김형민 석사 학위논문

정상 안저를 보이는 한국인의 황반이상증에 대한 임상적 및 유전적 특징

Clinical and Genetic Characteristics of Korean Macular Dystrophy Patients with Normal Fundus Appearances

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서울대학교 대학원

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지도교수 박규형

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위 원 장 (인)

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Abstract

Clinical and Genetic Characteristics of Korean Macular Dystrophy Patients with Normal Fundus Appearances

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Purpose: To investigate the clinical and genetic characteristics of Korean macular dystrophy patients with normal fundus appearances.

Methods: Twenty-one patients with macular dystrophies with normal fundus appearances were evaluated. Exome sequencing targeting 204 candidate genes of inherited retinal diseases and direct Sanger sequencing were performed. Examinations including best-corrected visual acuities (BCVA) and retinal morphologic abnormalities analyzed by spectral-domain optical coherence tomography (SD-OCT), electroretinogram (ERG), and multifocal ERG were performed.

Results: The median age at the initial examination (n=21) and the final visit (n=13) were 19 years with a range of 5 to 71 years, and 19 years with a range of 13 to 49 years. Genetic mutations in macular dystrophies with normal fundus appearances had *RP1L1, CNGA3*, *GNAT1, GNAT2*,

GUCY2D, *CACNA1F*, and *PROM1*. There were significant negative correlations between the BCVA and external limiting membrane-retinal pigment epithelium thickness (ERT) at the initial examination and final visit, and BCVA and central retinal thickness (CRT) at the initial examination. Retinal structural features based on OCT findings were documented as foveal bulge and notable changes in ellipsoid zone (EZ) and interdigitation zone (IZ).

Conclusions: In this study, unique pathogenic genetic mutations along with retinal morphologic changes were identified and correlated to the visual function in Korean macular dystrophy patients with normal fundus appearances. Further studies with larger number of macular dystrophy subjects should be investigated.

Keywords: macular dystrophy ; sequencing ; normal fundus ; OCT ; visual acuity

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Contents

Introduction

Macular dystrophies are a group of inherited retinal diseases (IRD) that cause devastating visual loss, characterized by bilateral, relatively symmetrical macular abnormalities with dysfunction of neural retina or retinal pigment epithelium (RPE) which significantly impair central visual function.[1] There are different types of macular dystrophies, such as occult macular dystrophy (OMD), cone dysfunction syndrome (CDS), cone dystrophy (CD), cone-rod dystrophy (CRD), Stargardt disease, and vitelliform macular dystrophy.[2] These macular dystrophies are known to have various kinds of genetic mutations and present phenotypic heterogeneities, thus classification and differential diagnosis of macular dystrophies are demanding.

OMD is a representative macular dystrophy known as Miyake's disease, and features normal fundus appearance, normal fluorescein angiogram and full-field electroretinogram (ERG), whereas abnormal multifocal electroretinogram (mfERG) on macular function.[3-5] *RP1L1* gene mutations were reported previously as a pathogenic source of OMD[6], and spectral-domain optical coherence tomography (SD-OCT) revealed the structural deformities in the photoreceptor layer.[7-13] Abnormal cone cell diseases (CDS, CD, CRD) show representative absent cone ERG responses, poor visual

acuity and color vision, and various spectrum of fundus appearances, from normal to central foveal RPE atrophy.[14-16] Inherited cone cell diseases can be classified based on the 1) disease progression : the stationary cone disorders (CDS) are mostly congenital or early-infantile onset and limited to pure cone dysfunction, whereas progressive cone dystrophies are diagnosed at later onset and usually involve rod photoreceptors, and 2) extent of photoreceptor cell involvement : cone dystrophies are confined to cone cells whereas cone-rod dystrophies involve both cone and rod cells.[16, 17] Approximately 30 gene mutations were reported to induce cone dystrophies, including *GUCY2D*, *PROM1*, *ABCA4*, *CNGA3*, and much more, which influence the photoreceptor functions of phototransduction, intraflagellar transport, and neurotransmitter release.[17-21]

Macular dystrophies as described above could present normal fundus appearances, thus multimodal imaging and electrophysiologic examinations should be performed for the diagnosis.[1, 2, 7, 8, 10, 12, 13, 22, 23] Recent development of SD-OCT enabled clinicians to demonstrate retinal structural abnormalities, specifically photoreceptor layers, and correlate to the visual function in inherited retinal disorders. Ahn et al. studied the genotype-phenotype correlation in patients with OMD, and proposed that the *RP1L1* gene mutations are related to the outer retinal morphologic features.[10, 11] Numerous researchers suggested that the SD-OCT findings in cone dystrophy patients may aid the diagnosis in accordance with electrophysiologic examinations.[22-24] Sundaram et al. documented

the genetic variants and OCT-based structural deformities in achromatopsia.[25] Latest study by Nakamura et al. investigated the clinical stages of OMD and photoreceptor defects based on OCT findings, and suggested the negative correlations between the duration of OMD, visual acuity and retinal thickness.[13] However, there are no definite prior investigations which compare the morphologic features among the macular dystrophies with various genetic mutations and normal fundus appearances.

Therefore, in this study, we selected the twenty-one macular dystrophy patients with normal fundus appearances who had undergone genetic sequencing, and attempted to analyze the retinal morphologic changes using SD-OCT, and correlate to the visual function. Subsequently, in the clinical settings, we could estimate the pathogenic genes in the macular dystrophy patients with normal fundus appearances and characteristic morphologic features.

