of optic nerve head and arterial narrowing in both eyes.

**Conclusion:** *NR2E3* gene mutation can cause heterogeneous clinical manifestations such as slight retinal changes in the absence of any visual symptoms to high hyperopia associated with helicoid peri-papillary sub-retinal fibrosis.

## Introduction

Mutation in *NR2E3* (nuclear receptor subfamily 2, group E, member 3; OMIM 604485) gene, although occurs rarely, can give rise to a group of retinal dystrophies with a wide spectrum of clinical manifestations. These include autosomal recessive Goldmann-Favre syndrome, autosomal recessive or dominant enhanced S-cone syndrome (ESCS), autosomal recessive clumped pigmentary retinal degeneration, autosomal recessive or dominant retinitis pigmentosa, and “torpedo-like” lesions in posterior pole or along the vascular arcades.<sup>2-11</sup> This mutation has been reported to cause both dominant and recessive form of retinal dystrophy in the same family. These variable presentations of a single genetic mutation make a challenge for establishing the correct diagnosis based on clinical findings. Describing various clinical characteristics of patients with genetically proven *NR2E3* mutation can help clinicians to order the relevant genetic studies in similar situations. Genetic background, environmental factors and incomplete penetrance of some ocular features associated with mutations may account for these variations.<sup>2</sup>

In this study, we describe the clinical and genetic findings of two unrelated Iranian families with *NR2E3* mutation associated retinal dystrophies. .

## Subjects And Clinical Presentation

### Family A

A one-year-old male child from a consanguineous marriage presented to strabismus clinic. He had a cyclorefraction of + 6.5 diopter in both eyes causing refractive accommodative esotropia. In fundus examination, helicoid sub-retinal fibrosis was observed in the peripapillary area of both eyes. There were also diffuse retinal pigment epithelium changes. Intra-ocular pressure was 12 mmHg in the right eye and 14 mmHg in the left eye. All other ophthalmologic exams were normal. Fundus images of both eyes were captured by fundus camera (RetCam, Clarity Medical Systems USA) (Fig. 1). Pediatric evaluation showed no systemic abnormality. Although a negative family history for any hereditary eye disorder in the first and second-degree relatives was reported, we performed a comprehensive ophthalmic examination for first degree relatives (parents and the younger sister) who were all normal. (Fig. 2)

Electro-Retino-Gram (ERG) using Metrovision (Pérenchies, France) was performed for both siblings according to the International Society for Clinical Electrophysiology of Vision standards and guidelines. The affected child showed severely reduced responses in both photopic and scotopic components of ERG (Fig. 1-c) while the normal child had a normal ERG. The proband was followed up for three years, no new lesion developed during this time period.

### Family B

A 13-year-old male patient was referred to retina clinic for decreased visual acuity in his right eye and abnormal retina examination. He denied any difficulty in night vision; however, he had an uncle, an aunt and two first cousins with nyctalopia. Visual acuity of the proband was counting finger at 4 meters in the right eye and 20/25 in the left eye. The visual acuity in his right eye could improve up to 20/40 with changing his gaze from primary position. There was no refractive error or anterior segment abnormality in his both eyes. In fundus examination, multiple nummular pigmentary changes alongside the vascular arcades were observed at the level of sub-retina in both eyes. In the right eye, thinning of retinal arteries as well as a white sub-retinal lesion, one disc diameter in size, with numerous hard exudates temporal to the fovea were also evident. In the left eye, a decreased foveal reflex and slight thinning in retinal arteries could be appreciated (See Fig. 3-a and b). Optical coherence tomography angiography (OCTA) and the corresponding B-scan (Optovue, CA, USA) of the macula of the right eye revealed a vascular tuft originating from choriocapillaris with sub-retinal and intra-retinal fluid compatible with choroidal neovascularization (CNV). OCTA and the corresponding B-scan of the macula of the left eye showed foveoschisis in the absence of neovascularization. (Fig. 3c and d). His right eye CNV was responsive to two intravitreal injections of bevacizumab biosimilar called Stivant (CinnaGen Co., Tehran, Iran).

