• Letter to the Editor •

Dominant cystoid macular dystrophy associated with mutations in the *RP1L1* gene

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Dear Editor,

We describe in detail a case of dominant cystoid macular dystrophy (DCMD) patient carrying a novel heterozygous *RP1L1* mutation. DCMD is a unique form of macular dystrophy; the appearance of cystic spaces in the macula indicates its onset, while the rest of the retina is essentially normal[1]. The disease usually occurs in the third decade of life. The visual acuity of patients with DCMD will gradually decline and, in some cases, may become restricted to finger counting. The present report highlights the multimodal imaging features and genetic detection of this condition. We performed a comprehensive mutation analysis in patients with DCMD, and provided a unique insight into its possible pathogenesis.

Our study included four family members from three generations. The research protocol was approved by the Ethical Committee of Baoding First Central Hospital (Hebei Province, China). Informed written consent was provided by all participants following a detailed explanation of the procedures. Blood samples were collected from the patient and her brother and genomic DNA was extracted from peripheral blood lymphocytes for genetic testing and subsequent analysis.

A 37-year-old female patient (proband, P3) presented with a 5-month history of visual dimness in both eyes without other discomfort (*e.g.*, photopsia, diplopia, night blindness, eye pain) or systemic symptoms (*e.g.*, headache). She had non-contributory family history. Her medical and social histories were unremarkable. Although subjectively declined, the best corrected visual acuity (BCVA) remained 1.0 and 0.4 in right and left eye, respectively. Color vision was normal. The intraocular pressure was 15 mm Hg bilaterally. There was no anterior chamber inflammation or significant pathologic changes observed in the anterior segments of each eye. The pupils were reactive in both eyes without obvious irregularity or afferent pupillary defects. The vitreous was clear in both eyes, the discs were healthy, the retinal vessel caliber was normal, and the pars plana was clear. Neither of the eyes had evident abnormalities in the fundus except cystoid macular edema (CME) at the posterior pole (Figure 1). Spectral domain optical coherence tomography showed cystoid spaces involving all the retinal layers in both eyes (Figure 1). Autofluroscence of both eyes showed very faint hyperautofluorescence surrounding the fovea, including the posterior pole extending within the arcades (Figure 2). There was no evidence of abnormal hyperfluorescence at the level of the retinal pigment epithelium. Fluorescein angiography (FA) showed normal retinal vessels and choroidal fluorescence in the early arterial phase; in the late stages of FA the well-described flower-like pattern of CME was noted in both eyes (Figure 2). One localized area of exudate was observed within the optic discs in the left eye. Electroretinography (ERG) of each eye revealed normal rod-specific and scotopic maximal flash responses. There were no obvious abnormalities in photopic single flash and 30 Hz flicker response time for each eye.

The family history of this patient was remarkable. She was the second child born to non-consanguineous Chinese parents. Her mother (P1), committed suicide in her thirties. The patient stated that her father (P2) and brother (P4) had a similar history of vision loss. Four family members, including the proband, her father (57 years old), older brother (39 years old), and nephew (9 years old) participated in the study. The clinical characteristics of the four individuals are shown in Table 1. Her brother first noted poor central vision at the age of approximately 30y. He was diagnosed with bilateral CME at the age of 34y. His BCVA was 0.2 and 0.6 in the right and left eye, respectively, and did not experience nyctalopia or photophobia. The anterior segments were clear in both eyes, and the intraocular pressure was normal. There was

Table 1 Clinical characteristics of the proband and family members

Patients	P3	P4	P2	P6
Age (y)	37	39	57	9
Onset (y)	37	34	Middle age	-
BCVA (OD/OS)	1.0/0.4	0.2/0.6	0.2/0.2	1.0/1.0
Fundus	Macular edema	Macular edema	Macular atrophy	Normal
OCT	CME in both eyes	CME in both eyes	Disruption and loss of the ellipsoid zone	Normal
FFA	Petaloid leakage at the fovea in both eyes	Petaloid leakage at the fovea in both eyes	-	-
FAF	Normal	Normal	-	-
Color vision test	Normal	Normal	Normal	Normal

BCVA: Best corrected visual acuity; OD: Right eye; OS: Left eye; OCT: Optical coherence tomography; FFA: Fundus fluorescein angiography; FAF: Fundus autofluroscence; CME: Cystoid macular edema.

