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Long Term Follow-up of a Family with GUCY2D Dominant Cone Dystrophy

Running title: Clinical Features in GUCY2D Dominant Cone Dystrophy

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ABSTRACT

The aim of this manuscript is to describe long term follow-up in a family with *GUC2YD* dominant cone dystrophy. OCT scans (Triton/OCT-2000 Topcon Ltd, Tokyo, Japan) and Fundus Autofluorescence (FAF) images (Spectralis Heidelberg Engineering, Heidelberg, Germany) were obtained. Goldmann Visual Field (GVF) testing was utilised to monitor the progression of central field loss. Flash and pattern electroretinograms (ERG) and occipital pattern reversal VEPs (VEP) were recorded in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) standards. Two members of the same family (father and son) were identified to have the heterozygous R838C mutation in the *GUC2YD* gene. The father presented at the age of 45 with bilateral bull's eye maculopathy and temporal disc pallor. Over 13 years of serial follow up visits, the bull's eye maculopathy progressed gradually into macular atrophy. The cone ERGs and visual evoked potentials (VEP) were significantly degraded suggesting poor macular function. Spectral Domain Optical Coherence Tomography (SD-OCT) scans showed progressive loss and disruption of the ellipsoid layer at the foveal level. Autofluorescence showed a central annular area of hypo-autofluorescence corresponding to macular atrophy and retinal pigment epithelial (RPE) loss with a surrounding ring of hyper-autofluorescence indicating the transitional zone between the abnormal-normal tissue. Goldmann Visual Fields (GVFs) showed enlargement of a central scotoma. His son presented at the age of 16 with bilateral granular RPE changes in both maculae. Electrophysiological testing was initially borderline normal but has gradually deteriorated to show reduced cone ERGs and macula function. SD-OCT demonstrated gradual macular thinning and atrophy bilaterally. Unlike his father, there was no disruption of the ellipsoid layer. GVFs showed progression of central visual field loss. In conclusion, both family members with cone dystrophy exhibited gradual changes in their fundi, electrophysiological testing and multimodal imaging. Changes were milder than those observed in other mutations of the same gene.

Keywords Autofluorescence (AF); Electroretinogram (ERG); Cone Dystrophy/Cone-Rod Dystrophy (CD/CRD); *GUC2YD*; Spectral Domain Optical Coherence Tomography (SD-OCT); Visual Evoked Potential (VEP)

INTRODUCTION

Cone dystrophies (CD) and Cone-Rod Dystrophies (CRD) are a group of genetic disorders, which demonstrate a large degree of heterogeneity and severity. The most frequent mode of inheritance is autosomal dominant (AD), although autosomal recessive (AR) and X-linked recessive (XLR) modes of inheritance have also been reported[1]. The main symptoms are decreased central visual acuity (VA), markedly decreased color vision (CV), hemeralopia, nystagmus and loss of peripheral vision[2]. In pure cone dystrophies, only cone function is affected, while rod function remains intact[1]. The photopic ERG demonstrates abnormalities but the scotopic ERG is grossly normal[3]. Conversely, in cone-rod dystrophies, patients demonstrate features suggestive of rod dysfunction as well[3]. In CRD, both photopic and scotopic ERGs will be abnormal[1-3]. It is rare to have a pure cone dystrophy because of the reciprocal relationship between the cone and rod system[3].

The usual natural history of CRD starts initially by forming some non-specific RPE granularity and mottling at the macular level[3]. As the disease progresses, a typical bull's eye lesion develops, but not universally[3]. End-stage disease with photoreceptor degeneration and RPE loss will result in geographic atrophy[3].

There is a wide range of genes implicated in the pathogenesis of CRD. The most common ones are *SEMA4A*, *AIPL1, CRX, GUCA1A, GUCY2D, PITPNM3, PRPH2, PROM1, RIMS1* and *UNC119*[4].

