Case Report

The First Case Series of Malattia Leventinese/Doyne Honeycomb Retinal Dystrophy in Türkiye Identified with *EFEMP1* Gene Mutation

Atakan İşbilir[1], Ahmet Güzel[1], Mehmet Kocabey[2], Ahmet Okay Çağlayan[2], Ömer Kartı[1], Ziya Ayhan[1], Ali Osman Saatci[1]

[1]Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
[2]Dokuz Eylül University Faculty of Medicine, Department of Medical Genetics, İzmir, Türkiye

Abstract

This report aims to describe the clinical characteristics of the first Turkish family diagnosed with Malattia Leventinese/Doyne honeycomb retinal dystrophy (ML/DHRD) associated with an *EFEMP1* mutation. Four affected individuals from the same family (one male and three females; aged 25, 51, 53, and 73 years) underwent comprehensive ophthalmological evaluation. The assessment included best-corrected visual acuity, spectral-domain optical coherence tomography (OCT), color fundus photography, and OCT angiography. In addition, genetic analysis for *EFEMP1* mutations was performed. The *EFEMP1* variant was identified in all four patients. Clinical examination revealed numerous drusen-like deposits with a radial distribution in the posterior pole, consistent with the ML/DHRD phenotype. OCT imaging demonstrated subretinal and retinal pigment epithelium alterations, which were more advanced in the 73-year-old female patient. Visual acuity was largely preserved in the youngest patient but markedly reduced in older individuals. This case series describes the first Turkish family with genetically confirmed ML/DHRD. Structural imaging demonstrated progressive macular changes associated with aging, highlighting the value of multimodal imaging in assessing disease course.

Keywords: Doyne honeycomb retinal dystrophy, Malattia Leventinese, *EFEMP1*

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Address for Correspondence: Ali Osman Saatci, Dokuz Eylül University Faculty of Medicine, Department of Ophthalmology, İzmir, Türkiye
E-mail: osman.saatci@deu.edu.tr
ORCID-ID: orcid.org/0000-0001-6848-7239

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Introduction

Malattia Leventinese/Doyne honeycomb retinal dystrophy (ML/DHRD) is a rare autosomal dominant retinal dystrophy. It was first identified in patients living in the Leventina Valley in southern Switzerland, from which it derives its name.[1]

This disease is caused by a defect in the *EFEMP1* (epidermal growth factor-containing fibulin-like extracellular matrix protein 1) gene, which encodes the fibulin-3 protein. It presents in the early stages with radially arranged drusen, while macular atrophy may develop in the advanced stages.[2,3,4,5]

Drusen is the most common finding in age-related macular degeneration (AMD), and ML/DHRD is the inherited macular disease that most closely resembles AMD in terms of clinical features. Aside from the later age of onset, the clinical findings of AMD largely overlap with those of ML/DHRD.[6,7,8]

Here we describe a Turkish family that underwent comprehensive clinical evaluation, revealing four patients with fundus and optical coherence tomography (OCT) findings consistent with ML/DHRD. Subsequent genetic analysis identified an *EFEMP1* gene mutation in these individuals, definitively establishing the diagnosis. This study is the first published case series related to this disease in Türkiye.

Informed consent was obtained from all participants in the study. The included cases comprised four related individuals aged 25, 51, 53, and 73 years determined to be carriers of *EFEMP1* mutations. The general clinical characteristics of these cases are summarized in Table 1.

Case Reports

Case Presentations and Genetic Evaluation

Case 1 (Index Case-Proband)

A 51-year-old male patient was evaluated in our clinic for a routine examination. His best-corrected visual acuity (BCVA) measured with a Snellen chart was 0.7 in the right eye and 0.5 in the left eye. Anterior segment examination was unremarkable, whereas fundus examination revealed dense drusen formations in the macula and peripapillary region (Figure 1A, B).

Fundus autofluorescence (FAF) imaging demonstrated distinct hyperautofluorescent areas corresponding to drusen with a tendency to coalesce around the fovea (Figure 1C-F). On spectral-domain OCT examination, diffuse, dome-shaped hyperreflective materials consistent with the presence of drusen were observed at the sub-retinal pigment epithelium (RPE) level, along with structural changes in the RPE (Figure 1G, H). Optical coherence tomography angiography (OCTA) images showed no macular neovascularization (MNV) in either eye. The foveal avascular zone (FAZ) was preserved in the superficial and deep capillary plexuses, while areas consistent with microvascular irregularities and decreased capillary density were observed in the perifoveal region. At the choriocapillaris level, diffuse, heterogeneous flow deficits and a mottled appearance were detected (Figure 1I, J).