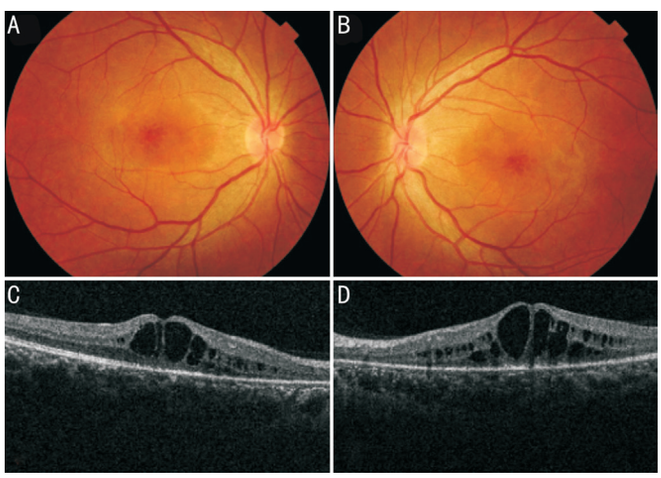

Figure 1 Color fundus photograph of right (A) and left (B) eye showing cystoid macular edema at posterior pole. Spectral domain optical coherence tomography line scan of right (C) and left (D) eye shows schisis at the inner nuclear layer and outer nuclear layer/outer plexiform layer involves the entire macular area.

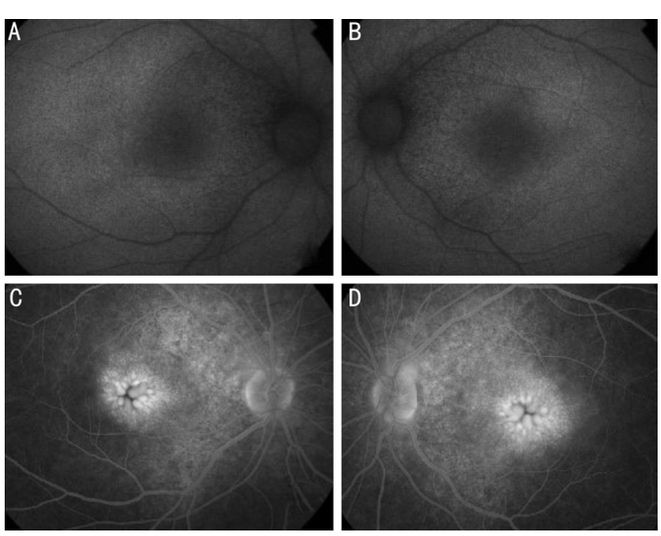

Figure 2 Autofluroscence of right (A) and left (B) eye showing very faint hyperautofluorescence surrounding the fovea involving the posterior pole extending within the arcades. Fundus fluoresce in angiography latephase of right (C) and left (D) eye showing very petaloid hyperfluorescence at the fovea, note the hyperfluorescence of the area around the disks. The retinal pigment epithelial has an indistinct granular hypopigmented changes.