Both family members were found to have mutation in the Retinal Guanylyl Cyclase 1 (also known as Guanylate Cyclase 2D/*GUCY2D*), which is known to be implicated in the AD form of cone/cone-rod dystrophy. The Retinal Guanylyl Cyclase 1 is an enzyme expressed within the retina responsible for the conversion of guanosine 5'-triphosphate (GTP) to cyclic guanosine monophosphate (cGMP)[4]. Like other membrane guanylyl cyclases, this enzyme has a hydrophobic amino-terminal signal sequence followed by a large extracellular domain, a single membrane spanning domain, a kinase homology domain, and a guanylyl cyclase catalytic domain. In contrast to other membrane guanylyl cyclases, this enzyme is not activated by natriuretic peptides. The Retinal Guanylyl Cyclase 1 helps photoreceptors return to their dark-adapted state after light exposure; cGMP plays a significant role as the second messenger molecule in the phototransduction cascade by keeping the voltage-gated sodium and calcium channels of photoreceptors open[4]. Photoactivation leads to conversion of cGMP to guanosine 5'-monophophate (GMP) by phosphodiesterase and this results in the closure of voltage-gated sodium and calcium channels and to hyperpolarization of the photoreceptor outer segments[4]. When the concentration of calcium cations is reduced, the Retinal Guanylyl Cyclase 1 restores the levels of cGMP and this allows the reopening of the relevant channels[4]. Restoration of cGMP levels is achieved by the presence of the guanylate cyclase-activating protein[4]. Mutations in *GUCY2D* gene have been described in cone-rod dystrophy-6 and Leber congenital amaurosis[5].

In this manuscript, we describe the long-term clinical and multimodal imaging findings over the course of 13 years in two family members diagnosed with *GUC2YD* cone dystrophy. To the best of our knowledge, this is the longest follow-up described so far in literature.

MATERIALS AND METHODS

All procedures were compliant and consistent with the tenets of the Declaration of Helsinki. Informed consent was obtained from all individual participants included in this retrospective study.

A retrospective review of the electronic records of two family members (father and son) was conducted at the Eye Unit of University Hospital Southampton NHS Foundation Trust, United Kingdom. Both patients were followed-up annually at the Eye Unit for the last 13 years and had a full past medical, ophthalmic and genetic history taken

during the initial presentation. Annual follow-up visits were conducted including multimodal imaging. OCT scans were obtained with the use of Triton/OCT-2000 (Topcon Ltd, Tokyo, Japan), whereas Fundus Autofluorescence (FAF) images were taken using Spectralis (Heidelberg Engineering, Heidelberg, Germany). Goldmann Visual Field (GVF) testing was utilised to monitor the progression of central field loss. Flash and Pattern ERGs were recorded using corneal DTL thread electrodes. Flash ERGs were recorded after dilatation in compliance with International Society for Clinical Electrophysiology of Vision (ISCEV) standards[6]. Occipital full-field checkerboard reversal VEPs were recorded to stimulus check sizes ranging from 10 to 120 minutes of arc.

Both patients underwent genetic testing: the participants underwent whole exome sequencing in order to identify the genetic cause of their CD. DNA was isolated from blood, exome enrichment performed using the Agilent SureSelect Human All Exon V5 kit (© Agilent Technologies, Inc), and sequencing performed on the Illumina HiSeq 2000 platform (© Illumina Inc®). Data analysis was performed as previously described[7]. Genetics variants were filtered to identify variants present in both individuals within candidate genes based upon the Human Gene Mutation Database (namely *ABCA4, CACNA2D4, CNGA3, CNGB3, CRB1, CRX, GUCA1A, GUCY2D, KCNV2, MERTK, orf15, PDE6C, PDE6H, PITPNM3 & PRPH2*).

Results

Genetic Testing

Exome sequencing identified the heterozygous variant *GUCY2D*:c.2512C>T:p.Arg838Cys (rs61750172, also known as R838C) in both patients (Figure 1). This mutation has been previously reported to cause cone-rod dystrophy 6 (CORD6; OMIM #601777) [8]. For abbreviation purposes, the father has been allocated the symbol P1 in generation II, whereas the son has been allocated the symbol P2 in generation III. There was also a history of eye problems in patient I1. There was insufficient data in past medical history to confirm a formal diagnosis of CD; hence the question mark symbol (Figure1).