Materials and Methods

Patients and Clinical Data Collection

From the 40 patients who were diagnosed as macular dystrophy and underwent genetic analysis, we selected twenty-one Korean macular dystrophy patients with normal fundus appearances confirmed by fundus photography who initially visited the Department of Ophthalmology of Seoul National University Bundang Hospital between January 2006 and December 2015 (a 10-year period). Thirteen patients visited the clinic on a regular basis and the final follow-up was done till July 2020. Approval of this study was obtained from the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-2008/628-107), and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients before genetic analysis.

All subjects underwent full thorough ophthalmic examinations including best-corrected visual acuity (BCVA), fundus photography, fluorescein angiogram (FA), full-field standard ERG, and mfERG (VERIS II; ElectroDiagnostic Imaging 45, Inc., San Francisco, CA), and SD-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany). Full-field ERG was performed with procedures with reference to the International Society for Clinical Electrophysiology

of Vision (ISCEV)[26], and mfERG was undergone using 61 scaled hexagons with procedures conforming to ISCEV guidelines.

The diagnostic criteria for macular dystrophy are as follows: for occult macular dystrophy (OMD), the diagnosis was made based on no abnormal findings on fundus photography, fluorescein angiography (FA), and full-field electroretinogram (ERG), whereas reduced foveal multifocal ERG (mfERG) and progressive visual acuity decrease; for inherited cone cell diseases (CDS, CD, CRD), the diagnosis was made based on the symptoms of visual acuity reduction, photophobia and poor color vision with accompanying profound loss of cone cell response in full-field ERG.

The SD-OCT analyses were done as the categorization of morphological abnormalities and measurement of retinal thickness. Deformities of central foveal area and photoreceptor layer were classified according to presence of foveal bulge (small arc-like protrusion), degree of interdigitation zone (IZ) defects (normal or extinguished), and degree of ellipsoid zone (EZ) defects (normal, blurred, and disrupted), as proposed by Japanese researchers.[12, 13] The quantitative data were acquired by measuring the retinal thickness manually by two retinal specialists (HMK and KSJ) independently, and the average of the two measurements was used for the statistical analyses. The retinal thickness profiles included the central retinal thickness (CRT), defined as the distance between the inner retinal surface and inner margin of the retinal pigment epithelium (RPE) at the foveola. Since the photoreceptor layers of

IZ and EZ in macular dystrophy patients were deformed, we measured the distance between the external limiting membrane (ELM) and inner margin of the RPE to evaluate the photoreceptor segment accurately, named as ELM–RPE thickness (ERT).

Genetic Analyses

Comprehensive custom gene panel of 204 known and candidate genes linked to inherited retinal disorders (IRD) were performed for genetic analyses as previously described in our reports.[27, 28] A total of 204 genes were covered for all coding exons, 5′ and 3′ untranslated regions, and each exon flanked alternative splicing areas. The construction of pre–capture libraries (Illumina, Inc., San Diego, CA, USA) and capture process (Roche NimbleGen, Madison, WI, USA) was performed according to the manufacturer's protocols. The captured libraries were sequenced using Illumina HiSeq 2000 using the paired–end (2100 bp) program (Illumina, Inc.).

Burrows–Wheeler Aligner was used to align the sequence reads in the human hg19 reference genome. The variants were annotated by GATK packages, SAMtools, and Dindel, the detected variants were annotated by ANNOVAR, and then the overall analyses were made by NextGENe software (SoftGenetics, State College, PA, USA). The 1,000 Genome database, dbSNP137, and the National Heart, Lung and Blood Institute (NHLBI) Exome Sequencing database were used to distinguish the common variants. The Human Gene Mutation Database professional database was utilized to find

out the known pathogenic mutations. The variants were selected in case they were not reported in the 1,000 Genome, dbSNP, or NHLBI Exome Sequencing databases or had low frequencies (< 1%) in the Korean population, and less than 30% heterozygous reads or less than 80% homozygous reads were excluded. Direct Sanger sequencing covering whole coding sequences (4 exons) and all splicing sites of *RP1L1* were performed using target-specific primers, which are previously reported (references).

The clinical importance of each variant was classified in regards to the latest recommendations of the American College of Medical Genetics and Genomics (ACMG) on standards for interpretation and reporting of sequence variations: pathogenic, likely pathogenic, uncertain significance, benign, and likely benign variant.[29, 30] All the variants reported in this article were confirmed by Sanger sequencing.

Statistical Analyses

In the study, we described the demographics and clinical features of each macular dystrophy patient along with genetic profiles and retinal morphologic findings and retinal thickness data from the SD-OCT were documented. Clinical characteristics such as age at initial examination, age at last visit, duration from first to last visit, sex, BCVA were analyzed. Specifically, BCVAs were converted to logarithmic minimum angle of resolution (logMAR) for analysis.

The overall statistical analyses in this study were undergone using SPSS software version 25.0 for Windows (SPSS, Inc., Chicago, Illinois, USA), and a P value less than 0.05 which were adjusted by Bonferroni method indicated a statistically significant difference. The association between BCVA and retinal thickness (CRT and ERT) at the initial examination and final visit were calculated by Spearman's rank-order correlation analyses.