All the first and second degree relatives as well as two first cousins with the history of nyctalopia were asked to be examined. All the first degree relatives were normal in ophthalmologic evaluation except his father that despite a 20/20 visual acuity in both eyes, showed some pallor in optic disc and slight arterial narrowing in both eyes without any pigment abnormality. The uncle, aunt and two mentioned first cousins showed retina abnormalities compatible with ESCS including bilateral thinning of retinal arteries, decreased foveal reflex and nummular pigmentary changes along the vascular arcade and at the level of retinal pigment epithelium (RPE).

## Molecular Genetic Analysis

Pedigree information was asked and blood samples were collected from all available members of both families (Fig. 4). Genomic DNA was extracted from peripheral blood leukocytes using salting out method. *NR2E3* gene have eight coding exons. We designed primer pairs for amplifying all coding exons and their boundary regions using GeneRunner version 3.05 software (Table-1). The primer pairs were tested for the specificity to the target regions in human genome using online NCBI Primer-Blast tool (<http://www.ncbi.nlm.nih.gov/tools/primer-blast/>). Polymerase chain reactions (PCR) were performed to amplify the target sequences. Subsequently all PCR products were sequenced with the Sanger protocol using ABI Big Dye terminator chemistry with an ABI 3730XL genetic analyzer instrument (Applied Biosystems, Foster city, CA, USA). Sequences were analyzed using Sequencher 5.0 software (Gene Codes Corporation, Ann Arbor, MI, USA). The sequencing data was aligned to their reference sequence of *NR2E3* (NG\_009113.2, NM\_014249.4, and NP\_055064.1) in order to find the sequence variations. Candidate causative variant were confirmed with sequencing of the genome of the healthy family members and genotype status of them for the mutation.

## Genetic Results

We found a pathogenic known splice acceptor variant c.119-2A > C (IVS1-2A > C) in *NR2E3* gene of the probands of both families in homozygous status. This variation with SNP ID rs2723341, has been reported in several studies for different phenotypic types of retinal dystrophies.<sup>6,12-22</sup> The parents and sister of the family A were all heterozygous for identified causing mutation.

In family B, the father of the family strangely had the same genotype as his affected child and was homozygous for the detected mutation, but the mother and the healthy brother were heterozygous for the same mutation (Fig. 5). Further clinical investigation of the father of family B showed relevant signs in retinal examination.

Genotypic data of all investigated individuals and phenotypic diagnosis of the affected individuals of both families have been summarized in table-2.

## Discussion

In this study, we showed phenotypic variability of *NR2E3* mutation in two different families as well as variable manifestation of this mutation among the affected individuals within the same family.

In the first consanguineous family (family A), a known pathogenic recessive mutation in *NR2E3* gene was found to be responsible for a symmetric bilateral helicoid peri-papillary sub-retinal fibrosis with diffuse retinal pigment epithelium changes observed in one child. There are few reports on such presentation in the literature. This report expands the phenotypic spectrum of recessive *NR2E3* mutations. The helicoid pattern of sub-retinal fibrosis around the optic nerve or in macular region without any evidence of inflammation or infection associated with high hyperopia seems to be unique and very suggestive of the ESCS spectrum.

Arif O. Khan et al reported such helicoid pattern in two affected siblings. Helicoid sub-retinal fibrosis typically is suggestive of Serpiginous and Serpiginous like choroiditis in adults.<sup>12</sup> In young infants, sub-retinal fibrosis can occur in a variety of situations like inflammatory, infectious or autoimmune as well as increased intra-cranial pressure. However, in the latter conditions, the fibrosis is not typically helicoid and usually evidence of underlying systemic disorder or ocular inflammation is accompanied.<sup>3</sup>

ESCS was first described in 1990 by Marmor et al.<sup>1</sup> It is unclear that why recessive mutation in *NR2E3* gene can cause sub-retinal fibrosis in a developing retina. In their reported case, Arif O. Khan et al. suggested that the sub-retinal fibrosis may develop as a result of RPE or macrophages reaction to cellular deposits resulting from *NR2E3* mutation.<sup>3,13</sup>

