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

Narges Hassanpoor
Tabriz University of Medical Sciences
Nazanin Ebrahimiadib
Farabi Eye Hospital
Hamid Riazi-Esfahani
Farabi Eye Hospital
Afrooz Moghaddasi
Shahid Beheshti University of Medical Sciences School of Medicine
Fatemeh Suri (fatemehsuri@gmail.com)
Shahid Beheshti University of Medical Sciences https://orcid.org/0000-0002-3170-2940

Research

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

Posted Date: September 7th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-871644/v1

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. [2–11] 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. [2]

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. [6, 12–22] 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.[12] 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. [3]

ESCS was first described in 1990 by Marmor et al. [1] 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*.[3, 13]

In another study, Cassiman et al [14] 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.[23] 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 inform 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 inform 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.

Acknowledgements:

None.

References

1. Marmor, M.F.; Jacobson, S.G.; Foerster, M.H.; Kellner, U.; Weleber, R.G. Diagnostic clinical findings of a new syndrome with night blindness, maculopathy, and enhanced S cone sensitivity. Am. J. Ophthalmol. 1990, 110, 124–134.

2. Al-khuzaei S, Broadgate S, Halford S, Jolly JK, Shanks M, Clouston P, et al. Novel Pathogenic Sequence Variants in NR2E3 and Clinical Findings in Three Patients. Genes 2020, 1-17.
3. Khan AO, Aldahmesh MA, Al-Harthi E, Alkuraya FS. Helicoid subretinal fibrosis associated with a novel recessive NR2E3 mutation p.S44X. Arch Ophthalmol. 2010 Mar;128(3):344-8. doi: 10.1001/archophthalmol.2010.15. PMID: 20212206.
4. Naik A, Ratra D, Banerjee A, Dalan D, Jandyal S, Rao G, Sen P, Bhende M, Jayaprakash V, Susvar P, Walinjkar J, Rao C. Enhanced S-cone syndrome: Clinical spectrum in Indian population. Indian J Ophthalmol. 2019 Apr;67(4):523-529. doi: 10.4103/ijo.IJO_1480_18. PMID: 30900587; PMCID: PMC6446635.
5. Murro V, Mucciolo DP, Sodi A, Passerini I, Giorgio D, Virgili G, Rizzo S. Novel clinical findings in autosomal recessive NR2E3-related retinal dystrophy. Graefes Arch Clin Exp Ophthalmol. 2019 Jan;257(1):9-22. doi: 10.1007/s00417-018-4161-z. Epub 2018 Oct 15. PMID: 30324420.
6. Yzer S, Barbazetto I, Allikmets R, van Schooneveld MJ, Bergen A, Tsang SH, Jacobson SG, Yannuzzi LA. Expanded clinical spectrum of enhanced S-cone syndrome. JAMA Ophthalmol. 2013 Oct;131(10):1324-30. doi: 10.1001/jamaophthalmol.2013.4349. PMID: 23989059; PMCID: PMC4405536.
7. Sharon D, Sandberg MA, Caruso RC, Berson EL, Dryja TP. Shared mutations in NR2E3 in enhanced S-cone syndrome, Goldmann-Favre syndrome, and many cases of clumped pigmentary retinal degeneration. Arch Ophthalmol. 2003; 121(9):1316-1323.
8. Hayashi T, Gekka T, Goto-Omoto S, Takeuchi T, Kubo A, Kitahara K. Novel NR2E3 mutations (R104Q, R334G) associated with amild form of enhanced S-cone syndrome demonstrate compound heterozygosity. Ophthalmology. 2005;112(12): 2115.
9. Coppieters F, Leroy BP, Beysen D, et al. Recurrent mutation in the first zinc finger of the orphan nuclear receptor NR2E3 causes autosomal dominant retinitis pigmentosa. Am J Hum Genet. 2007;81(1):147-157.
10. Escher P, Gouras P, Roduit R, et al. Mutations in NR2E3 can cause dominant or recessive retinal degenerations in the same family. Hum Mutat. 2009;30(3): 342-351.
11. Bernal S, Solans T, Gamundi MJ, et al. Analysis of the involvement of the NR2E3 gene in autosomal recessive retinal dystrophies. Clin Genet. 2008;73(4):360- 366.
12. Jampol LM, Orth D, Daily MJ, Rabb MF. Subretinal neovascularization with geographic (serpiginous) choroiditis. Am J Ophthalmol. 1979;88(4):683-689.
13. Wang NK, Fine HF, Chang S, et al. Cellular origin of fundus autofluorescence in patients and mice with a defective NR2E3 gene. Br J Ophthalmol. 2009;93(9): 1234-1240.
14. Cassiman C, Spileers W, De Baere E, de Ravel T, Casteels I. Peculiar fundus abnormalities and pathognomonic electrophysiological findings in a 14-month-old boy with NR2E3 mutations. Ophthalmic Genet. 2013 Mar-Jun;34(1-2):105-8. doi: 10.3109/13816810.2012.726395. Epub 2012 Oct 5. PMID: 23039133.