Results

Detailed demographics of the 21 Korean macular dystrophy patients with normal fundus appearances are presented in Table 1. The age at the first examination, the age at the last visit, follow-up duration period, sex, initial and final BCVA, genetic profiles and confirmed diagnosis were documented in all 21 cases. The median age at the first examination was 19 years with a range of 6 to 71 years (mean ± SD, 24.2 ± 19.7 years), and the median age at the final visit was 19 years with a range of 13 to 49 years (mean ± SD, 26.5 ± 9.9 years). Only 13 patients (62%) visited the clinic on a regular basis, and the median follow-up duration period was 10 years with a range of 6 to 13 years (mean ± SD, 9.6 ± 2.1 years).

Genetic mutations and confirmed diagnosis are also presented in Table 1. Detected mutations in 3 cases of cone dystrophy are *CNGA3*, *GNAT2*, and *GUCY2D*, 4 cases of cone dysfunction syndrome are GNAT1 and *RGS9BP*, 3 cases of cone-rod dystrophy are *CACNA1F*, *GUCY2D*, and *PROM1*, and 11 cases of occult macular dystrophy are all *RP1L1*. The representative multimodal images of cone dystrophy, cone dysfunction syndrome, and occult macular dystrophy patients were described in Figure 1, 2, and 3,

including initial and final fundus photography, SD-OCT, ERG, and multifocal ERG.

The initial and final BCVA of both right and left eye are presented in logMAR values in Table 1. In addition, initial and final central retinal thickness (CRT) and ELM-RPE thickness (ERT) were measured at the central foveal area, and documented in Table 2. SD-OCT findings were also classified according to the presence of foveal bulge and deformities in the interdigitation zone (IZ) and ellipsoid zone (EZ), as depicted in the methods. Figure 4 visualizes the characteristic SD-OCT morphologic features. In most macular dystrophy cases, there were structural changes in IZ and EZ found in SD-OCT, while all of the cone dysfunction syndrome (CDS) cases showed normal IZ and EZ. The overall scatter plots of BCVA in logMAR units and CRT, ERT were described in Figure 5. The associations between BCVA at the first examination and the CRT (right eye, $R^2 = 0.284$, Rho = −0.591, $P = 0.005$ (Fig. 5A) ; left eye, $R^2 = 0.303$, Rho = −0.616, $P = 0.003$ (Fig. 5B)) and ERT (right eye, $R^2 = 0.326$, Rho = −0.647, $P = 0.002$ (Fig. 5C) ; left eye, $R^2 = 0.251$, Rho = −0.471, $P = 0.031$ (Fig. 5D)), and BCVA at the final visit and the ERT (right eye, $R^2 = 0.266$, Rho = −0.724, $P = 0.005$ (Fig. 5E) ; left eye, $R^2 = 0.385$, Rho = −0.654, $P = 0.015$ (Fig. 5F)) showed significant negative correlations (Spearman's rank-order correlation), whereas BCVA at the final visit and the CRT were not statistically significant. Moreover, there were no correlations between the age of first examination, final visit, duration period and the BCVA, CRT, and ERT.

Discussion

Our study investigated the clinical and genetic characteristics of twenty-one Korean macular dystrophy patients with normal fundus appearances. Various disease entities such as cone dysfunction syndrome (CDS), cone dystrophy (CD), cone-rod dystrophy (CRD), occult macular dystrophy (OMD) showed normal fundus, and numerous genetic mutations were identified. Moreover, the retinal morphologic defects in photoreceptor layer and retinal thickness were associated with the visual acuities.

We figured out different unique genetic mutations of macular dystrophies with normal fundus appearances. Pathogenic genes are summarized as follows : *CNGA3*, *GNAT2*, *GUCY2D*, *RGS9BP*, *CACNA1F*, *GUCY2D*, *PROM1*, *GNAT1*, and *RP1L1*. Previously, no definite clinical studies have been performed to evaluate the phenotype-genotype correlations of macular dystrophies with normal fundus appearances in Korean patients.

Hereditary macular dystrophy is a heterogenous disease entity comprised of various inherited retinal disorders (IRDs).[1] Retinitis pigmentosa (RP) is a representative IRD with deteriorating visual dysfunction and bone-spicule pattern in the fundus examination.[1]

Other famous IRD is cone dystrophy and related cone dysfunction diseases, which is characterized by the loss of cone cells, leading to poor color vision, sensitivity to bright light, and gradual visual loss.[14, 15] Additionally, mostly diagnosed in East Asians, uncommon IRD of OMD has been studied, which is characterized by the progressive visual decline with normal fundus and ERG pattern.[3, 4] Moreover, other diseases such as Stargardt disease and vitelliform macular dystrophy are investigated. In most macular dystrophy cases, abnormal fundus with distinct lesions are observed, however, normal fundus appearances could be shown not uncommonly, which make the clinicians being confused with the differential diagnosis. Therefore, multimodal imaging techniques such as SD-OCT are performed to identify the morphologic defects of the macular area accurately.[10, 11, 16, 24]

Birch et al. have reported that the changes in photoreceptor layer and outer nuclear layer evaluated by SD-OCT in macular dystrophy were associated to the visual sensitivity.[31] Hood et al. proposed that the cone dystrophy and achromatopsia patients showed structural defects in ellipsoid zone than normal controls.[32] Previous articles published by our group which studied occult macular dystrophy and cone dystrophy patients suggested that the qualitative features of SD-OCT could be categorized by the severity of photoreceptor layer deformities (IZ, EZ defects).[7, 10, 11, 24] Quantitatively, the photoreceptor layer thickness was correlated to the BCVA in OMD patients, and central retinal thickness was correlated to the BCVA in cone dystrophy patients. Nakamura et al. also suggested that in