In another study, Cassiman et al<sup>14</sup> reported a 14-month-old boy with sub-retinal fibrosis and sub-retinal hemorrhages due to *NR2E3* mutation. As their case showed sub-retinal hemorrhage without CNV formation, they concluded that vascular abnormality in early months of life could be the underlying cause of sub-retinal fibrosis in their patient. In our case, three possible mechanisms can be considered for sub-retinal fibrosis formation including RPE reactive response, secondary inflammatory response to cellular deposits and choroidal vascular abnormalities due to the gene product malfunction.

The proband of family B showed typical ESCS findings like pigmentary changes at the level of RPE alongside the vascular arcades with CNV formation in right eye and foveoschisis in his left eye. CNV formation has been reported as a rare presentation in ESCS previously.<sup>23</sup> Choroidal neovascularization in ESCS has been showed to be responsive to anti-vascular endothelial growth factor injection. Our patient was also responsive to two injections of bevacizumab.

*NR2E3* gene sequencing led to identification of the same pathogenic mutation in the gene. The father of the family B was also homozygous for the mutation and although did not have ocular symptoms, He showed to have slight retinal abnormalities. In addition, the proband has an uncle and an aunt with night blindness, decreased visual acuity and typical fundus changes for ESCS. He also has two nieces with same symptoms and signs.

In summary, our study showed that identical mutation in *NR2E3* gene can have variable expressivity in ocular phenotypic manifestations in different families and a wide range of clinical severity even within the same family. Such studies evaluating *NR2E3* mutations and clinical features of the affected individuals can improve our knowledge about genotype-phenotype correlations in *NR2E3* mutations.

## Declarations

### **Ethics approval and consent to participate:**

This study was conducted based on principles of the Declaration of Helsinki. The study protocol was supervised and approved by the Ethical Committee of ... University of Medical Sciences. The written informed consent was received from all the participants or their legal parents to participate in this study and for publication of resulted data.

### **Consent for publication:**

The written informed consent was received from all the participants or their legal parents for publication of the provided data.

### **Availability of data and material:**

Our data are available upon request for non-commercial research purpose.

### **Competing interests:**

There is no conflict of interests/competing interests for all authors.

### **Funding:**

None.

### **Authors' contributions:**

All authors participated in data collection. NH, FS and NE contributed in paper preparation.

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None.