15. Haider NB, Jacobson SG, Cideciyan AV, Swiderski R, Streb LM, Searby C, Beck G, Hockey R, Hanna DB, Gorman S, Duhl D, Carmi R, Bennett J, Weleber RG, Fishman GA, Wright AF, Stone EM, Sheffield VC. Mutation of a nuclear receptor gene, NR2E3, causes enhanced S cone syndrome, a disorder of retinal cell fate.Nat Genet. 2000 Feb;24(2):127-31. doi: 10.1038/72777.PMID: 10655056
16. Bandah D, Merin S, Ashhab M, Banin E, Sharon D. The spectrum of retinal diseases caused by NR2E3 mutations in Israeli and Palestinian patients. Arch Ophthalmol. 2009 Mar;127(3):297-302. doi: 10.1001/archophthalmol.2008.615.PMID: 19273793
17. Schorderet DF, Escher P.Hum Mutat. NR2E3 mutations in enhanced S-cone sensitivity syndrome (ESCS), Goldmann-Favre syndrome (GFS), clumped pigmentary retinal degeneration (CPRD), and retinitis pigmentosa (RP). 2009 Nov;30(11):1475-85. Doi: 10.1002/humu.21096.PMID: 19718767 Review.
18. Collin RW, van den Born LI, Klevering BJ, de Castro-Miró M, Littink KW, Arimadyo K, Azam M, Yazar V, Zonneveld MN, Paun CC, Siemiatkowska AM, Strom TM, Hehir-Kwa JY, Kroes HY, de Faber JT, van Schooneveld MJ, Heckenlively JR, Hoyng CB, den Hollander AI, Cremers FP. High-resolution homozygosity mapping is a powerful tool to detect novel mutations causative of autosomal recessive RP in the Dutch population. Invest Ophthalmol Vis Sci. 2011 Apr 6;52(5):2227-39. doi: 10.1167/iovs.10-6185.PMID: 21217109
19. Glöckle N, Kohl S, Mohr J, Scheurenbrand T, Sprecher A, Weisschuh N, Bernd A, Rudolph G, Schubach M, Poloschek C, Zrenner E, Biskup S, Berger W, Wissinger B, Neidhardt J. Panel-based next generation sequencing as a reliable and efficient technique to detect mutations in unselected patients with retinal dystrophies. Eur J Hum Genet. 2014 Jan;22(1):99-104. doi: 10.1038/ejhg.2013.72. Epub 2013 Apr 17.PMID: 23591405 Free PMC article.
20. Wang J, Zhang VW, Feng Y, Tian X, Li FY, Truong C, Wang G, Chiang PW, Lewis RA, Wong LJ. Dependable and efficient clinical utility of target capture-based deep sequencing in molecular diagnosis of retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2014 Aug 5;55(10):6213-23. doi: 10.1167/iovs.14-14936.PMID: 25097241
21. von Alpen D, Tran HV, Guex N, Venturini G, Munier FL, Schorderet DF, Haider NB, Escher P. Differential dimerization of variants linked to enhanced S-cone sensitivity syndrome (ESCS) located in the NR2E3 ligand-binding domain. Hum Mutat. 2015 Jun;36(6):599-610. doi: 10.1002/humu.22775. Epub 2015 Apr 27.PMID: 25703721 Free PMC article.
22. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5.PMID: 25741868.
23. Broadhead, G.K., Grigg, J.R., McCluskey, P. et al. Bevacizumab for choroidal neovascularisation in enhanced S-cone syndrome. Doc Ophthalmol 133, 139–143 (2016). https://doi.org/10.1007/s10633-016-9555-9

