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Retinal Manifestations in Autosomal Recessive *MPDZ* Maculopathy: Report of Two Cases and Literature Review

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Abstract

Background: To present the retinal and systemic findings in two siblings with compound heterozygous *MPDZ* variants that were found to have different chorioretinal manifestations.

Materials and Methods: Two sibling patients underwent comprehensive ophthalmic examination, including ophthalmoscopy, fundus photography, optical coherence tomography (OCT), and genetic testing by whole exome sequencing.

Results: A 4-year-old male presented with intermittent exotropia and decreased vision in both eyes. Ophthalmologic examination was notable for macular colobomas and far temporal chorioretinal atrophy in both eyes. OCT of the macula in both eyes demonstrated a caldera with severe retinal and choroidal thinning. Fluorescein angiography of the central macula showed hypofluorescence with persistence of deep choroidal vessels. An ocular gene panel was nondiagnostic, but subsequent whole exome sequencing noted compound heterozygous, likely pathogenic *MPDZ* variants (c.3100C>T p.(Arg1034*) from father and c.747+2T>G p.(?) from mother). His older brother, a 9-year-old male, had a history of macrocephaly but had not undergone further workup. On exam, he had a visual acuity of 20/25 in the right eye and 20/40 in the left eye and was found to have subtle changes in the foveal reflex of both eyes. OCT revealed

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thinning of the outer nuclear layer (ONL) temporal to the fovea bilaterally. Sanger sequencing revealed he was positive for the same two *MPDZ* variants.

Conclusions: *MPDZ* variants have been described in cases of congenital hydrocephalus with varying ophthalmologic manifestations. We present a case series describing retinal phenotypes associated with *MPDZ* variants in a single family through multimodal imaging.

Keywords

chorioretinal coloboma; claudin; hydrocephalus; inherited retinal dystrophy; MPDZ; multi-PDZ domain protein-1; MUPP1; tight junctions

INTRODUCTION

Macular dystrophies are a group of inherited retinal disorders with significant clinical and genetic heterogeneity that can be associated with vision loss.[1] Many subtypes have been well described through advances in multimodal genetic testing, and these include Stargardt disease (*ABCA4*), Best disease (*BEST1*), Sorsby fundus dystrophy (*TIMP3*), pattern dystrophy (*PRPH2*), X-linked retinoschisis (*RS1*), autosomal dominant drusen (*EFEMP1*), and North Carolina macular dystrophy (*PRDM13*). The majority of these commonly seen macular dystrophies are non-syndromic, but there are a few notable examples of syndromes with primary or exclusive involvement of the macula. These include cases of Bardet-Biedl syndrome (*BBS1*),[2] maternally inherited diabetes and deafness (*MIDD*),[3] and spinocerebellar ataxia (*SCA7*).[4] Here, we describe two siblings with retinal findings and variants in *MPDZ*, a gene that encodes multiple PDZ domain protein (also known as MUPP1) that is found in retinal tight junctions and has been implicated in rare cases of severe congenital hydrocephalus, some with macular and iris anomalies.[5–7]

MATERIALS & METHODS

This was a retrospective observational case series that adhered to the tenets of the Declaration of Helsinki. Institutional Review Board approval was obtained at the Children's Hospital of Los Angeles (CHLA-18-00467) with consent from the patients' legal guardians prior to publication of this report. The patients are male siblings with genetically confirmed variants in the *MPDZ* gene (c.3100C>T p.(Arg1034*) and c.747+2T>G p.(?)), which encodes the MUPP1 protein. The exome (+mtDNA capture) sequencing library was generated using the Agilent SureSelect Human All Exon V6 plus a custom mitochondrial genome capture kit. Captured DNA fragments were then sequenced using the Illumina Nextseq 500 sequencing system with 2x101 basepair (bp) paired-end reads.

The clinical history, examination findings, ancillary testing, and imaging for these patients were collected and analyzed. Snellen visual acuity was measured and the eyes were examined by a single retina specialist (A.N.) at each visit. For Case 1, ancillary testing was performed using RetCam 3 (Natus Medical, Middleton, WI) to obtain color fundus and fluorescein angiography and Bioptigen hand-held OCT (Bioptigen/Leica, Durham, NC) to obtain spectral-domain OCT images. For Case 2, imaging was performed using a Canon fundus camera (Canon Medical Systems, Tustin, CA) to obtain color fundus

photographs and Heidelberg Spectralis (Heidelberg Engineering, Heidelberg, Germany) to obtain spectral-domain OCT.