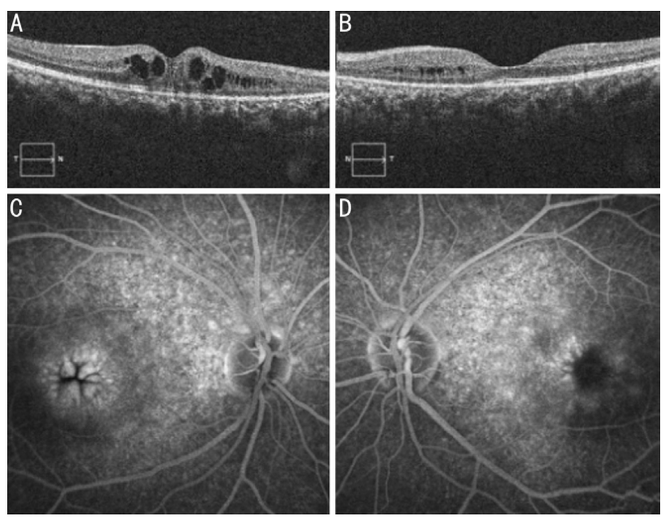

Figure 3 Spectral domain optical coherence tomography showed cystoid spaces in both eyes (A: right eye; B: left eye). Fluorescein angiography study demonstrating the typical petalloid pattern observed in cystoid macular edema (C: right eye; D: left eye).

no evidence of abnormalities, such as uveitis, vitreous cells, disk edema, and vasculitis. Ophthalmoscopy revealed that both fundi showed a delicate microcystoid macular edema. The refracting media were normal. On his optical coherence tomography image, schisis at the inner nuclear layer and outer nuclear layer/outer plexiform layer involved the entire foveomacular area (Figure 3). FA showed petaloid leakage at the fovea in both eyes (Figure 3). The ERG showed normal dark adapted cone, adapted rod, light adapted, and the 30 Hz flicker response time was also normal for both eyes.

A diagnosis of DCMD was reached based on the history, clinical examination, and imaging findings. The proband's father had a visual acuity of 0.2 in both eyes. His vision had been poor since middle age and was gradually deteriorating. There were no significant pathologic changes observed on slit-lamp biomicroscopy, except mild cataracts in both eyes. Funduscopy showed that both maculae had an atrophic appearance. The disk, vessels, and retinal periphery were normal. Optical coherence tomography revealed disruption

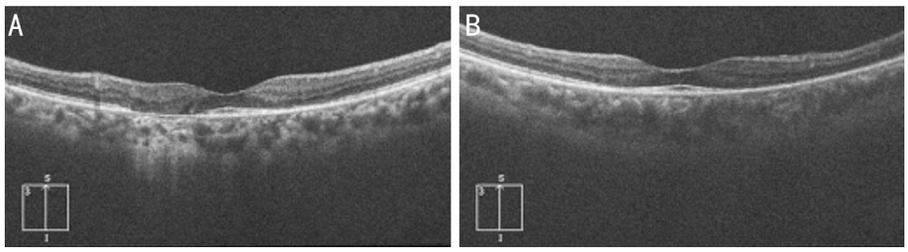

Figure 4 Optical coherence tomography showed disruption and loss of the ellipsoid zone, nodular elevations on retinal pigment epithelium. The photoreceptor inner segment/outer segment junction line was intact at the macula in right (A) and left (B) eye.

