Macular maldevelopment in *ATF6*-mediated retinal dysfunction

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Abstract

Background: Achromatopsia has been previously associated with mutations in the *ATF6* gene. Rod-monochromatism, foveal hypoplasia and disruption of the subfoveal photoreceptor layer are described as phenotypical features. We report detailed structural and electrophysiological assessment of 2 patients from 2 families, one manifesting severe macular maldevelopment and one with foveal hypoplasia.

Materials and methods: The patients underwent a complete ophthalmic examination including electroretinography (ERG), spectral domain optical coherence tomography (SD-OCT), fundus autofluorescence, and fundus photography. Genetic testing was performed by next generation sequencing.

Results: In one patient, fundoscopy and SD-OCT revealed well demarcated coloboma-like excavated lesions at the central macula of both eyes. Genetic analysis identified a novel homozygous p.Asp140Ter mutation in the *ATF6* gene. The second patient had foveal hypoplasia in association with a homozygous *ATF6* mutation affecting a splice donor site (c.1187+5G>C). In both patients, electrophysiological assessment showed normal rod-specific (DA 0.01) and dark-adapted bright white-flash ERGs (DA 10.0). 30Hz flicker ERGs were undetectable. There were low-amplitude single-flash photopic ERGs (LA 3.0) with timing and shape suggesting S-cone origin.

Conclusions: The findings, particularly a case with severe macular maldevelopment, may expand on the phenotype previously associated with *ATF6*-mediated achromatopsia. In addition, comprehensive electrophysiological assessment suggests that preserved S-cone activity can be detected in this particular molecular sub-type of cone dysfunction.

Key Words

Achromatopsia, ATF6, macular maldevelopment

Introduction

Achromatopsia (ACHM) is a rare autosomal recessive inherited retinal disorder with an incidence of approximately 1 in 30,000 (1). Currently, six genes have been linked to ACHM. Five genes, *CNGA3, CNGB3, GNAT2, PDE6C,* and *PDE6H,* encode components of the cone phototransduction cascade. Mutations in those genes result in dysfunction of all three cone types (S, M, and L). Mutations in the *CNGA3* and *CNGB3* genes account for approximately 80% of all complete ACHM cases (1-3). More recently, mutations in the *ATF6* gene (encoding activating transcription factor 6A; MIM 605537) have also been associated with ACHM (4) suggesting a crucial role of ATF6 in human foveal development and cone function.

The previously described patients with *ATF6*-associated ACHM presented with nystagmus and photophobia, similar to other patients with ACHM at birth or early infancy. Ophthalmological examination revealed reduced visual acuity and very poor or absent colour vision. The clinical diagnosis was determined based on typical functional findings including absent cone responses and normal rod responses on full field electroretinography (ERG). There was severe foveal hypoplasia with a poorly formed or absent foveal pit. This was regarded as a hallmark of *ATF6*-related disease, and distinguished it from other forms of ACHM. However, examples of varying degrees of foveal hypoplasia have been reported in about 50% of patients with different forms of ACHM (5).

Herein, we report detailed structural and electrophysiological assessment of 2 patients from 2 families with confirmed ATF6-related disease, one manifesting severe macular maldevelopment and one with foveal hypoplasia, and with detailed electrophysiological findings suggesting preserved S-cone function.