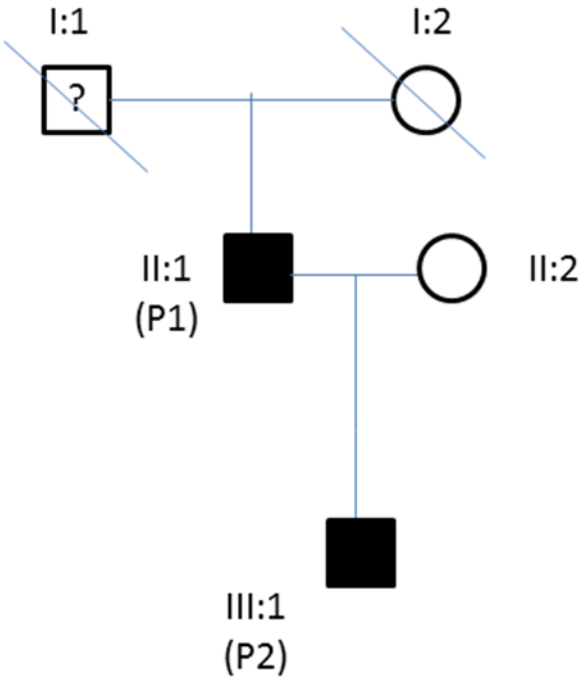
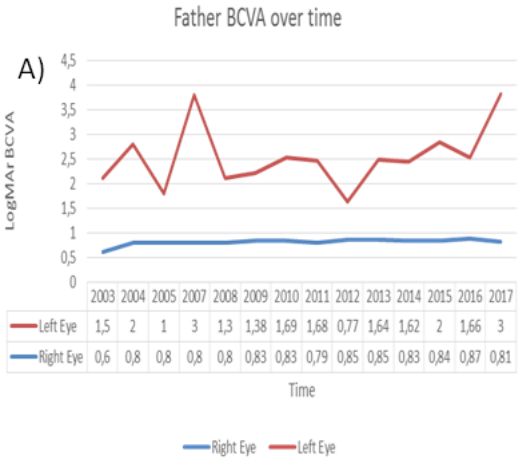


Figure 1 Family Pedigree

Clinical Findings The cumulative clinical features for each patient are summarized in table 1. Both patients exhibited decline in VA combined with hemeralopia in adolescence but neither of them complained of nyctalopia. In addition, there were no significant media opacities to account for decline in VA in both of our patients. Figure 2 2 demonstrates the fluctuation of best corrected visual acuity (BCVA) in both family members over the 13 year follow-up at Southampton Eye Unit.

Pedigree	Current Age (Years)	Onset of symptoms	Ocular Comorbidities	Visual Acuity (Snellen), OD/OS	Ishihara Plates	Dilated Fundal Examination Findings	GVF Findings	ERG/VEP findings
II: 2 (P1)	59	Photophobia since adolescence	Left Eye Amblyopia due to squint	6/36/ Hand movements	OD: 1/17 OS: 0/17	Bilateral bull's eye maculopathy and temporal disc pallor	Progressive central scotoma	Impaired cone function, Preserved rod function, Degraded and attenuated VEP
III: 3 (P2)	28	Photophobia in early adolescence	Bilateral astigmatism, Left Eye Amblyopia	6/15/ 6/48	OD: 5/17 OS: 1/17	Bilateral RPE changes	Progressive central scotoma	Impaired cone function, Preserved rod function, Degraded and attenuated VEP

Table 1 Cumulative table summarizing the clinical features in both family members. None of the two family members complained about nyctalopia and none of them had significant cataracts



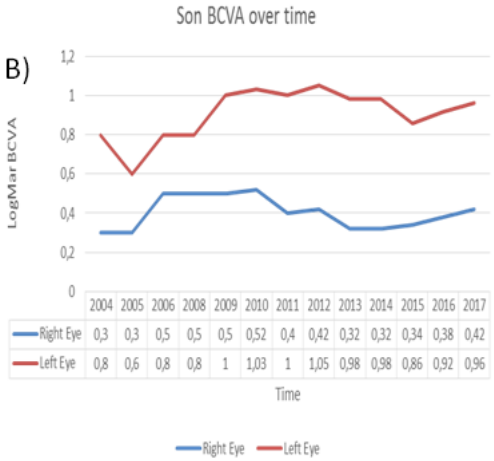


Figure 2 Changes in best corrected visual acuity (BCVA) for both patients from initial presentation in 2004 until 2017. A) Left side**:** Father (P1) B) Right side: Son (P2)