Due to the patient's young age and clinical findings suggestive of ML/DHRD, his other family members also underwent ophthalmological evaluation. Upon observing a similar fundus appearance in three individuals (Cases 2, 3, and 4), they and the proband were referred to the medical genetics department for genetic analysis. Four other examined individuals from the same family did not exhibit any clinical findings, and two of these individuals underwent genetic analysis. The family pedigree is shown in Figure 2. The patient's father, who had died prior to the study, had a history of Behçet syndrome with associated visual loss (I.1). The genetic analysis performed on the four patients with fundus findings revealed a mutation in the *EFEMP1* gene. No mutations were detected in the two individuals (II.4 and III.7) in the family pedigree who exhibited no clinical findings.

Case 2

A 73-year-old female patient, the mother of the index case, presented with a complaint of significant visual impairment. Visual acuity was measured as 0.05 in both eyes using a Snellen chart. Fundus examination revealed widespread drusen accumulation and pigmentary changes, which were particularly dense in the peripapillary region (Figure 3A, B). FAF imaging demonstrated hypoautofluorescent areas consistent with RPE atrophy (Figure 3C-F). OCT revealed hyperreflective materials consistent with sub-RPE drusen and RPE atrophy (Figure 3G, H).

Case 3

The 53-year-old older sister of the index case presented with decreased vision in both eyes, which was more pronounced in the right eye. BCVA using a Snellen chart was 0.15 in the right eye and 0.8 in the left eye. Fundus examination of both eyes revealed numerous drusen that showed a radial distribution and tendency toward confluence in the macula and peripapillary region (Figure 4A, B). Broad hyperautofluorescent areas were present on FAF imaging (Figure 4C-F). OCT examination demonstrated diffuse sub-RPE deposits and disrupted ellipsoid zone integrity in both eyes (Figure 4G, H).

Case 4

The 25-year-old daughter of the index case had no visual complaints. Visual acuity was measured as 1.0 in both eyes with a Snellen chart. Fundus examination revealed a small number of small, radially arranged drusen in the macular region bilaterally, as well as a few small drusen nasal to the optic disc (Figure 5A, B). FAF imaging showed a few small hyperautofluorescent areas in the parafoveal region (Figure 5C-F). A few drusen were also identified in the parafoveal region on macular OCT (Figure 5G, H). OCTA imaging confirmed that the FAZ was preserved in the superficial and deep capillary plexuses of both eyes, with mild microvascular irregularities noted in the perifoveal region. The deep capillary plexus generally maintained a normal appearance. Focal flow deficits and mild heterogeneity were present in places at the choriocapillaris level, though these findings were more limited and less pronounced compared to the index case. No abnormal vascular network indicative of MNV was observed (Figure 5I, J).

Mutation Analysis

Total genomic DNA was isolated from the peripheral blood of six individuals, including the proband (Case 1) and his family members, using the HiPurA® Pre-filled Clinical Multipurpose Nucleic Acid Purification Kit (HiMedia, USA) in accordance with the manufacturer's

Table 1. General clinical characteristics of the cases

Case	Age (years)	Sex	BCVA	Lens status	Intraocular pressure	Fundus view	FAF	OCT	OCTA	Mutation
1	51	Male	OD: 0.7, OS: 0.5	OU: Phakic	OD: 12 mmHg OS: 14 mmHg	Dense drusen in the macula and peripapillary region	Hyperautofluorescent areas corresponding to the drusen showing a tendency to coalesce around the fovea	Diffuse, dome-shaped hyperreflective materials originating from drusen in the sub-RPE region and RPE changes	No macular neovascularization	*EFEMP1* (heterozygous)
2	73	Female	OU: 0.05	OU: Phakic	OD: 10 mmHg OS: 11 mmHg	Diffuse drusen deposition and pigmentary changes, more concentrated in the peripapillary region	Hypoautofluorescent areas consistent with RPE atrophy	Sub-RPE hyperreflective materials and widespread RPE loss	No macular neovascularization	*EFEMP1* (heterozygous)
3	53	Female	OD: 0.15, OS: 0.8	OU: Phakic	OD: 16 mmHg OS: 18 mmHg	Diffuse drusen showing radial arrangement and a tendency to coalesce in the macula and peripapillary region	Broad areas of hyperautofluorescence	Widespread deposits in the sub-RPE area in both eyes	No macular neovascularization	*EFEMP1* (heterozygous)
4	25	Female	OU: 1.0	OU: Phakic	OD: 17 mmHg OS: 18 mmHg	A small number of small, radially arranged drusen in the macula and a few small drusen nasal to the optic disc	A few small areas of hyperautofluorescence in the parafoveal region	A few drusen in the parafoveal region	No macular neovascularization	*EFEMP1* (heterozygous)