REPORT OF CASES

Case 1 and Case 2 are brothers born to the same unaffected parents with a normal sister. Of note, another sister died at 1 month of age secondary to an unknown cardiovascular issue, but records are unavailable.

Case 1:

A 4-year-old male presented to the ophthalmology clinic for left exotropia noticed by his parents. His birth history was unremarkable, and his medical history was notable for bilateral cryptorchidism and a nonobstructive subaortic membrane diagnosed by echocardiography. On ophthalmic examination, his uncorrected visual acuity was 20/100 OD and 20/80 OS (single pictures) with normal pupils and intraocular pressure, an unremarkable anterior segment examination, and 20 prism diopters of intermittent exodeviation. Dilated fundus examination was notable for symmetric excavated colobomatous lesions involving the macula of both eyes, as well as bilateral chorioretinal scars in the temporal periphery (Figure 1, A–D). Fluorescein angiography revealed absence of the choroidal flush at the fovea corresponding to the colobomas (Figure 1, E–F). Hand-held spectral domain OCT demonstrated a deeply excavated caldera with severe thinning of the retina and choroid and no associated fluid or photoreceptor loss outside of the coloboma (Figure 1, G–H). Given the concern for a retinal dystrophy, a focused ocular exome panel was performed which found no causative variants. This prompted expansion to whole exome analysis, which identified two variants in the *MPDZ* gene (c.3100C>T p.(Arg1034*) and c.747+2T>G p.(?)) based on reference sequence NM_003829.4. Each of these variants is predicted to disrupt gene function through the introduction of a premature stop codon in the case of the c.3100C>T p.(Arg1034*) variant, or by disrupting RNA splicing through the alteration of position +2 of a canonical splice site in the case of the c.747+2T>G p.(?) variant. Parental testing was performed which revealed these variants to segregate from the mother and father, respectively, indicating compound heterozygosity. Follow-up examinations over 3 years revealed no change in the retinal appearance and a slight improvement in visual acuity to 20/60 in both eyes at last follow-up (age: 7 years).

Case 2:

The 9-year-old older brother of Case 1 was tested for segregation of the variants and subsequently examined, as he carried both *MPDZ* variants above. His medical history included macrocephaly (90th percentile), which was evaluated by neurosurgery at age five and felt to not require neuroimaging or any intervention. He also had left cryptorchidism and a bicuspid, mildly hypoplastic aortic valve without insufficiency. The visual acuity was 20/25 and 20/40 in the right and left eyes, respectively, with normal pupils and intraocular pressure and an unremarkable anterior segment examination. Dilated fundus examination revealed subtle changes in the foveal reflex of both eyes (Figure 2, A–B). OCT of the macula demonstrated thinning of the outer nuclear layer temporal to the fovea bilaterally, with preservation of the ellipsoid zone band and RPE layer (Figure 2, C–F).

DISCUSSION

Here we describe two brothers with biallelic pathogenic variants in the *MPDZ* gene that possessed variable structural abnormalities of the retina. Case 1 had large bilateral macular colobomas with symmetric patches of chorioretinal atrophy in the temporal periphery, whereas Case 2 had subtle thinning of the temporal fovea in both eyes.

To our knowledge, only one previous case of *MDPZ* maculopathy has been characterized with multimodal imaging.[7] In this study, a 26-year-old male of nonconsanguineous parents presented with 13 years of blurry vision and was noted to have bilateral macular colobomas with heterozygous *MPDZ* variants, without any other systemic manifestations noted. Autosomal recessive *MPDZ* variants have been identified in rare cases of severe congenital hydrocephalus in multiple case series, including a consanguineous Saudi Arabian family with homozygous loss of function alleles of the *MPDZ* gene.[5,6] Examination in one patient with confirmed homozygous *MPDZ* variants and congenital hydrocephalus was notable for bilateral chorioretinal coloboma of the maculae.[5] Another patient, a 3-year-old male from unrelated Northern European parents, was noted to have foveal dysplasia with a thin inner retina, along with bilateral lacrimal duct stenosis, downslanting palpebral fissures, microretrognathia, small teeth, and joint hypermobility; exome sequencing revealed two heterozygous variants in *MPDZ* (Table 1).[6] However, detailed ophthalmologic examination and retinal imaging for these patients was not performed. Additional patients with biallelic *MPDZ* variants have also been reported to have numerous systemic abnormalities in the literature, including recessive non-syndromic congenital hydrocephalus, macrocephaly, atrial septal defects, aberrant subclavian arteries, congenital diaphragmatic hernias, and hypotonia.[5,6] Of note, one study screened 276 patients with previously diagnosed retinal dystrophies (149 with retinitis pigmentosa and 127 with Leber congenital amaurosis) and identified 10 patients with heterozygous *MPDZ* sequence changes (3 null alleles and 7 missense changes); however, no cases of autosomal recessive *MPDZ* disease were identified in this cohort.[8]