Multimodal Imaging

The macular OCT scans of P1 showed progressive loss of the ellipsoid layer at the level of the fovea with gradual thinning and atrophy of the adjacent retinal tissue and reverse shadowing due to cone and RPE cell loss (Figures 3a and 3b). FAF showed a central annular area of hypo-autofluorescence corresponding to macular atrophy and RPE loss with a surrounding ring of hyper-autofluorescence indicating the transition zone between normal and abnormal retina. (Figures 4a and 4b). These changes have occurred in both eyes but the left eye appears to be more affected than the right. The macular OCT scan of the right eye of P2 demonstrated gradual macular thinning and atrophy, whereas the macular structure in the left eye remained relatively stable. Unlike the father's OCT scans, there was no disruption of the ellipsoid layer (Figures 3c and 3d). FAF images of the son showed features suggestive of bilateral foveolar hyper-autofluorescence (hyper-AF). The hyper-AF involving the central foveolar area which can be seen in figures 4c and 4d, are similar to the changes previously reported in Type-2 idiopathic macular telangiectasia, which may be a consequence of decreased foveal pigment density and secondarily reduced masking effect of the RPE fluorescence[9]. The FAF findings also demonstrated RPE granular changes (Figures 4c and 4d).

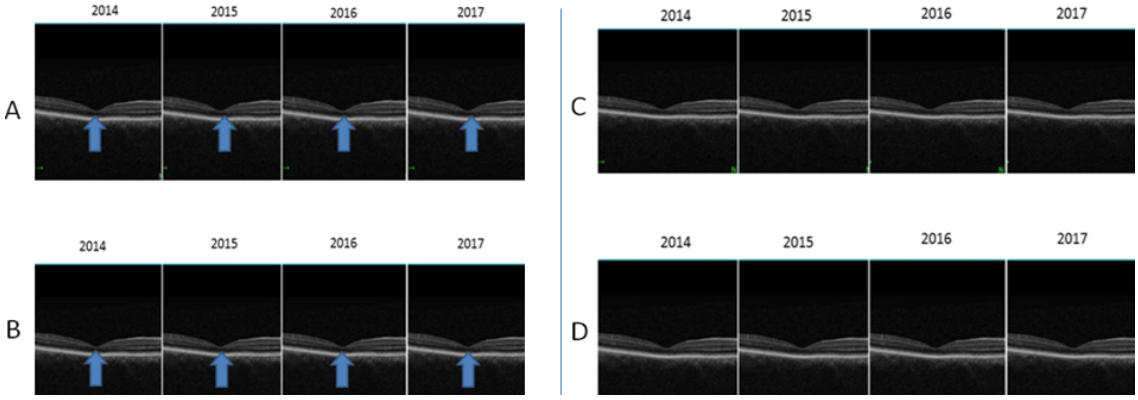


Figure 3 Serial OCT images both patients A) Top row: Serial OCT images from P1's right eye. Note the loss of ellipsoid layer at the foveal level and the gradual thinning and atrophy of the outer retinal layers as shown by the blue arrows B) Bottom row: Serial OCT images from P1's right eye. Note the loss of ellipsoid layer at the foveal level and the gradual thinning and atrophy of the outer retinal layers as shown by the blue arrows. C) Top row: Serial OCT images from P2's right eye. Progressive atrophy of the ellipsoid layer but no breaks in the continuity of the ellipsoid layers on the OCT images D) Bottom row: Serial OCT image from P2's left eye. Progressive atrophy of the ellipsoid layer but no breaks in the continuity of the ellipsoid layers on the OCT images