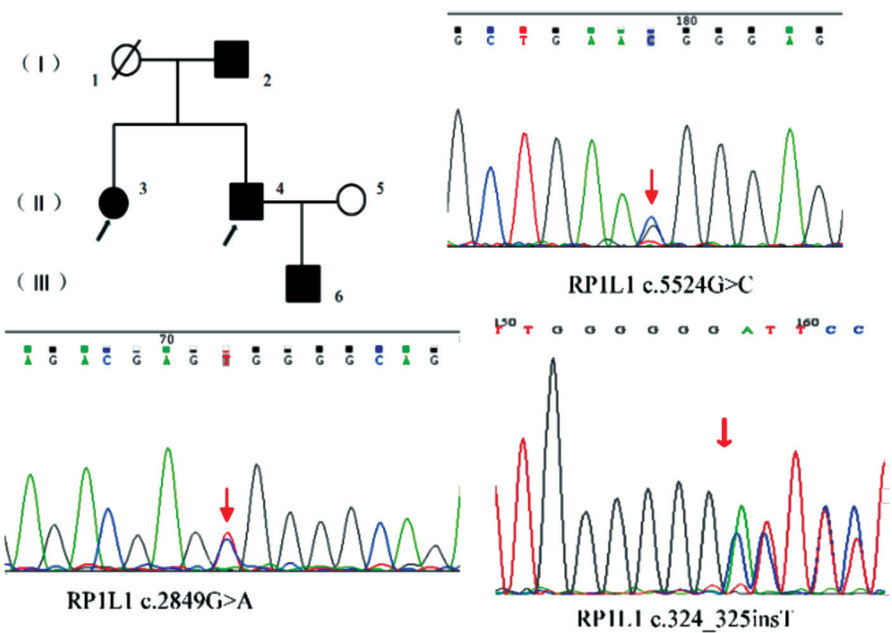

Figure 5 Pedigree and identified mutations of a family with DCMD Affected patient is shown with a solid symbol and unaffected with open symbols. Black arrows: Genotype analysis performed; Squares: Male; Circles: Female; Slashed symbols: Deceased; Red arrows: The position of the mutated nucleotide.

and loss of the ellipsoid zone, nodular elevations and punctate hyperreflectivity on retinal pigment epithelium. The photoreceptor inner segment/outer segment junction line at the macula was intact (Figure 4). More extensive investigation was not possible. The fundus and optical coherence tomography for the nephew (P6; BCVA: 1.0 in both eyes) did not reveal abnormalities. Thus far, no other family members were available for examination.

Informed consent for genetic analysis was provided by the proband and her brother. In our study, we comprehensively screened all 381 genes associated with common eye diseases, identifying three mutations in the *RP1L1* gene. The first mutation was c.5524G>C(p.G1842R) in exon 4, which leads to missense mutation. This mutation is not found in the 1000 Genome, ESP6500, ExAC_ALL, and ExAC_EAS population databases. The second mutation, c.2849G>A, results in an amino acid change from Arg to His at codon 2849. The frequency of this mutation is extremely low in haplotype map samples, and the 1000 Genome, ESP6500, ExAC_ALL, and ExAC_EAS population databases. This mutation has been associated with macular dystrophy. The third mutation is c.324_325insT in exon 2, which leads to a frame shift of the reading code box, encoding proteins from 29th Pro frame-shift mutations. The proband's brother carried the same heterozygous mutation located in the *RP1L1* gene, which was identified through Sanger sequencing (Figure 5). Thus, the transmission pattern in this family was identified as autosomal dominant. Unfortunately, blood samples from her father and nephew were not available.

DISCUSSION

DCMD is an inherited autosomal dominant disease causing an early onset of cystic edema in the posterior pole of the eye. Pinckers *et al*[1] first described the retinal functinon in DCMD, while Saksens *et al*[2] reported the clinical features and long-term follow-up outcome of the disease. In many different hereditary macular dystrophies, CME exhibits a specific pattern of presentation. Roy *et al*[3] described the multimodal imaging features in a case with DCMD. In the present article, we report a family affected by this dystrophy and note its clinical characteristics. We performed genetic testing and

comprehensive mutation analysis, and demonstrated that the *RPIL1* gene may be responsible for the retinal phenotype.

This is a case of a female patient who had bilateral visual loss and remarkable early onset of CME in her 30 years. Her father and brother had a history of bilateral visual loss. Her brother having similar fundus findings. The brother and sister had CME at the posterior pole. Otherwise, there were no evident abnormalities in the fundus. Spectral domain optical coherence tomography revealed cystoid spaces. FA showed the typical characteristics of petaloid hyperfluorescence leakage. The ERG was normal.

Several other diagnoses with early-onset CME should be considered in this clinical setting, such as anterior, intermediate and posterior uveitis[4], retinal vascular disease, intra-ocular surgery history, vitreo-macular traction syndrome, age-related macular degeneration, following cataract extraction, choroidal tumors, toxic retinopathy, X-linked juvenile retinoschisis (XLRS), and retinitis pigmentosa.