Tables

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

Figures

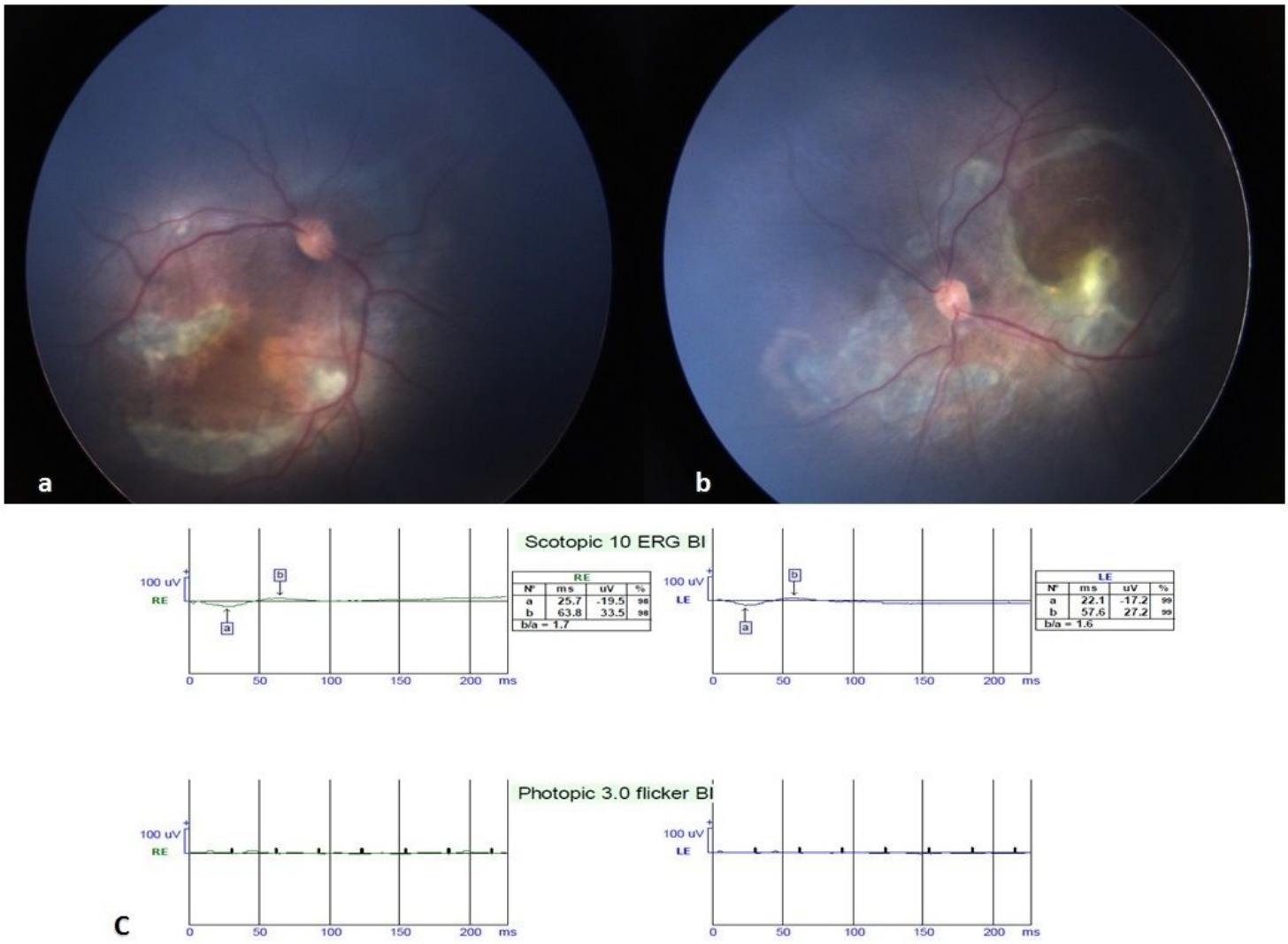

Figure 1

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.