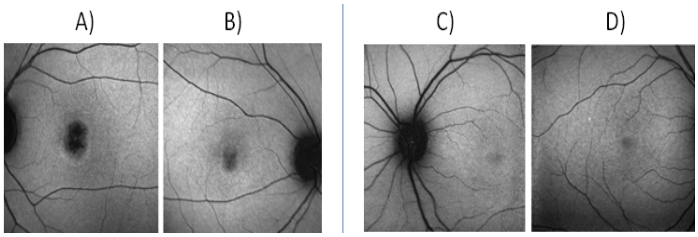


Figure 4 Autofluorescence Images from both patients. A, B**)** Left side: Father (P1). Note central area of hypo-autofluorescence, left worse than right. C, D) Right side: Son (P2): Bilateral foveolar hyper-autofluorescence (hyper-AF). The hyper-AF mimics the changes previously reported in Type-2 idiopathic macular telangiectasia, which may be a consequence of decreased foveal pigment density and secondarily reduced masking effect of the RPE fluorescence.

Electrophysiology

The father's flash ERGs showed well-preserved rod function (amplitude of responses smaller than average but within normal range) but significantly impaired cone function. Pattern ERGs as well occipital pattern VEPs were attenuated and degraded indicating reduced macular function.

The son's cone responses were of borderline normal amplitude on initial presentation but became significantly degraded ten months later suggesting cone dysfunction (Figure 5). Rod responses were normal. Pattern ERGs and occipital pattern VEPs were significantly degraded indicating reduced macular function. Figure 6 also features the most recent GVFs for father (Figures 6A and 6B) and his son (Figures 6C and 6D).