BCVA: Best-corrected visual acuity (Snellen), FAF: Fundus autofluorescence imaging, OCT: Optical coherence tomography, OCTA: OCT angiography, OD: Right eye, OS: Left eye, OU: Both eyes, RPE: Retinal pigment epithelium

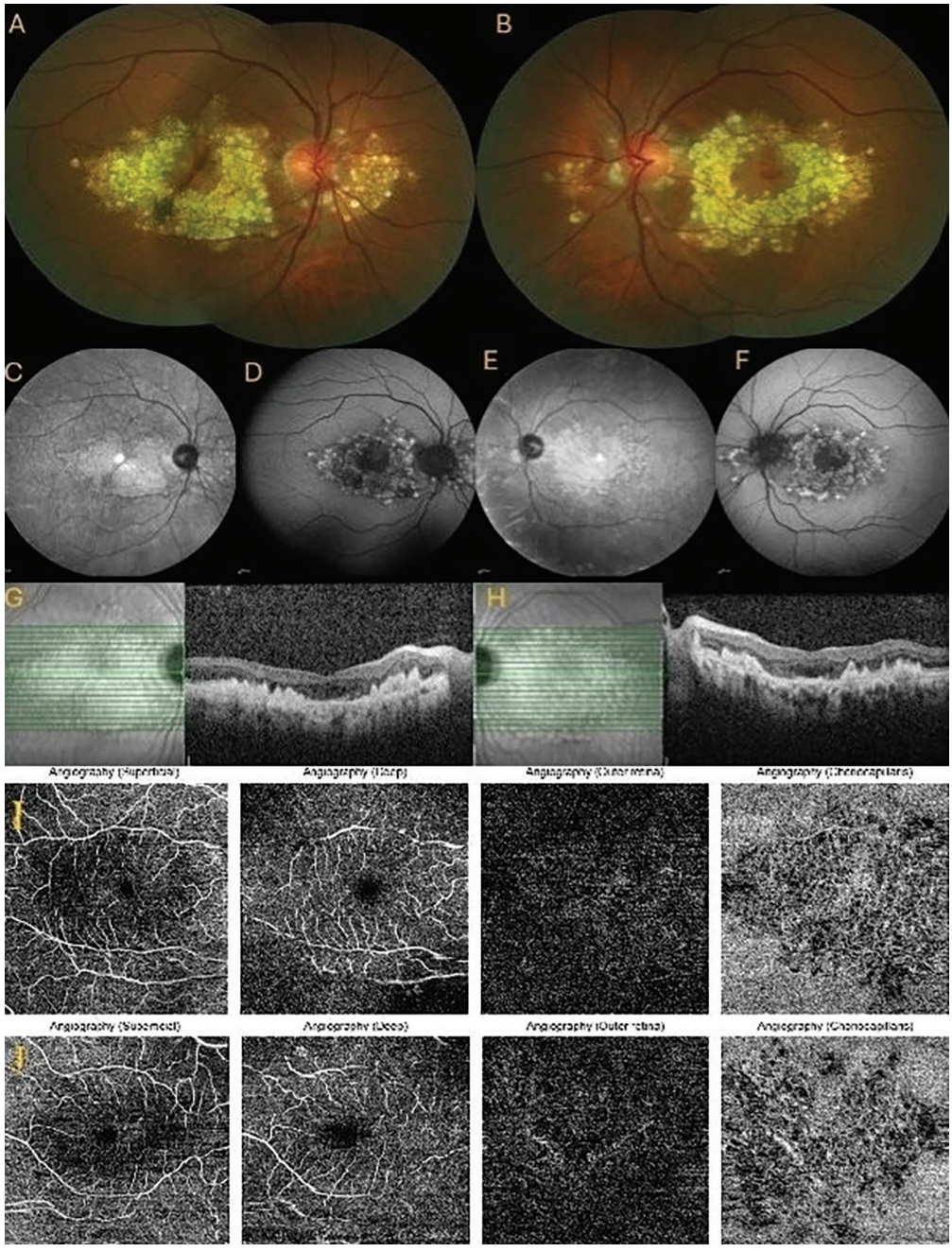

Figure 1. Color fundus photographs of the index case show clustered drusen involving the macular and peripapillary regions in the right (A) and left (B) eyes. Fundus autofluorescence images of the right (C, D) and left (E, F) eyes demonstrate multiple hyperautofluorescent foci corresponding to drusen, particularly in the perifoveal region, with a tendency toward confluence. Optical coherence tomography images (G, H) reveal diffuse, dome-shaped hyperreflective deposits located between the Bruch's membrane and the retinal pigment epithelium (sub-RPE deposits). Optical coherence tomography angiography images show no evidence of macular neovascularization in the right (I) and left (J) eyes. The superficial and deep capillary plexuses demonstrate a preserved foveal avascular zone, with perifoveal microvascular irregularities and areas suggestive of reduced capillary density. At the level of the choriocapillaris, widespread heterogeneous flow deficits with a mottled appearance are observed