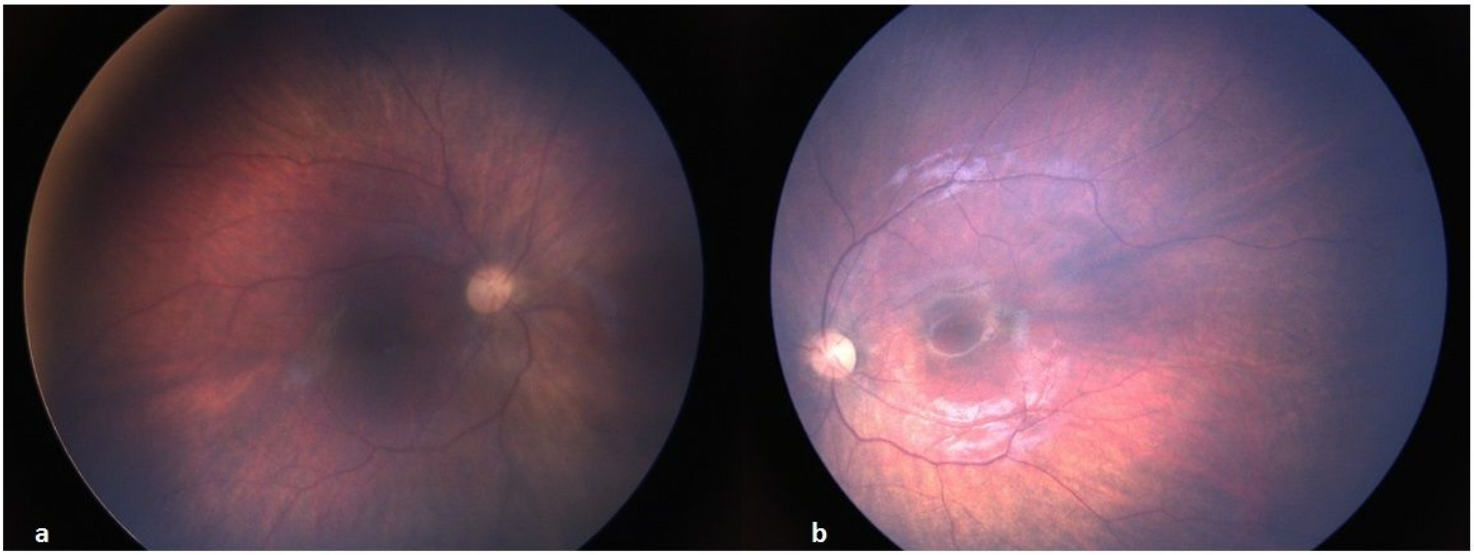

Figure 2

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.