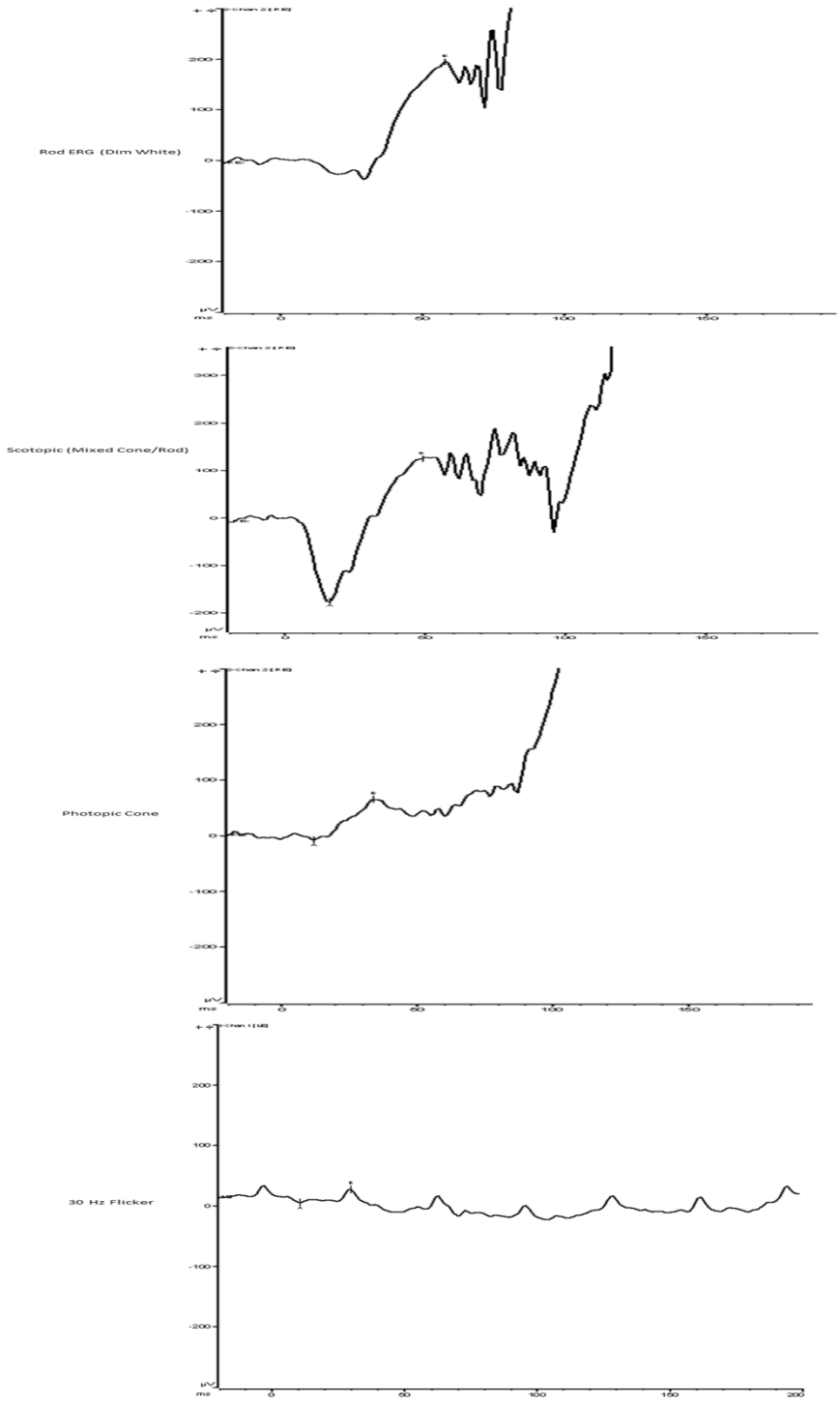


Figure 5 P2's ERG Responses Figure shows P2's repeated ERG responses a few months after initial presentation. There was a significant reduction in the amplitude of the cone mediated responses, which were more degraded compared to the initial ERGs.