OMD patients, there were correlations between BCVA and retinal thickness.[13] As described in previous studies, we documented the SD-OCT findings by the presence of foveal bulge, morphologic changes of IZ (normal and distinguished), and EZ (normal, blurred, and disrupted).[10, 12, 13, 22, 23, 25] Then, we measured the CRT and ERT, and concluded that the BCVAs at the first examination and final visit are correlated to the CRT and ERT in both right and left eyes, similar to the prior investigations.[12, 13]

Furthermore, previous studies have revealed the numerous genetic mutations and novel variants in different types of macular dystrophy and associations to the clinical features of visual acuity and SD-OCT findings.[6, 15, 17-19, 21] Our prior report focused on the genetic diagnosis of 38 Korean inherited retinal disorder patients, and pathogenic mutations of *RHO*, *RP1*, *EYS*, *PDE6B*, *USH2A*, *ABCA4*, and et cetera were identified.[28] Novel variants of ABCA4-associated retinopathy were discovered in our Korean macular dystrophy cohort, and various phenotypes and disease severities were investigated.[33] According to our occult macular dystrophy cohort patients, clinical phenotypes considered as visual function and photoreceptor disruption were associated to the different genotypes of RP1L1 gene mutations, grouped as c.133C>T, p.R45W, novel variants, and no mutation.[11] Gill et al. reviewed the cone and cone-rod dystrophies regarding the genotype-phenotype correlations, and specific findings of *GUCA1A*, *PRPH2*, and *ABCA4*-associated CD/CRD were described.[34] Fundoscopy findings could be varied, from typical bull's eye maculopathy-like appearance with

retinal flecks to mild RPE disturbance, and SD-OCT also showed varied degree of photoreceptor disruption.

In this study, we have some limitations to discuss. First of all, there were only twenty-one confirmed cases of genetic profiles in heterogenous disease entities of macular dystrophies. Therefore, we could not separate each inherited retinal disorders for analysis. Larger subject enrollment and additional genetic sequencing should be followed. Second, there were only thirteen patients with regular follow-up, thus correlation results between BCVA at the final visit and retinal thickness (CRT and ERT) should be accepted carefully. Furthermore, our data were obtained from single ethnic group of Korean, so it may not be applicable to other ethnic groups. Lastly, the age of first examination does not exactly match the symptom onset of disease, therefore initial BCVA may not determine the patient's baseline visual function of macular dystrophy.

In conclusion, we have demonstrated the clinical and genetic characteristics of Korean macular dystrophy patients with normal fundus appearances, and we suggested that the BCVAs are negatively correlated to the CRT and ERT, except final BCVA and CRT. Comprehensively, characteristic normal fundus appearances, retinal morphologic changes identified by SD-OCT and retinal functional changes presented by full-field and multifocal ERG, along with the genetic information of identified pathogenic genes could assist clinicians to diagnose various types of macular dystrophies easily. Further investigations should be followed to focus on the

each macular dystrophy disease entities with larger population.

Table 1. Summary of Genetics and Clinical Characteristics of Macular Dystrophy with Normal Fundus Appearance in 21 Patients

No.	Diagnosis	Sex	Gene	Allele	Age at exam (yr)	Age at last visit (yr)	Duration from exam to last visit (yr)	Initial BCVA (logMAR)		Final BCVA (logMAR)	
								OD	OS	OD	OS
1	CD	M	CNGA3	c.[553C>G]+[848G>A] p.[L185V]+[R283Q]	6	19	13	0.7	1.0	0.8	1.2
2	CD	F	GNAT2	c.[730_743del]+[481C>T] p.[H244Sfs]+[R161X]	11	21	10	0.7	0.7	0.8	0.8
3	CD	M	GUCY2D	c.[2513G>A] p.R838H	34	40	6	0.4	0.4	0.5	0.5
4	CDS	M	GNAT1	c.C753A p.N251K	9	–	–	0.4	0.4	–	–
5	CDS	M	RGS9BP	–	8	19	11	0.2	0.2	0.2	0.2
6	CDS	F	RGS9BP	–	10	21	11	0.4	0.4	0.4	0.4
7	CDS	F	RGS9BP	c.[211G>T]+[614_615insG] p.[E71X]+[G205delinsGLfs]	12	23	11	0.4	0.4	0.4	0.4
8	CRD	M	CACNA1F	c.4049G>A p.G1350D	5	13	8	0.4	0.4	0.5	0.5
9	CRD	F	GUCY2D	c.[2649delT]+[2891G>T] p.[F883Lfs]+[R964L]	19	26	7	0.1	0.1	0.2	0.2