The *MPDZ* gene localizes to autosome 9p23 and encodes the MUPP1 protein (multiple PDZ domain protein), which is found in tight junctions of the retina and central nervous system.[8] MUPP1 has 13 PDZ domains that may serve as a multivalent scaffold for tight junction proteins to preserve the structural integrity of these junction complexes.[9] Through its PDZ domains, MUPP1 may also help regulate cell processes such as cell proliferation, cytoskeleton organization, cell polarity, and intercellular signaling.[7,10] Prior work suggests MUPP1 may form complexes with the CRB1 protein, which has been implicated in retinal dystrophies.[8,11] Of note, the *rdd* chicken model bears premature stop codon mutations in *MPDZ* with absent retinal MUPP1 expression and is blind by 10 weeks of life due to severe early onset retinal degeneration.[8,12] In humans, *MPDZ* is expressed throughout the retina, with particular concentration in the RPE and Müller glia, which may explain the structural abnormalities seen in these cases.[13] Whereas Case 1 demonstrated bilateral macular colobomas involving all retinal layers, which bears resemblance to a recently published case of bilateral macular colobomas in a patient with heterozygous *MPDZ* variants, Case 2 had thinning of the outer nuclear layer temporal to the fovea.[7] The latter phenotype resembles that of the *MPDZ*-null avian model, which showed disorganization of

the photoreceptor layer and resulting undulation of the outer plexiform layer.[12] Further study is needed to establish the pathophysiology of *MPDZ* loss in the retina.

In summary, we report two brothers with autosomal recessive *MPDZ* retinopathy with disparate retinal manifestations. Case 2 also had mild macrocephaly; given the association of *MPDZ* with congenital hydrocephalus, it is tempting to speculate this was a result of mild hydrocephalus. Additional cases of autosomal recessive *MPDZ* maculopathy will need to be identified to further characterize the phenotypic spectrum of *MPDZ* retinopathy.

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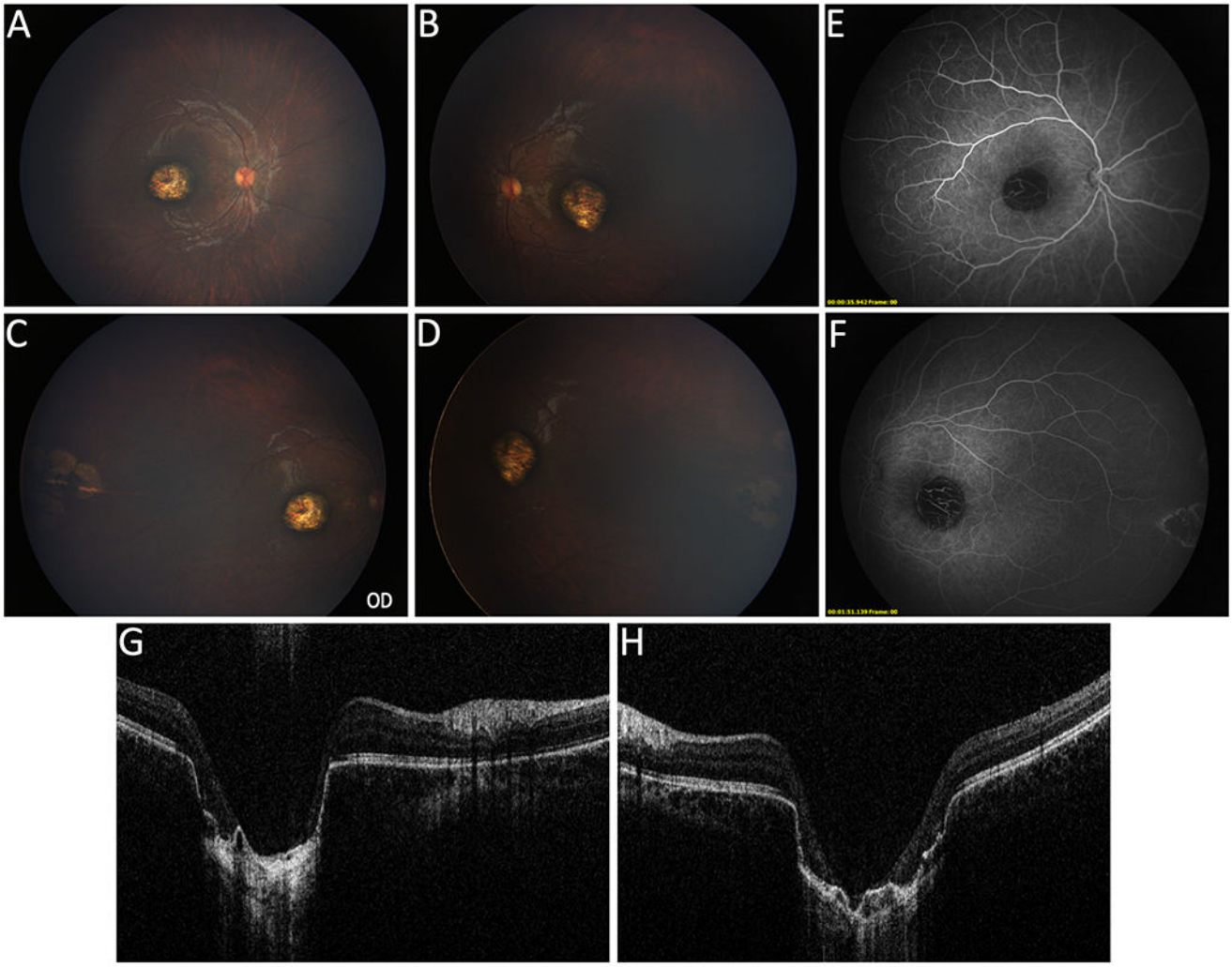