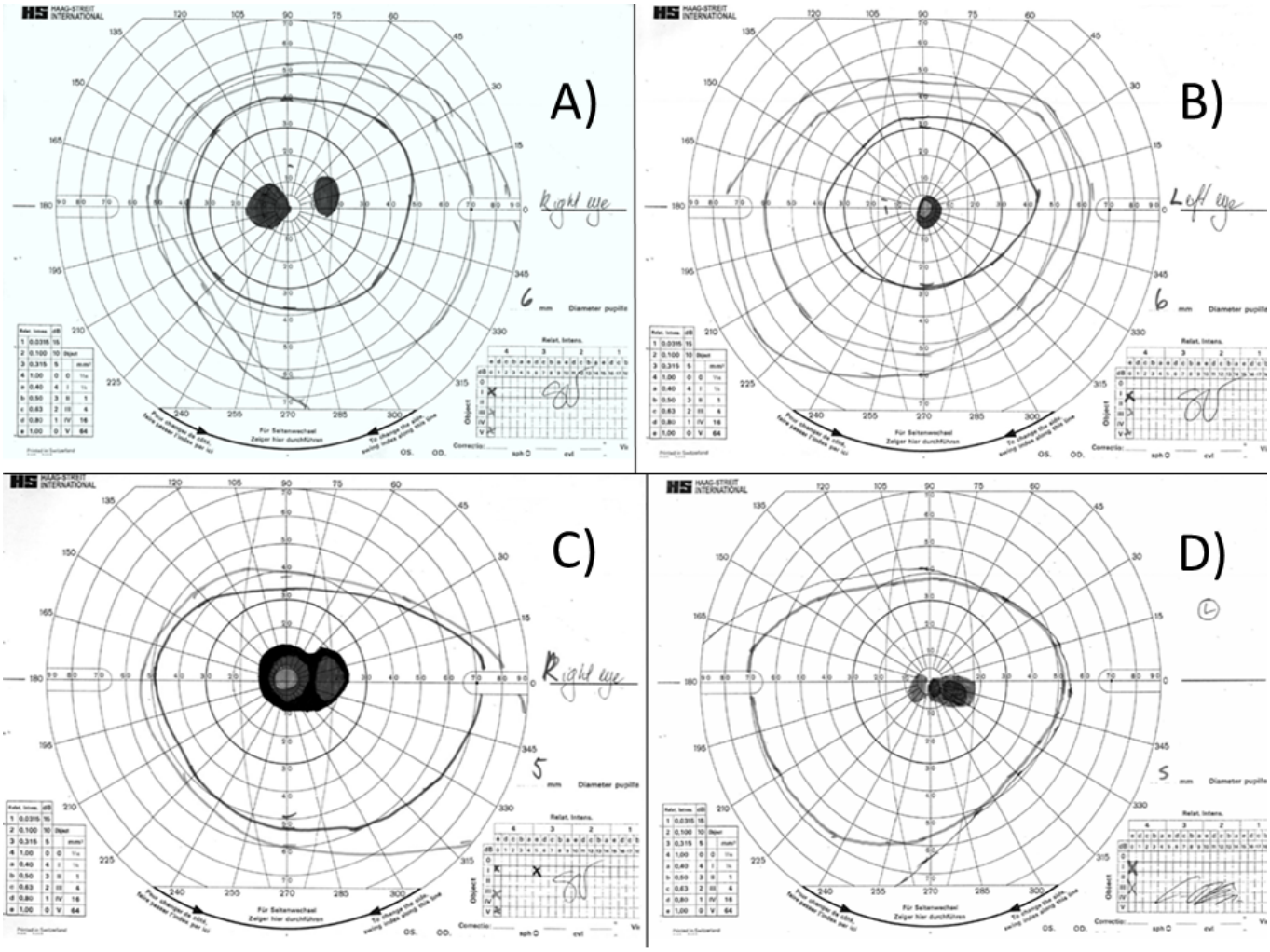


Figure 6 Most recent Goldmann Visual Fields (GVFs) of both patients. Top Row**:** A, B) Father (P1). Bottom Row: C, D) Son (P2). Note the central scotomas in all four eyes consistent with poor macular dysfunction as part of cone dystrophy.

DISCUSSION

So far, 223 mutations in the *GUC2YD* gene have been described. The *Arg838Cys (R838C)* mutation described in both of our patients has been previously reported by Kellsell et al[10] in 1998 in cone dystrophy 6. It is reported to cause a milder clinical phenotype compared to other mutations in the *GUC2YD* gene [11]. The mild phenotype of this particular mutation has been described by others in the past[12,13]. Other *GUCY2D* mutations *on the same codon* (*R838S, R838H, R838P, R838G*) can lead to a more aggressive clinical picture[14,15]. Based on ERG recordings, two major types of cone-rod dystrophy were differentiated according to the phenotypic classification by Szlyk and colleagues[16]. In type 1, cone amplitudes were reduced to a greater degree than rod amplitudes, while in type 2, cone and rod ERG amplitudes were reduced in equal proportion. According to the phenotypic classification by Szlyk and colleagues[16], both of our patients could be classified as phenotype 1a.

The father presented to the Ophthalmology Department with bilateral bull's eye maculopathy and mild temporal disc pallor. Bull's eye maculopathy can be caused by genetically inherited conditions or toxic retinopathies, hence it is not disease specific for cone/cone-rod dystrophy[3]. Disc pallor is also a non-specific finding but has been reported previously in a patient with cone dystrophy[17], who had normal to near normal visual acuity and color vision and abnormal peripheral cone function. However, in the father's case, the macula function was already

compromised and the peripheral retina was normal. His son exhibited non-specific RPE granular changes but no other significant abnormalities. Bull's eye maculopathy was not observed in the son's case confirming that bull's eye maculopathy is not a universal sign[3]. This may be merely due to the chronicity of the disorder in his father. Moreover, the presence of a bull's eye maculopathy does not always correlate accurately with the extent of retinal dysfunction[18]. All the above observations confirm that the diagnosis of CD/CRD cannot rely exclusively on fundoscopy due to the non-specific clinical findings[19].

On SD-OCT, the father exhibited progressive loss of the ellipsoid layer and gradual thinning and atrophy of the parafoveal retinal tissue and reverse shadowing due to cone and RPE cell loss. There was also obscurity at the level of the external limiting membrane (EML). This is consistent with the findings of others[19-23]. His son, however, had thinning but no loss of the ellipsoid layer. FAF imaging from the father's fundus was consistent with the OCT findings. Furthermore, the surrounding hyper-autofluorescence around the annular area of hypo-autofluorescence suggests gradual deposition of lipofuscin material, a byproduct of the photoreceptor cell visual cycle and RPE metabolism. Lipofuscin accumulation can be toxic to the RPE and photoreceptor cells and this can lead to death of RPE and photoreceptors and that can cause further thinning and atrophy of the macula[24]. The FAF findings from the father's fundus are consistent with observations of another paper[25]. The RPE granular changes observed in the son's fundus were also observed by FAF. Hence, FAF is useful as an adjuvant means of imaging when SD-OCT cannot detect subtle RPE or retinal abnormalities.