Materials and methods

Patients

Patients were ascertained from the inherited retinal clinics of Moorfields Eye Hospital. Informed written consent and peripheral blood samples were obtained for genetic analysis from participants according to the protocols approved by the Research Management Committees of Moorfields Eye Hospital in agreement with the Declaration of Helsinki (6). A detailed family history of both patients was recorded and they underwent a complete ophthalmic examination, including best-corrected visual acuity, slit-lamp biomicroscopy and dilated fundus examination. Fundus photographs and green light fundus autofluorescence (FAF) images were obtained in patient No 1 by ultra-wide field (up to 200°) confocal laser scanning ophthalmoscopy (Optos plc). Retinal fundus images in patient 2 were obtained by conventional 35° fundus color photographs (Topcon Great Britain Ltd) and blue light FAF imaging (30°) performed with a confocal scanning laser ophthalmoscope (HRA+OCT Spectralis; Heidelberg Engineering Ltd). Spectral-domain optical coherence tomography (OCT) was performed in both patients using a HRA+OCT Spectralis. Full-field electroretinography (ERG) (both patients) and pattern ERG (PERG) (patient 1) were performed to incorporate the International Society for Clinical Electrophysiology of Vision Standards. (7,8) Normative ERG values have been previously published. (9) The patients were unable to accurately see the test plates on attempted Ishihara and HRR (Hardy Rand and Rittler) colour assessment.

Molecular Investigation

Genomic DNA was isolated from peripheral blood lymphocytes (Puregene kit; Gentra Puregene Blood Extraction Kit; QIAGEN). Genetic testing was performed by next generation

sequencing. Patient 1 underwent whole-genome sequencing as previously described in Carss et al (10). Patient 2 underwent exome-sequencing and is reported in reference 4 (4).

Results

Patient 1

This 27-year-old female patient had nystagmus and poor vision noted at the age of two months. She had never been able to name colours. No other general medical condition was reported. The patient is one of three children to first cousin parents from South Asian descent. There was no family history of eye disease.

Ocular examination

Best-corrected visual acuity was 6/60 bilaterally. The patient was noted to be mildly myopic. The anterior segment was unremarkable with a clear visual axis. Fundoscopy revealed symmetrical, well demarcated excavated lesions at the central macula of both eyes. The peripheral retina was unremarkable. On FAF imaging, the macular lesions were hypoautofluorescent with a mildly hyperautofluorescent border (fig 1). OCT images showed deep, excavated lesions with loss of inner and outer retinal layers in both eyes; the left eye possibly had an associated scleral protrusion. On electrophysiological examination (Fig. 2), Rod-specific (DA 0.01) and bright flash dark-adapted (DA 10.0) ERGs showed no clinically significant abnormality; there was a mildly subnormal DA 10.0 a-wave amplitude, not uncommon in patients lacking a cone photoreceptor contribution to the dark-adapted a-wave. The 30-Hz flicker ERGs were undetectable. There were detectable low-amplitude single-flash photopic ERGs (LA 3.0) with the b-wave timing (approximately 50ms) and shape suggestive of an S-cone origin. PERGs showed severe reduction in both eyes, indicating severe macular dysfunction.

Genetics

Following whole genome sequencing (WGS), the patient (GC20498) had 534 coding (±8bp splice region) rare variants (Minor allele frequency ≤0.01in the Exome Aggregation Consortium database, ExAC) and passing standard quality filters. Assuming autosomal recessive inheritance and considering parental consanguinity, 22 genes contained homozygous variants (supplementary table), 2 of which were predicted to cause loss of function (LOF). One was a predicted splice site variant in the predicted non-coding RNA (RP11-10M2.1) and although rare, was interpreted as unlikely to be contributing to disease. The other was identified in *ATF6*. The variant, a frameshifting single nucleotide duplication: GRCh37 (hg19) chr1:g.161761260dupT NM_007348.3: c.417dupT, p.(Asn140*); was absent from gnomAD. The variant p.(Asn140*) on exon 5 of 16 was expected to act as a true null since the transcript is likely to undergo nonsense mediated decay (NMD). All other IRD genes and variants which may account for this phenotype were excluded based on rarity, genotype, variant effect and phenotypic fit, including variants known to be associated with North Carolina Macular Dystrophy (NCMD).

Patient 2

The second patient (GC4040) was a 28-years-old Asian-Indian female who was reported to have reduced vision, photophobia, no colour perception and a very mild degree of nystagmus since early childhood. Her sister was similarly affected (not available for detailed examination).