10	CRD	M	PROM1	c.1117C>T p.R373C	30	38	8	0.1	0.1	0.2	0.2
11	OMD	M	RP1L1	c.133C>T p.Arg45Trp	6	–	–	1.0	1.0	–	–
12	OMD	M	RP1L1	c.133C>T p.Arg45Trp	10	–	–	0.1	0.1	–	–
13	OMD	M	RP1L1	c.133C>T p.Arg45Trp	10	18	8	0.7	0.7	0.8	0.8
14	OMD	M	RP1L1	c.133C>T p.Arg45Trp	19	27	8	0.6	0.6	0.7	0.7
15	OMD	M	RP1L1	c.133C>T p.Arg45Trp	19	31	12	0.4	0.4	0.5	0.5
16	OMD	M	RP1L1	c.133C>T p.Arg45Trp	28	–	–	0.9	0.9	–	–
17	OMD	F	RP1L1	c.133C>T p.Arg45Trp	43	–	–	0.8	0.7	–	–
18	OMD	M	RP1L1	c.133C>T p.Arg45Trp	37	49	12	1.2	1.2	1.5	1.5
19	OMD	M	RP1L1	c.133C>T p.Arg45Trp	51	–	–	0.2	0.2	–	–
20	OMD	M	RP1L1	p.Ser1199Cys	71	–	–	0.9	0.9	–	–
21	OMD	M	RP1L1	c.133C>T p.Arg45Trp	70	–	–	0.3	0.3	–	–

BCVA, Best-Corrected Visual Acuity ; logMAR, logarithm of the Minimum Angle of Resolution
CD, Cone Dystrophy ; CDS, Cone Dysfunction Syndrome ; CRD, Cone-Rod Dystrophy ; OMD, Occult Macular Dystrophy

Table 2. Summary of SD-OCT features of Macular Dystrophy with Normal Fundus Appearance in 21 Patients

No.	Diagnosis	SD-OCT Findings			Initial CRT (μm)		Final CRT (μm)		Initial ERT (μm)		Final ERT (μm)	
					OD	OS	OD	OS	OD	OS	OD	OS
		Foveal bulge	IZ	EZ								
1	CD	(−)	Extinguished	Blurred	174	170	182	180	70	66	69	63
2	CD	(+)	Normal	Blurred	214	217	219	218	95	102	94	96
3	CD	(−)	Extinguished	Blurred	131	134	130	133	92	87	90	82
4	CDS	(−)	Normal	Normal	196	211	−	−	105	94	−	−
5	CDS	(−)	Normal	Normal	213	217	210	216	100	98	101	106
6	CDS	(+)	Normal	Normal	230	231	225	232	99	96	100	101
7	CDS	(−)	Normal	Normal	243	227	237	226	98	100	100	102
8	CRD	(+)	Extinguished	Blurred	204	198	207	204	97	92	99	96
9	CRD	(+)	Extinguished	Blurred	216	220	210	213	107	104	109	106

10	CRD	(+)	Extinguished	Blurred	198	197	197	184	87	85	89	87
11	OMD	(+)	Extinguished	Blurred	158	160	–	–	93	99	–	–
12	OMD	(+)	Normal	Normal	228	230	–	–	100	109	–	–
13	OMD	(+)	Extinguished	Disrupted	178	183	185	188	92	95	86	91
14	OMD	(+)	Extinguished	Disrupted	192	199	188	182	88	89	81	82
15	OMD	(+)	Extinguished	Disrupted	217	216	201	207	93	96	89	87
16	OMD	(+)	Extinguished	Disrupted	174	179	–	–	85	84	–	–
17	OMD	(+)	Extinguished	Disrupted	142	141	–	–	77	74	–	–
18	OMD	(+)	Extinguished	Disrupted	196	191	191	184	90	94	88	86
19	OMD	(+)	Extinguished	Blurred	194	197	–	–	103	99	–	–
20	OMD	(+)	Extinguished	Disrupted	139	113	–	–	87	64	–	–
21	OMD	(+)	Extinguished	Blurred	249	219	–	–	105	98	–	–

SD-OCT, Spectral-Domain Optical Coherence Tomography
CRT, Central Retinal Thickness ; ERT, ELM (external limiting membrane) - RPE (retinal pigment epithelium) Thickness
CD, Cone Dystrophy ; CDS, Cone Dysfunction Syndrome ; CRD, Cone-Rod Dystrophy ; OMD, Occult Macular Dystrophy
IZ, Interdigitation zone ; EZ, Ellipsoid zone