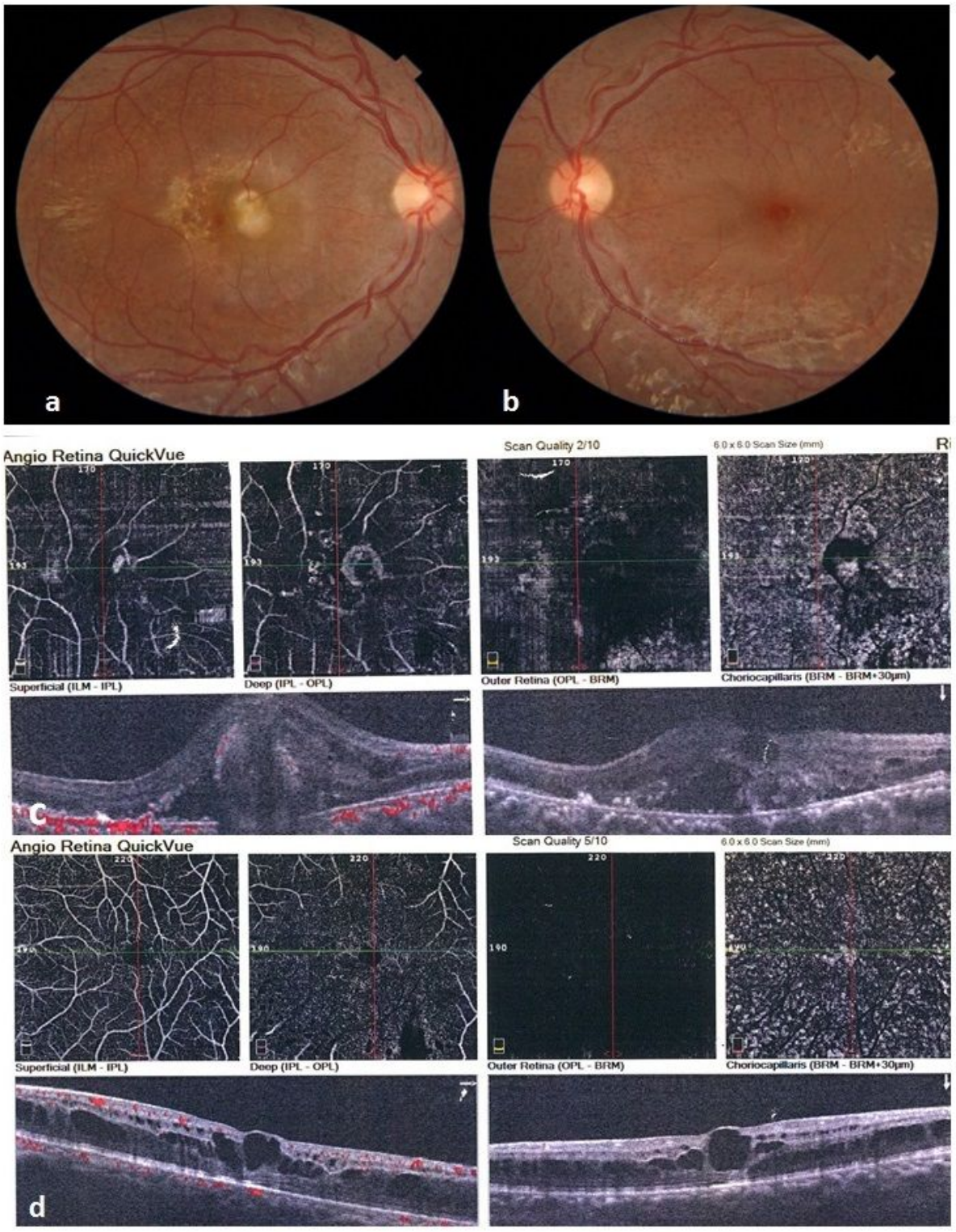

Figure 3

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.