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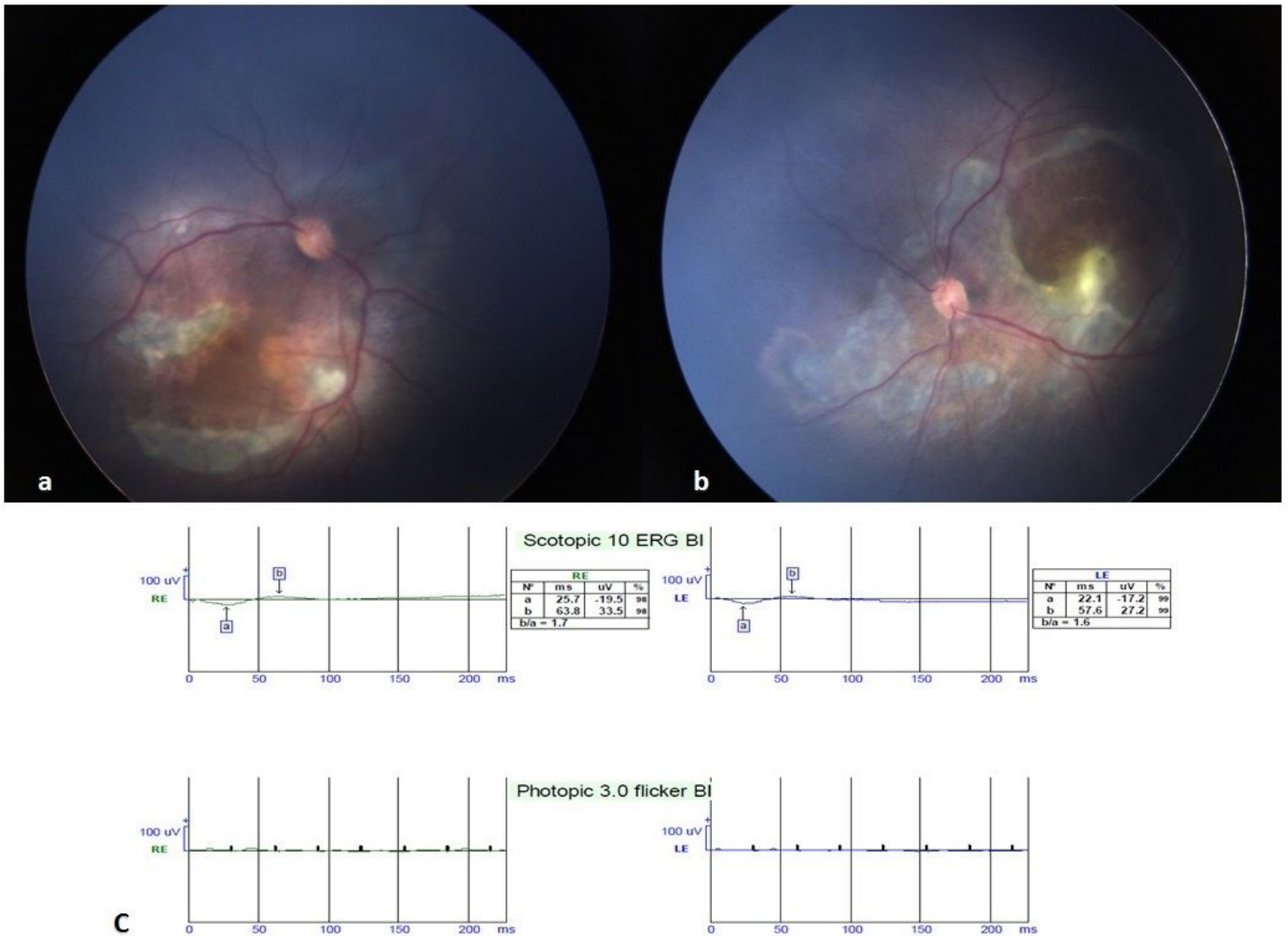
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# Tables