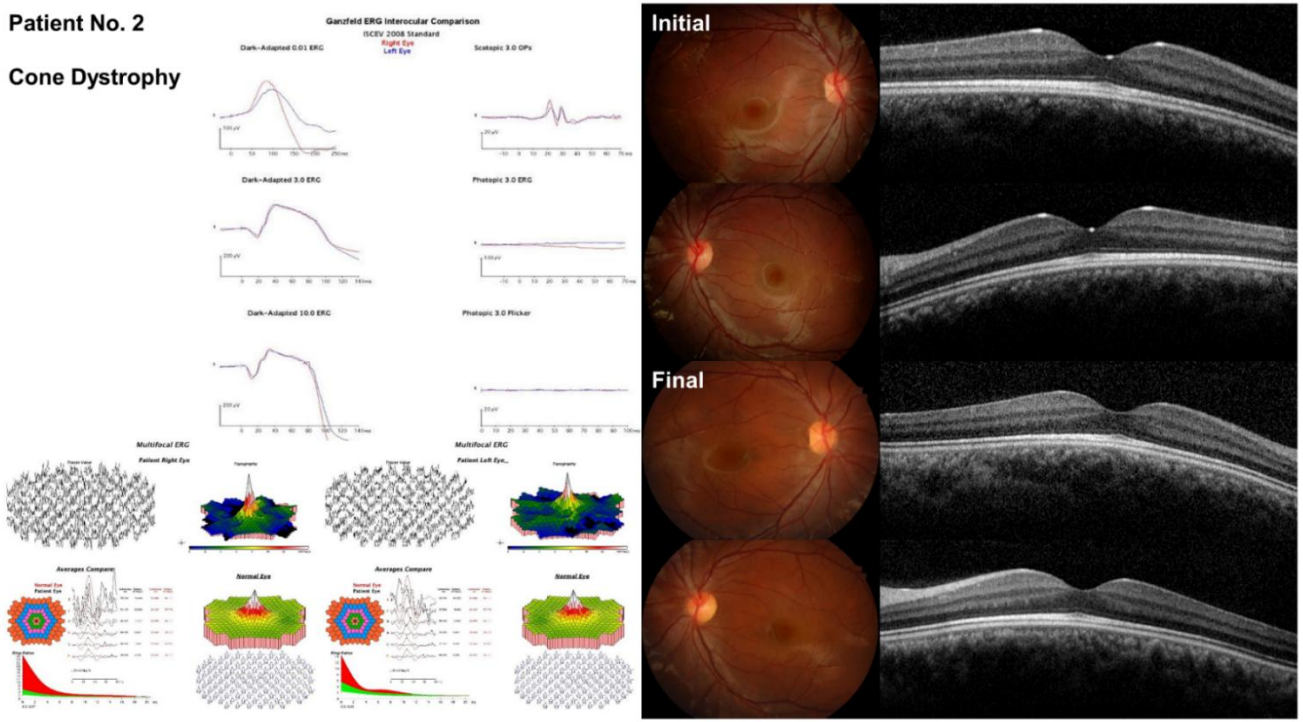

Figure 1. Representative images of cone dystrophy patient (case 2). The patient was diagnosed as CD at age 11, and the last visit was at age 21. *GNAT2* was sequenced as pathogenic gene. ERG, mfERG suggest abnormal cone cell function. Initial and final fundus photography showed normal fundus appearances. SD-OCT features showed positive foveal bulge, normal IZ, and blurred EZ.

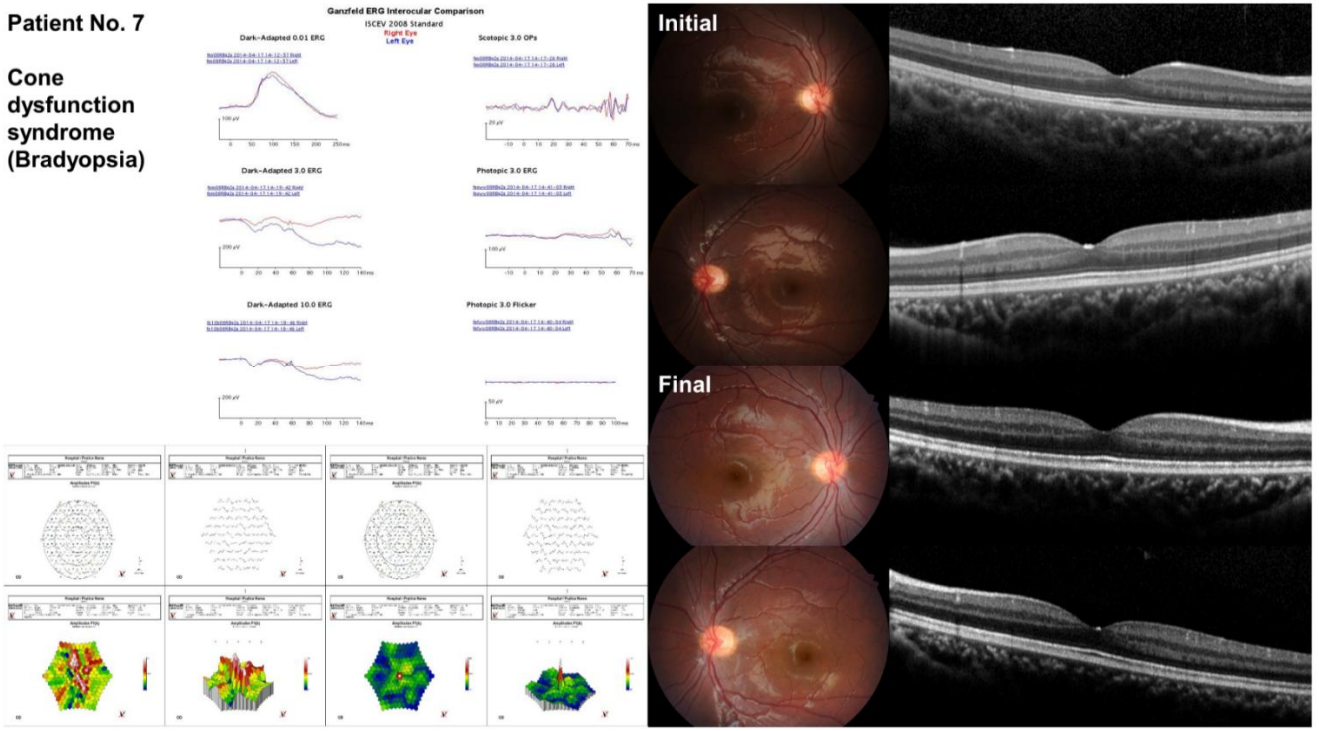

Figure 2. Representative images of cone dysfunction syndrome patient (case 7). The patient was diagnosed as CDS at age 12, and the last visit was at age 23. *RGS9BP* was sequenced as pathogenic gene. ERG, mfERG suggest abnormal cone cell function. Initial and final fundus photography showed normal fundus appearances. SD-OCT features showed negative foveal bulge, normal IZ and normal EZ.