The patient had no history of uveitis. Peripheral fundus examination was performed, and biomicroscopy showed that the anterior vitreous was clear. There was no evidence of pars planitis and posterior choroiditis. Several vascular retinal abnormalities have been related to the development of CME (*e.g.*, Coat's disease, central or branch retinal vein occlusion[5], diabetic retinopathy, and perifoveal retinal telangiectasis). The patient did not have an underlying systemic disorder that could predispose her to ocular retinal vascular occlusion or inflammation. Specifically, there were no clinical signs of retinal ischemia or neovascularization. Choroidal tumors, such as choroidal hemangioma and choroidal melanoma, are occasionally associated with CME. There was no evidence of choroidal tumors. Various retinal toxicities associated with CME have been described for agents such as tamoxifen, nicotinic acid, and epinepherine. This condition is reversible and the macular cyst will resolve following the cessation of drug intake[6]. The patient denied using any medication, and did not mention vitreo-retinal traction or prior intra-ocular surgery.

XLRS, which is inherited in an X-linked pattern compared with DCMD, is frequently diagnosed prior to school age, indicating a juvenile onset. The XLRS is marked by the typical presence of a spoke-wheel pattern in the macula of patients aged <30y. The cystoid spaces are mainly situated in the inner and outer nuclear layers, without characteristic fluorescein leakage into the cystoid schisis cavities, as shown on FA[7]. The distinctive ERG symbol is a 'negative' ERG caused by a bright flash of light in the dark-adapted retina, in which the a-wave is larger than the b-wave as opposed to DCMD. Retinitis pigmentosa should also be considered[8]. Patients with retinitis pigmentosa exhibit bone-spicule pigmentary changes, arteriolar attenuation in the early stages of the disease and early experience of night blindness in contrast to those with DCMD.

The hallmark of family history is that both the older brother and father of the proband had poor vision. The presence of typical clinical features led to the diagnosis of DCMD. Thus far, there are no effective treatments for DCMD. Intramuscular long-acting octreotide acetate appeared effective in the stabilization of visual acuity[9]. The later stages of DCMD manifest as macular atrophy. The progression of the disease is accompanied by reduction in the cystic spaces, giving rise to chorioretinal atrophy with subsequent loss of vision. The patient's father may be an evolution of DCMD.

DCMD is an autosomal dominantly inherited condition. However, thus far, the related genes and mutations have not been identified. Previous linkage analysis showed that DCMD is associated with the interval D7S493 to D7S526 at 7p15-p21[10-11]. We analyzed the haplotypes at the DCMD locus, and a novel heterozygous *RP1L1* mutation was identified in this patient.

The human *RP1L1* gene is encoded in four exons that span 50 kb on chromosome 8p[12]. *RP1L1* has the highest sequence similarity to *RP1*. Mutations in the *RP1L1* gene are linked to autosomal dominant occult macular dystrophy[13]. The length of *RP1L1* mRNA is >7 kb, and the specific length varies among individuals due to the presence of several length polymorphisms. The size of the protein encoded by *RP1L1* with a minimal length of 2400 amino acids is predicted to be 252 kDa. Immunohistochemistry has shown that the RP1L1 protein seems to be specific to photoreceptors and the expression of RP1L1 protein is limited to the retina[14]. Research confirmed that *RP1L1* was conserved in distant vertebrates. Several putative pathogenic variants of the *RP1L1* gene (*i.e.*, p.R45W[15], p.Arg.45Trp[15], p.S1199C[15], p.Gln2311Pro[16], p.Asp1425His[16], p.Ser676Cyss[16], and p.W960R[13]) have been reported in sporadic cases or families. In this patient, a new *RP1L1* mutation (c.5524G>C, c.2849G>A in exon 4, c.324_325insT in exon 2) was identified. The present study demonstrates that *RP1L1* mutation is responsible for the development of DCMD; mutations in those codons may lead to harmful effects. This study provides guidance to clinicians for the management and prognosis of patients, and deepens our understanding of the genetic basis of DCMD.

Our study has a number of limitations. Our findings revealed a case of a patient with DCMD carrying a novel heterozygous *RP1L1* mutation. It is likely that heterozygous mutations of the *RP1L1* gene are responsible for the development of DCMD. However, thus far, we have only detected this mutation in one family. Therefore, we cannot rule out the possibility that other causative genes may be involved in this process.

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