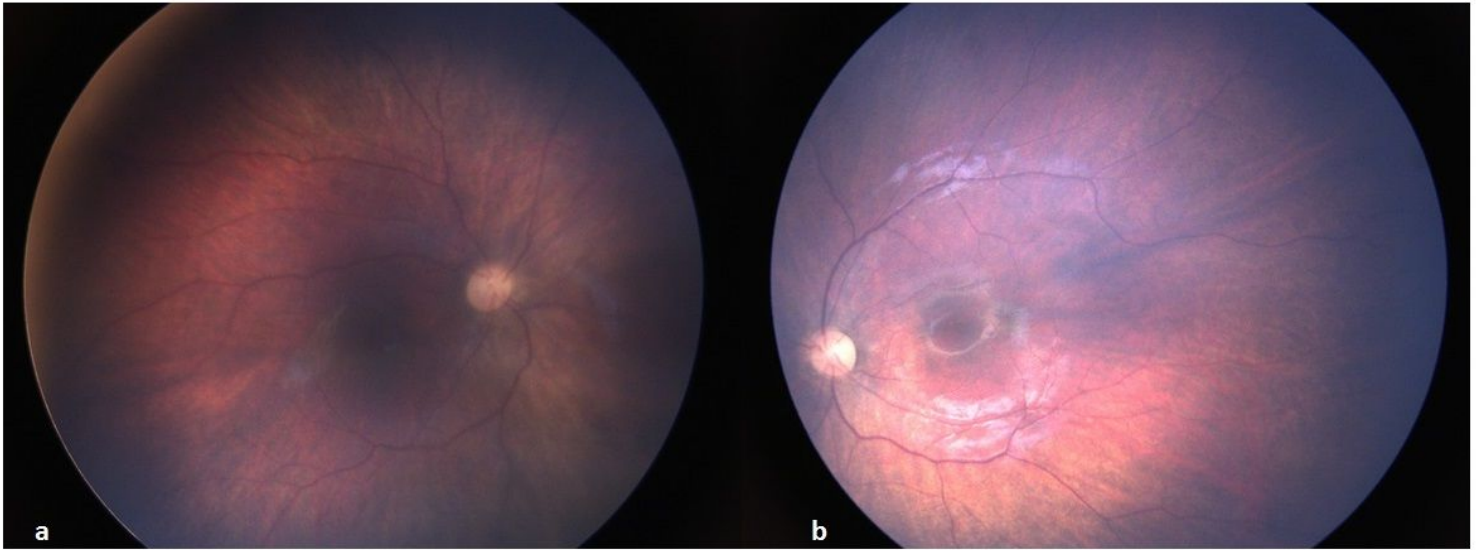
Due to technical limitations, tables 1 and 2 xlsx are only available as a download in the Supplemental Files section.