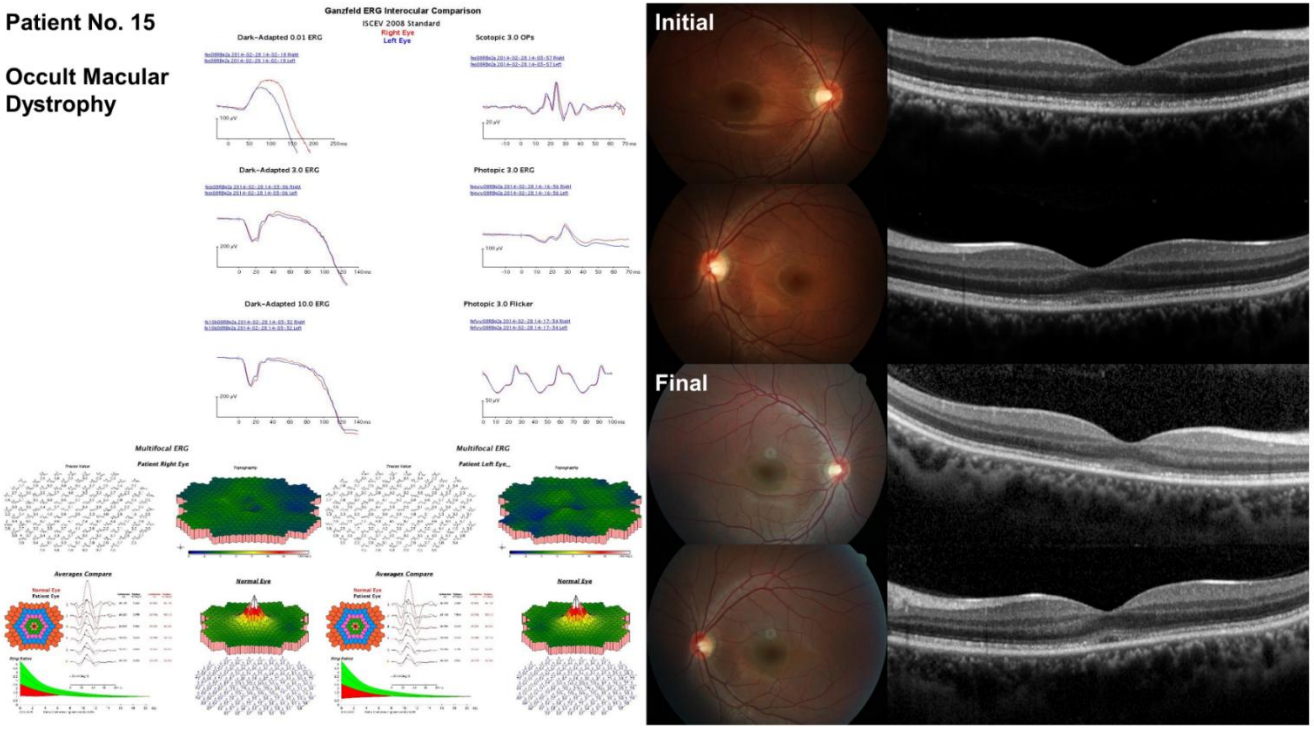

Figure 3. Representative images of occult macular dystrophy patient (case 15). The patient was diagnosed as OMD at age 19, and the last visit was at age 31. *RP1L1* was sequenced as pathogenic gene. ERG, mfERG suggest normal rod and cone cell function. Initial and final fundus photography showed normal fundus appearances. SD-OCT features showed positive foveal bulge, extinguished IZ, and disrupted EZ.

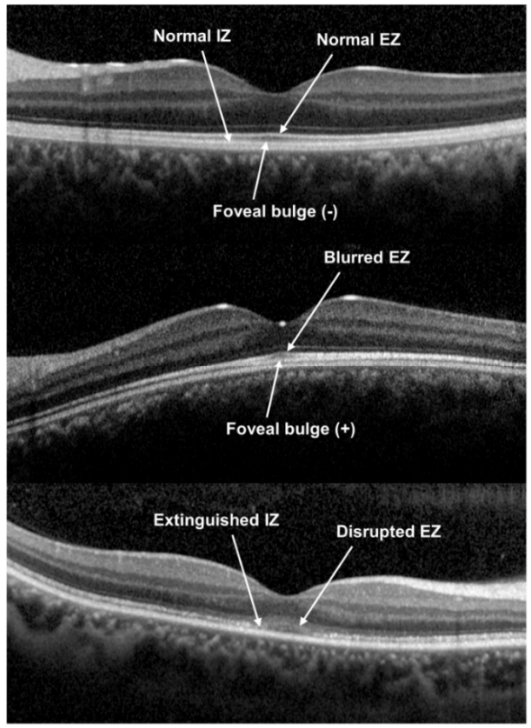

Figure 4. Visualization of characteristic SD-OCT morphologic features in macular dystrophy patients. The presence of foveal bulge, ellipsoid zone (EZ) changes (normal or extinguished), and interdigitation zone (IZ) changes (normal, blurred, or disrupted) were described in each cases, and summarized in Table 2.