Ocular examination

Best-corrected visual acuity was 6/60 in both eyes. The patient was noted to be mildly myopic. No abnormalities of the anterior segment were detected. Fundoscopy revealed blunted foveal reflexes in both eyes. SD-OCTs showed an absent foveal depression,

persistence of inner retinal layers through the foveal center and subfoveal disruption of the photoreceptor layers (commonly described as foveal cavitation; Fig 3). FAF showed a small oval shaped sub-foveal area of reduced autofluorescence in both eyes corresponding to the subfoveal cavitation observed on OCT. In each eye the areas of reduced FAF was surrounded by an hyperautofluorescent ring. Full field ERG findings showed normal rod-specific (DA 0.01) and dark-adapted bright white-flash ERGs (DA 10.0), the values falling well within the normal range. Dark-adapted red flash ERGs showed no detectable cone component but a preserved rod component. 30-Hz flicker ERGs were undetectable (Fig.4). The very low-amplitude single-flash photopic ERGs with b-waves at approximately 50ms are suggestive of an S-cone derived ERG.

Genetics

The patient and her sister harboured a homozygous disease-causing variant in the *ATF6* gene affecting a canonical splice donor site: c.1187+5G>C. This patient's mutational data have previously been reported (4).

Discussion

This study demonstrates that mutations in ATF6 can be associated with severe macular maldevelopment. It further demonstrates that electrophysiological investigation may reveal preserved S-cone function.

The previously published studies on *ATF6* describe rod-monochromacy as the functional phenotype of *ATF6* disease. However, patient 1, with severe macular maldevelopment, has detectable single flash photopic ERGs, responses which are not detectable in rod monochromats, with the b-wave timing of 50ms consistent with an S-cone origin (11-13). The ERGs in patient 2 show a similar electrophysiological phenotype but are associated with the more typical macular phenotype of severe foveal hypoplasia. The genetics

on that patient were included in the first report describing *ATF6*-associated ACHM (4). However, preserved S-cone ERGs have also been reported in *GNAT2*-associated ACHM (12), where preserved tritan colour discrimination was also demonstrated; the preservation of S-cone function is not diagnostic for *ATF6*-associated ACHM.

The structural changes are worthy of comment. Greenberg et al categorized ACHM into 5 stages on SD-OCT (14). Findings in patient 2 are consistent with stage 4 showing presence of an optically empty space with minimal retinal pigment epithelium disruption indicated by mild choroidal hyperreflectance. The sharply demarcated optically empty space with disruption of the inner segment ellipsoid was assumed a sign of cone photoreceptor degeneration (14-16). SD-OCTs show also severe foveal hypoplasia as defined previously in ACHM as persistence of inner retinal layers through the foveal center (5). Although foveal hypoplasia has previously been described in *ATF6*-associated ACHM, the severe with bilateral atrophic macular maldevelopment with excavation down to the sclera in patient 1 is a novel observation. A similar appearance has been reported in a patient with *CNGA3*-associated ACHM (14). Those authors described the appearance as bilateral coloboma-like macular lesions and compared it to macular colobomata described in other retinal dystrophies, including Leber congenital amaurosis, cone-rod dystrophy, adult-onset vitelliform dystrophy and North Carolina macular dystrophy (17-19). Other authors reported macular colobomata in patients with Down syndrome (20-22), *DHX38*-associated retinitis pigmentosa (23) and secondary to *CLDN19* mutations (24) or a variant in *IDH3A* (25). Recently, macular colobomata were suggested to be characteristic features of *NMNAT1*-associated Leber congenital amaurosis. NMNAT1 encodes for the enzyme Nicotinamide nucleotide adenylyltransferase 1 essential for nicotinamide adenine dinucleotide biosynthesis, and mutations in the gene result in a severe, early-onset neurodegeneration (26).