# Figures



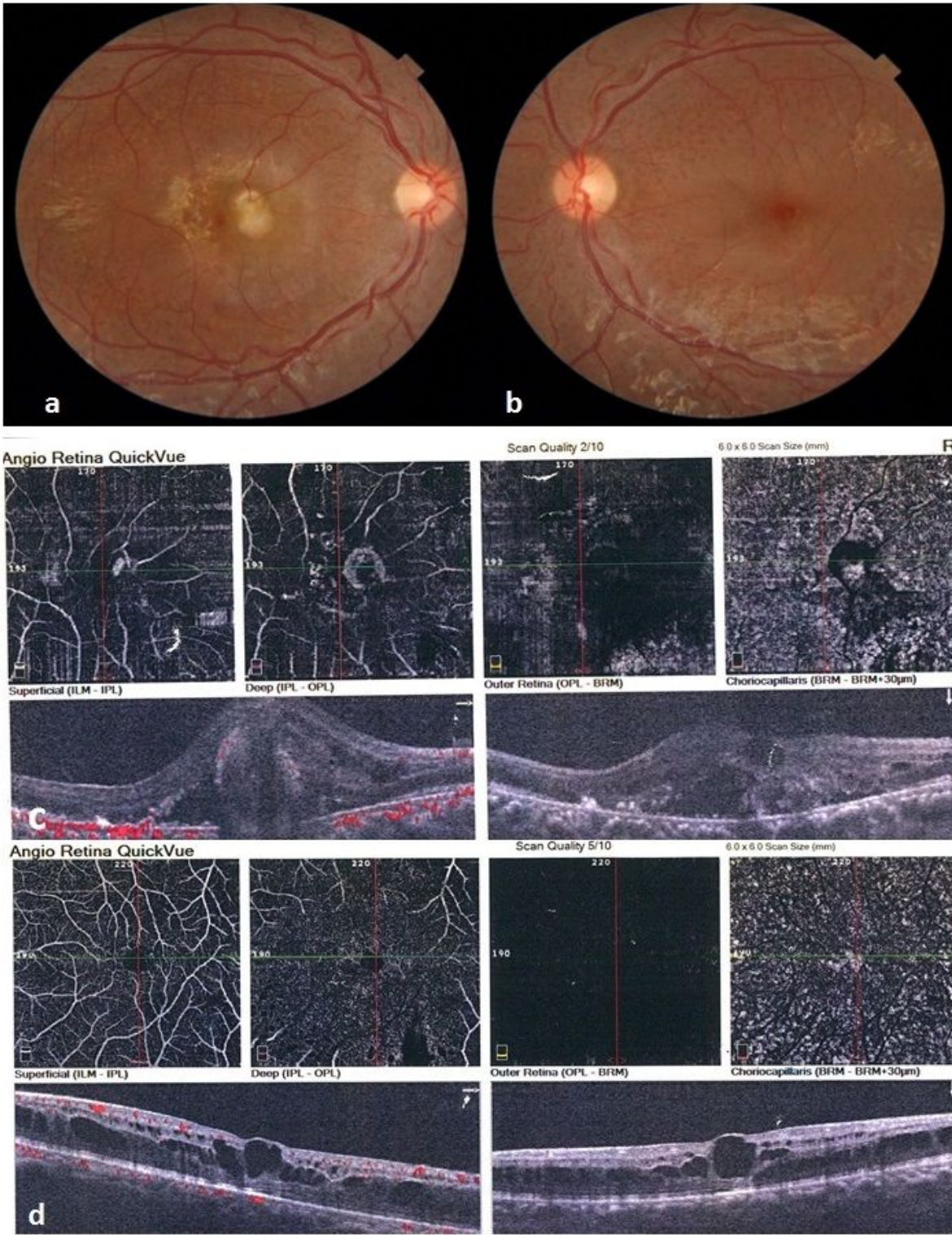
**Figure 1**

Right (a) and left (b) eye RetCam fundus images of the affected male child (first case). Diffuse retinal pigment epithelium changes and bilateral helicoid peri-papillary sub-retinal fibrosis with macula involvement in both eyes are visible. His ERG (c) showed severely reduced responses in both photopic and scotopic components.



**Figure 2**

Right (a) and left (b) eye RetCam fundus images of the unaffected sister of the first case. No abnormality can be appreciated. ERG showed near normal responses in this sibling.