Figure 1.

Retinal findings in Case 1. A-B, Color fundus photographs of the right (A) and left (B) eyes demonstrating symmetric, excavated colobomatous lesions involving the central macula in both eyes. C-D, Color fundus photographs of the posterior pole and periphery of the right (C) and left (D) eyes displaying the macular colobomas in addition to symmetric chorioretinal scars in the temporal periphery. E-F, Fluorescein angiography of the right (E) and left (F) eyes show absence of the choroidal flush at the fovea corresponding to the colobomas. G-H, Hand-held spectral-domain OCT of the right (G) and left (H) macula showed deeply excavated calderas with severe thinning of the retina and choroid, without associated intraretinal/subretinal fluid or photoreceptor loss outside of the coloboma.

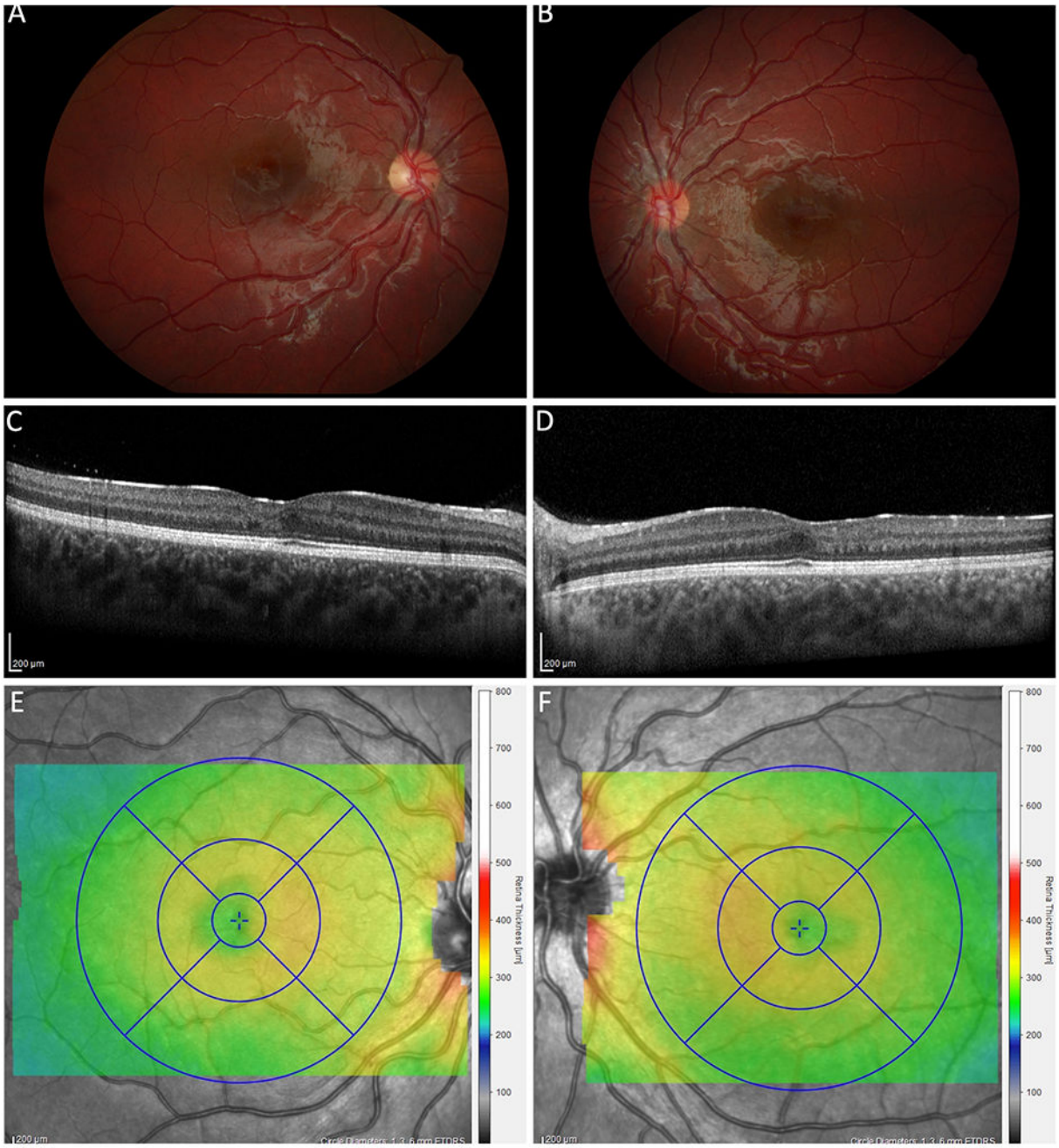

Figure 2.

Retinal findings in Case 2. A-B, Color fundus photographs of the right (A) and left (B) retina revealing subtle changes in the foveal reflexes of both eyes. C-D, OCT macula of the right (C) and left (D) eyes demonstrating thinning of the outer nuclear layer temporal to the fovea bilaterally, with relative preservation of the ellipsoid zone band and RPE layer. E-F, Retinal thickness maps of the right (E) and left (F) eyes highlighting symmetric thinning of the temporal foveae bilaterally.

Table 1.

Published cases of *MPDZ* variants with associated ophthalmologic and orbital changes

Reference	Age/Sex	*MPDZ* Variants	Ophthalmic Findings	Systemic Findings