FAF images showing a subtle bilateral hyper-AF signal mimicking changes that were previously described in Type 2 Macular Telangiectasia might be a reliable early indicator of the disease especially when ERGs are found to be border-line normal as in P2 in this case series[7].

Only one paper by Cho et al[26] has attempted to describe in depth and classify the different types of structural retinal abnormalities in patients with CD/CRD. This was a five year observational follow-up in 15 patients with cone dystrophy[26]. Prior to this study, Hood et al[20] reported decreased intensity in the ellipsoid layer in 6 patients with cone dystrophy. Birch et al[27] reported that the thickness of the outer nuclear layer and the sum of thickness of the RPE and outer segment correlated well with visual field sensitivity[20,24]. However, neither paper described the structural changes of the retina in patients with cone dystrophies.

Cho et al[26] divided the morphological changes in the retinal structure in cone dystrophy patients into four different categories: 0, 1, 2 and 3. Category 0 exhibited no structural abnormalities, whereas category 1 showed foveal ellipsoid layer loss and obscurity of the border between the ellipsoid band and the external limiting membrane (ELM). Category 2 showed foveal thinning and focal foveal ellipsoid layer disruption with an intact ELM. Finally, category 3 showed foveal thickening and perifoveal disruption of the ellipsoid layer.

Based on this classification, the father demonstrated changes matching category 1. The son did have foveal thinning but no disruption of the ellipsoid layer, hence he could potentially be classified as category 0. In the Cho et al paper[26], it was observed that category 0 patients were younger than the other categories, although this observation was not proven to be statistically significant. Ageing is likely to be a contributing factor to disease progression with subsequent disruption of the photoreceptor outer segment/ellipsoid layer.

Moreover, in the paper by Cho et al[26], only one patient was found to meet the category 3 criteria. The authors formed the hypothesis that the thickening of the fovea could be attributed to the gradual deposition of tissue remnants of the unhealthy and gradually dying photoreceptors[26]. This SD-OCT finding has been described previously in patients with *peripherin/RDS* gene mutations[28]. However, in patients with CD due to *GUCY2D*

mutations, category 1 abnormalities have been previously described (*GUC2YD Arg838His*)[29]. The difference to the case described by Kim et al (*GUC2YD Arg838His)*[29] is that our patients had the *GUC2YD Arg838Cys* mutation compared to the patient described by Kim et al[29]. Nevertheless, the morphological features on SD-OCT are similar.

Electrophysiological testing is arguably the most diagnostic test, should CD/CRD be suspected. Fundus examination can show non-specific changes and the multimodal imaging findings in patients with cone dystrophy are quite heterogeneous and therefore fundoscopy, SD-OCT and FAF are not diagnostic. This is also supported by Cho et al[26], who observed that category 0 patients had a significantly affected ERG, while no structural abnormalities were observed. In addition, it is obvious that electrophysiological responses do not correlate well with SD-OCT findings. Thus, ERG and VEP can confirm the macula/cone dysfunction much earlier than other imaging modalities and therefore they both are an irreplaceable adjuvant diagnostic tool for any Medical Retina Specialist in the diagnosis and management of patients diagnosed with CD/CRD.

To the best of our knowledge, this is the longest duration of follow-up of patients with CD associated with mutations in *GUCY2D*. We describe the progression of the disease based on visual acuity and multimodal imaging. Electrophysiological testing is most useful for the clinical diagnosis of CD/CRD, while SD-OCT and FAF imaging are both useful for monitoring disease progression and genotype-phenotype correlations can be identified by molecular analysis.

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CONFLICTS OF INTEREST

Tsokolas G, None**; Almuhtaseb H,** None**; Shawkat F,** None**; Pengelly R,** None; **Lotery A,** None

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