However, since the mechanisms of macular coloboma formation are still unclear, it may also be considered an independent phenotype coexisting in the same patient. It has been proposed

that macular colobomata are a consequence of arcuate bundles along the horizontal raphe undergoing incomplete differentiation (27), with the authors emphasizing that although such lesions have been termed “colobomas”, they are not related to failure of the embryonic fissure to close during embryogenesis. Macular coloboma has also been associated with ocular or systemic abnormalities and may result from either a developmental abnormality or intrauterine inflammation, (17) but no embryonic or infectious explanation was revealed in that patient (14). Previous studies on FAF imaging in ACHM showed variable pathologic features, correlating with morphologic changes observed on SD-OCT (14,16). Patient 2 demonstrates reduced foveal autofluorescence corresponding to the foveal disruption of the inner segment ellipsoid on SD-OCT. The ring shaped area with increased autofluorescence in the perifoveal region is suggestive of progressive retinal degeneration. In contrast, patients 1 shows nearly absent autofluorescence in the area of the coloboma-like macular lesions with only a narrow hyperautofluorescent margin indicating limited progression.

The variant associated with the severe macular abnormality, a frameshift insertion on exon 5, is expected to act as a true null allele since the transcript is likely to undergo NMD. However, since loss of function mutations have also been reported in less severe *ATF6* phenotypes (4,28), this patient may represent a broader spectrum of *ATF6* disease or other modifiers may play a role. That there is a common electrophysiological phenotype between the two patients in the present report suggests a crucial role of *ATF6A* in human foveal development and cone function. This is surprising as *ATF6* encodes the ubiquitously expressed activating transcription factor 6, a key regulator of the unfolded protein response (UPR), and a key component of cellular endoplasmic reticulum (ER) homeostasis. It therefore adds *ATF6* to the list of genes that, despite ubiquitous expression, when mutated can result in an isolated retinal phenotype such as splicing factor *PRPF31, NMNAT1, PRPF8* or *HK1* (29-32).

In conclusion, the findings may expand the phenotype associated with *ATF6*-mediated ACHM by reporting novel findings of severe macular maldevelopment and the possibility of preserved S-cone function.

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Declaration of interest statement

There is no potential conflict of interest.

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Figure captions

Figure 1 Fundus photographs (top right), fundus autofluorescence (FAF) imaging (top left), and optical coherence tomography (OCT) (bottom) for patient 1 (right eye [RE] and left eye [LE]). Fundus photographs and FAF and OCT images show deep, coloboma-like central macular lesions in both eyes.

Figure 2 Full-field ERGs and pattern ERGs (PERGs) in patients 1 and traces from a representative normal individual for comparison; (right eye [RE] and left eye [LE]). Rod-specific (DA 0.01) ERGs are normal, dark-adapted bright white-flash ERGs (DA10.0) contain marginally subnormal a-waves consistent with loss of the dark-adapted cone contribution. 30-Hz flicker ERGs are undetectable. There are very low amplitude single flash photopic ERGs (LA 3.0) with a peak time and shape consistent with an origin in S-cones. DA indicates dark-adapted; LA, lighted adapted. PERG is bilaterally undetectable.

Figure 3 Fundus photographs (top right), fundus autofluorescence (FAF) imaging (top left), and optical coherence tomography (OCT) (bottom) for patient 2 (right eye [RE] and left eye [LE]). Fundus photographs show an absent or barely visible foveal pit in both eyes. OCTs indicate severe foveal hypoplasia bilaterally. FAF images show foveal areas of reduced FAF surrounded by a hyperautofluorescent ring.

Figure 4 Full-field ERGs in patient 2 and traces from a representative normal individual for comparison; (right eye [RE] and left eye [LE]). Full field ERG findings show normal rod-specific (DA 0.01), a dark-adapted red flash ERG with a normal rod component but no detectable cone component; and normal dark-adapted bright white-flash ERGs (DA10.0). The 30-Hz flicker ERG is undetectable. There are very low amplitude single flash photopic ERGs (LA 3.0) with a peak time and shape suggesting an origin in S-cones. DA indicates dark-adapted; LA, lighted adapted.