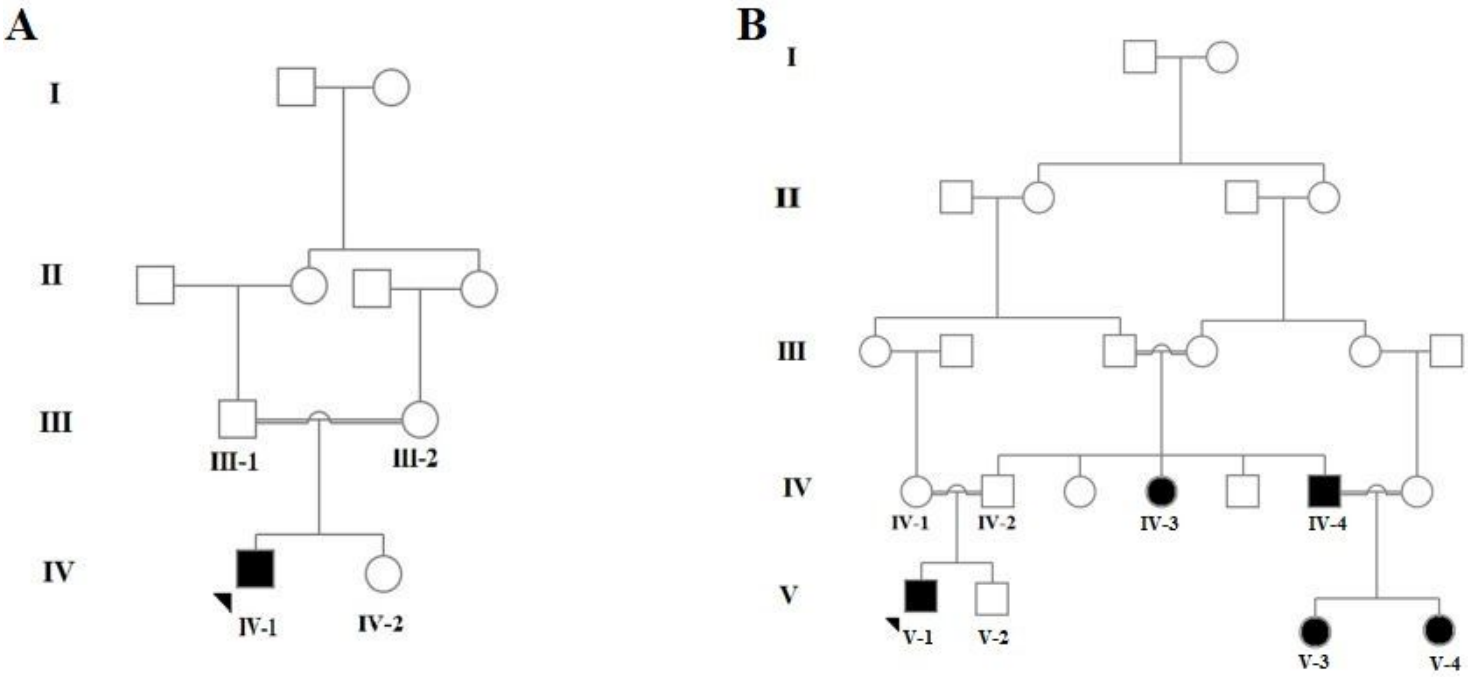

Figure 4

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

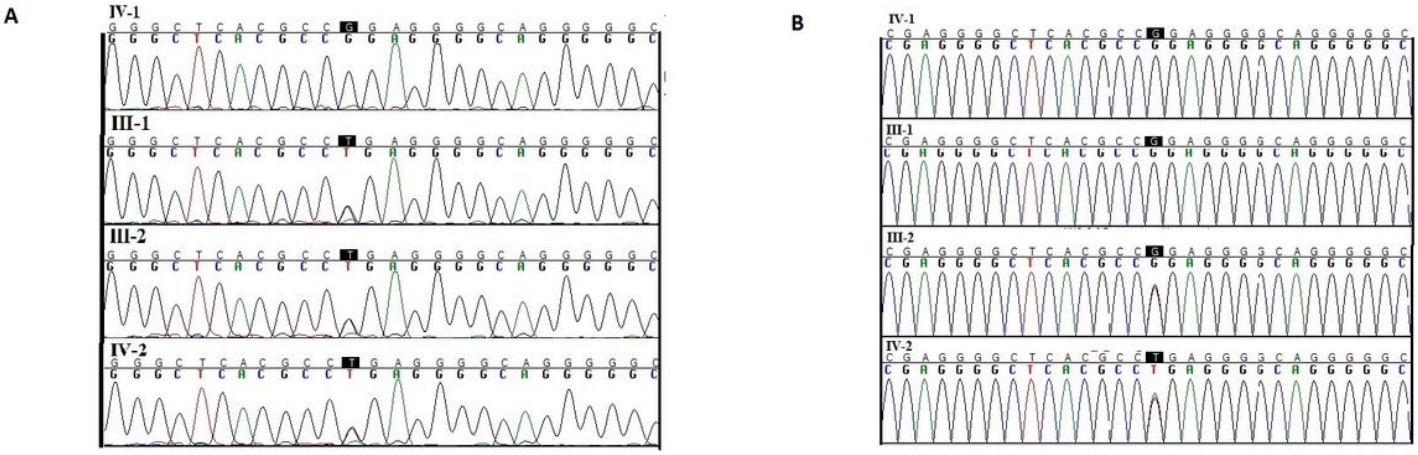

Figure 5

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