RPE: Retinal pigment epithelium

protocols. The NanoDrop ND1000® Spectrophotometer (Thermo Fisher Scientific, USA) was used for DNA concentration and purity measurements. After obtaining DNA of sufficient quality (50-100 ng/µL concentration and A260/A280: 1.8-2.0 purity), polymerase chain reaction (PCR) amplification was performed using primers targeting all exons and exon-intron boundaries of the *EFEMP1* gene (NM_001039348.3). AmpliTaq Gold™ 360 DNA Polymerase (Applied Biosystems/Thermo Fisher Scientific, USA) and an Eppendorf 5332 Mastercycler (Eppendorf AG, Germany) device were used in the standard PCR procedure. PCR products were prepared for next-generation sequencing using the Nextera XT DNA Library Preparation Kit (Illumina, USA). The Miniseq® (Illumina, USA) platform was used for the runs. The obtained raw data were uploaded to and analyzed on the SEQ analysis platform (Genomize, Türkiye). Manufacturer protocols were followed at all stages. Data with 100% coverage at a minimum reading depth of 1000x were obtained for all cases.

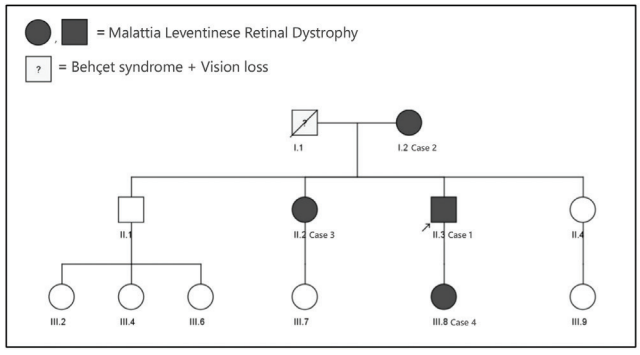

Figure 2. Pedigree chart. A heterozygous pathogenic *EFEMP1* mutation was identified in individuals I.2, II.2, II.3, and III.8. Genetic testing yielded normal results in individuals II.4 and III.7