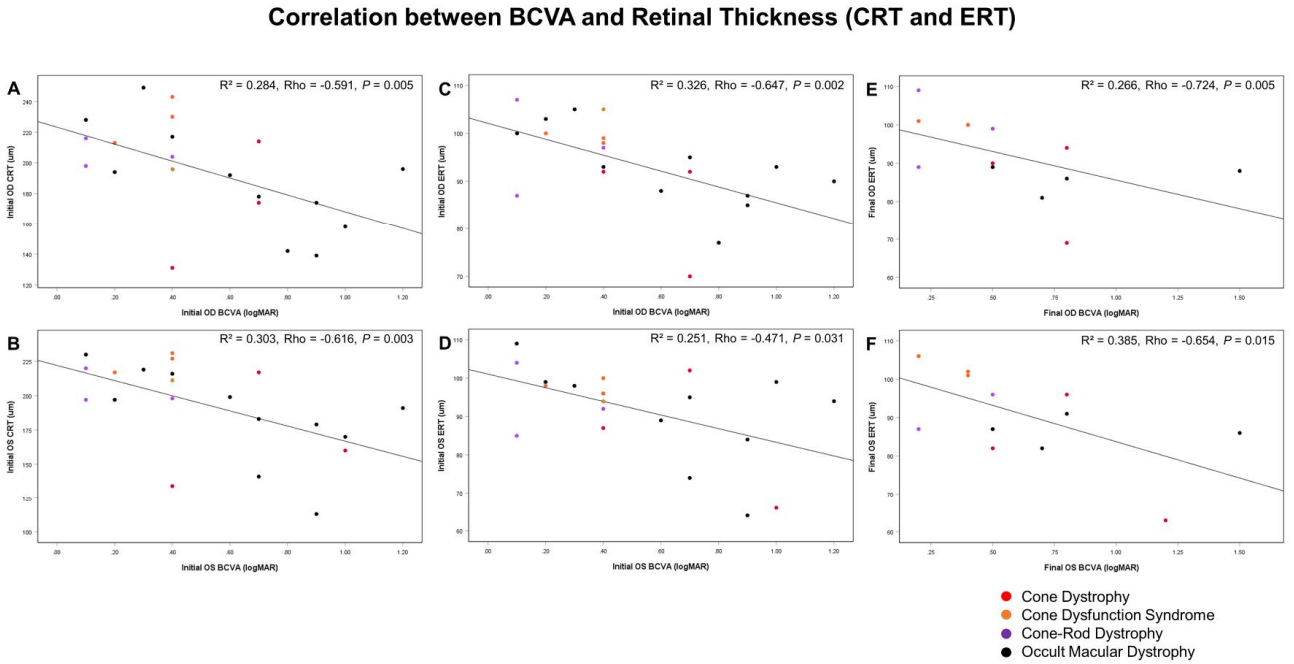

Figure 5. Scatter plots of correlation between best-corrected visual acuities (BCVA, logMAR) and retinal thickness. Central retinal thickness (CRT) and ELM-RPE thickness (ERT) were measured for analyses. Initial BCVA and CRT/ERT were correlated, whereas only final BCVA and ERT was correlated.

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초록

정상 안저를 보이는 한국인의 황반이상증에 대한 임상적 및 유전적 특징

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목적 : 정상 안저를 보이는 한국인 황반이상증 환자의 임상적 및 유전적 특징을 조사한다.

방법 : 정상 안저를 보이는 21명의 한국인 황반이상증 환자를 대상으로 유전성 망막질환과 관련된 204개의 후보 유전자를 목표로 하는 exome sequencing과 direct Sanger sequencing을 시행하였다. 임상적인 데이터로는 최대교정시력과 안저검사, 빛간섭단층촬영, 망막전위도검사, 다초점 망막전위도검사를 시행하였다.

결과 : 21명의 초기검사에서 나이 중간값은 19세에 5세부터 71세까지의 범위였고, 그 중 13명의 환자가 정기검사를 시행받았으며 마지막 검사에서 나이 중간값은 19세에 13세부터 49세까지의 범위였다. 정상 안저 소견을 보이는 황반이상증의 유전적인 변이는 RP1L1, CNGA3, GNAT1, GNAT2, GUCY2D, CACNA1F와 PROM1 유전자가 도출되었다. 임상적으로 초기검사에서 최대교정시력과 중심망막두께 및 외경계막-망막상피세포층 두께는 음성적인 연관성이 있었고, 마지막 검사에서도 최대교정시력과 외경계막-망막상피세포층 두께 또한 음성적인 연

관성이 있었다. 빛간섭단층촬영으로 분석한 망막의 구조적인 변화에서는 황반의 변화 및 ellipsoid zone과 interdigitation zone의 변화가 관찰되었다.

결론 : 정상 안저를 보이는 한국인의 황반이상증에서는 특징적인 유전자 변이와 동반된 망막의 구조적인 변화가 관찰되었고, 이는 시력과 연관성이 있었다. 많은 수의 환자를 대상으로 한 추가적인 연구가 필요하겠다.

주요어 : 황반이상증 ; 시퀀싱 ; 정상 안저 ; 빛간섭단층촬영 ; 시력

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