Case 1	4yo M	Heterozygous, *in trans* c.3100C>T p.(Arg1034*) c.747+2T>G p.(?)	- Bilateral chorioretinal colobomas - Bilateral temporal chorioretinal atrophy - Exotropia	- Bilateral cryptorchidism - Non-obstructive subaortic membrane
Case 2	9yo M	Heterozygous, *in trans* c.3100C>T p.(Arg1034*) c.747+2T>G p.(?)	- Temporal foveal ONL thinning	- Macrocephaly - Left cryptorchidism - Bicuspid hypoplastic aortic valve without insufficiency
Shaheen et al, 2017[6]	15mo M	Homozygous c.5278G>A p.(Ala1760Thr)	- Bilateral iris colobomas - Prominent optic nerves	- Small for gestational age - Cholestatic jaundice - Dysplastic kidney - Hypotonia - Hydrocephalus
Shaheen et al, 2017[6]	3yo M	Heterozygous, *in trans* c.2230C>T p.(Arg744*) c.3211C>T p.(Arg1071*)	- Bilateral foveal dysplasia - Thin inner retina - Bilateral lacrimal duct stenosis - Down-slanting palpebral fissures	- Absent lung bronchus - Retrognathia - Small teeth - Joint hypermobility - Structural brain abnormalities
Al-Dosari et al, 2013[5]	10mo F	Homozygous c.628C>T p.(Gln210*)	- Bilateral chorioretinal colobomas	- Severe hydrocephalus - Broad frontal gyri - Shallow parietal sulci - Seizures - Hypotonia - Atrial septal defect
Zhang et al, 2022	26yo M	Heterozygous, *in trans* c.5255C>G p.(Ser1752Ter) c.4301delA p.(Asp1434fs*3)	- Bilateral chorioretinal colobomas - Axial anisometropia	- No systemic abnormalities

Abbreviations: ONL – outer nuclear layer; yo – year old; mo – month old