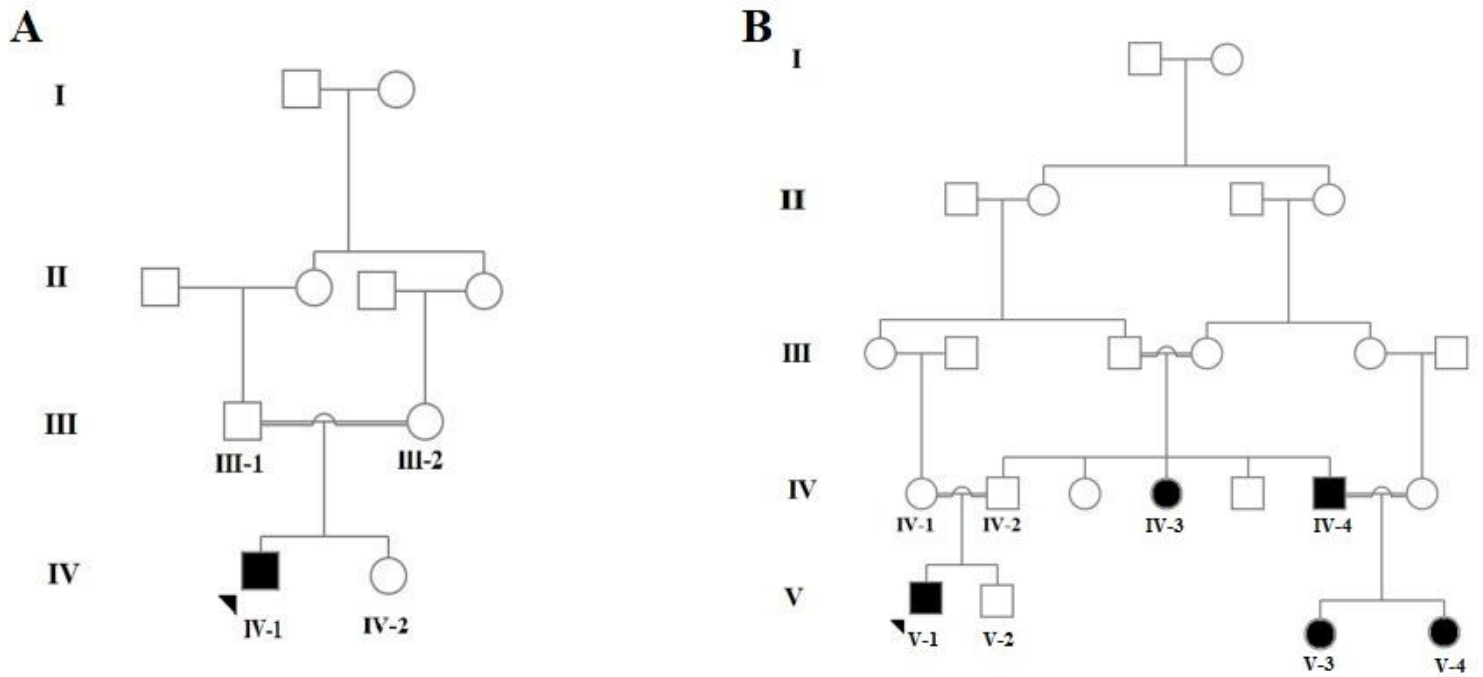


**Figure 3**

Right (a) and left (b) eye fundus images of the second case. There were multiple nummular pigmentary changes at subretinal level along the vascular arcades in both eyes. Right eye fundus photo shows thinning in retinal arteries and one disc diameter subretinal white lesion with hard exudates temporal to the lesion in fovea. Left eye fundus photo shows decreased foveal reflex and slight thinning in retinal arteries. Optical coherence tomography angiography (OCTA) and the corresponding B-scan of the right

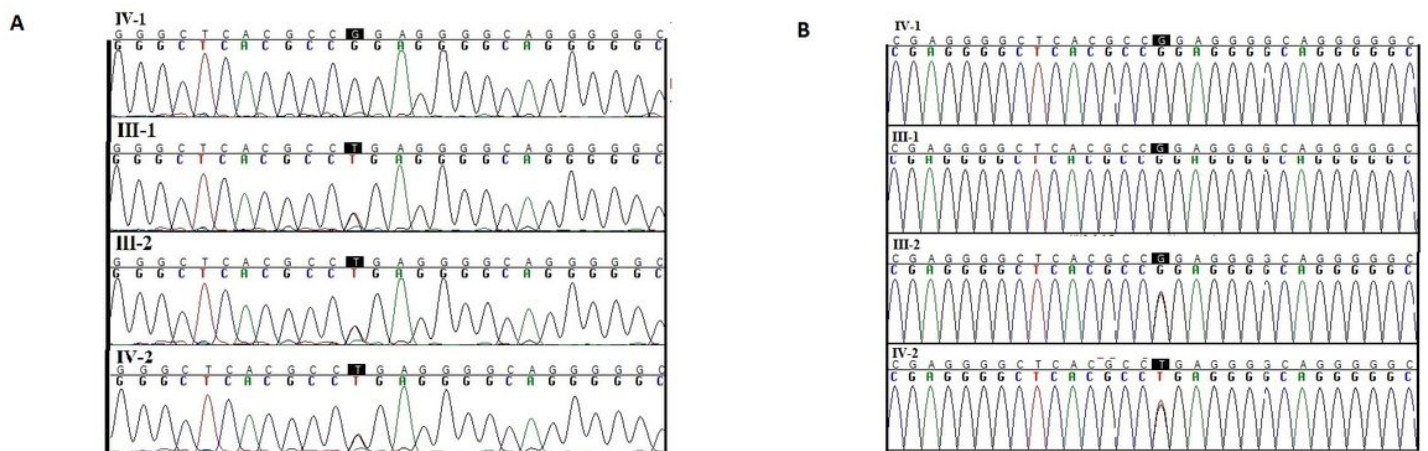


eye (c) showed vascular tuft with subretinal and intra-retinal fluid compatible with coroidal neovascularization (CNV). OCTA and the corresponding B-scan of the left eye (d) showed foveoschisis without neovascularization.



**Figure 4**

Pedigrees of the two investigated families. A, family A; B, family B. □, male; ●, female. Filled symbols indicate affected status.



**Figure 5**

Chromatograms of sequence variation in NR2E3 gene in all investigated individuals of both families. A, family A; B, family B.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Table1.xlsx](#)
- [Table2.xlsx](#)