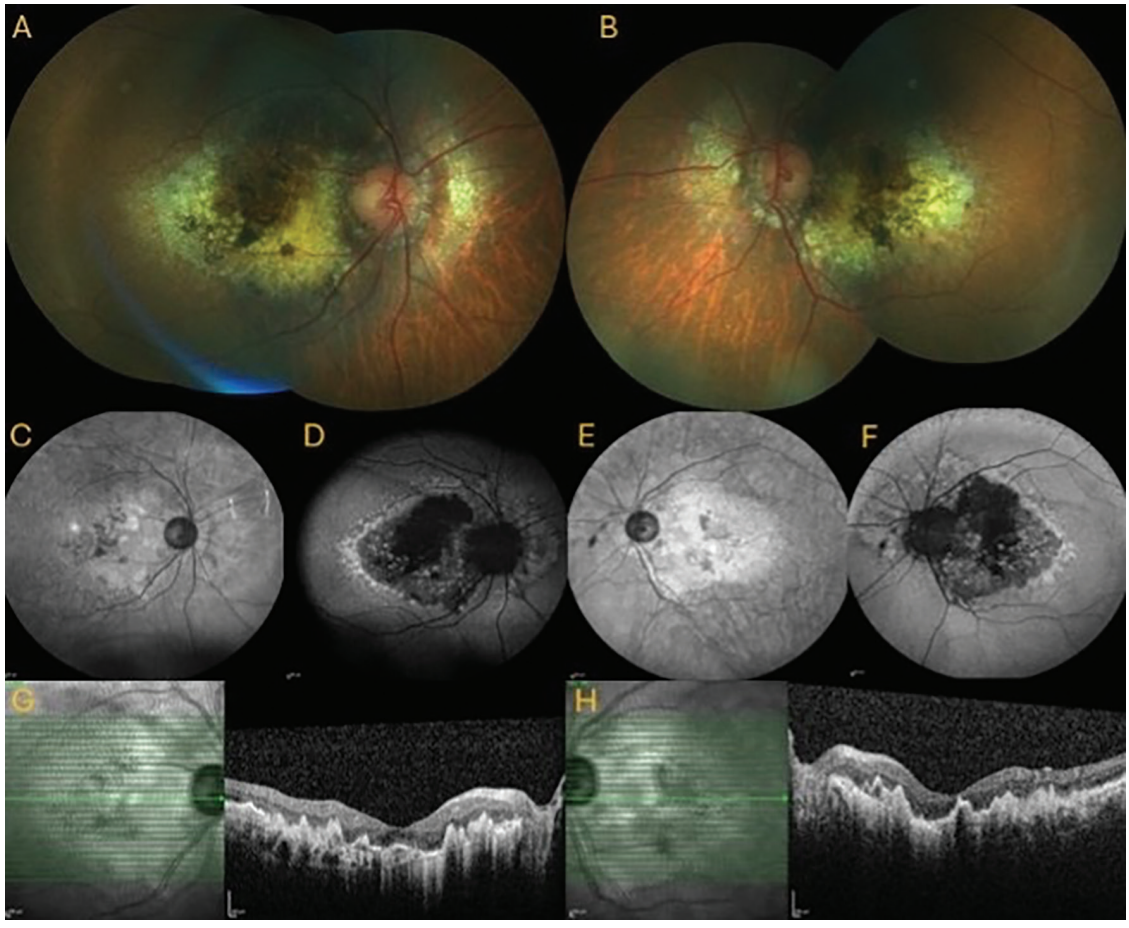

Figure 3. Color fundus photographs of Case 2 demonstrate widespread drusen accumulation and pigmentary changes in the right (A) and left (B) eyes, more prominently in the peripapillary region. Fundus autofluorescence imaging shows hypoautofluorescent areas consistent with retinal pigment epithelium (RPE) atrophy in the right (C, D) and left (E, F) eyes. Optical coherence tomography reveals RPE atrophy together with hyperreflective sub-RPE deposits consistent with drusen in both the right (G) and left (H) eyes

The c.1033C>T (p.Arg345Trp) alteration in exon 10 of the *EFEMP1* gene was detected as heterozygous in all 4 patients presenting with fundus findings. The p.Arg345Trp variant identified in the *EFEMP1* gene is the variant most strongly associated with ML/DHRD in the literature and is considered characteristic of the disease. This alteration leads to the misfolding of the fibulin-3 protein, causing abnormal accumulation in the extracellular matrix, which constitutes the fundamental pathophysiological mechanism of drusen formation.[5,8,9,10] The fact that this specific variant has been detected in the vast majority of cases reported in the literature supports the notion that it exhibits high penetrance and strong genotype-phenotype correlation. The two patients with normal fundus examination findings also had normal genetic analysis results. The detected alteration was evaluated as pathogenic in accordance with current guidelines using the criteria "PM1" (located in a functionally critical region), "PM2" (absent in the general population), "PP3" (*in silico* pathogenicity predictions), and "PP5" (reported as pathogenic in reliable databases).[11] Furthermore, the long-established and repeatedly demonstrated strong association of the p.Arg345Trp variant with ML/DHRD in the literature supports the acceptance of this variant as the disease-causing mutation.[5,8,9,10]

Discussion

ML/DHRD is a disease most commonly seen in young individuals and is characterized by radial drusen. Clinically, patients typically present with complaints of decreased vision, metamorphopsia, and scotoma. The drusen show a radial distribution along the arcades, in the peripapillary region, and in the central macula and gradually enlarge and approximate each other to create a honeycomb-like appearance.[3,5,7]

FAF examinations reveal hyperautofluorescent drusen and areas of hypoautofluorescence associated with RPE atrophy. Patients generally have good visual acuity in the

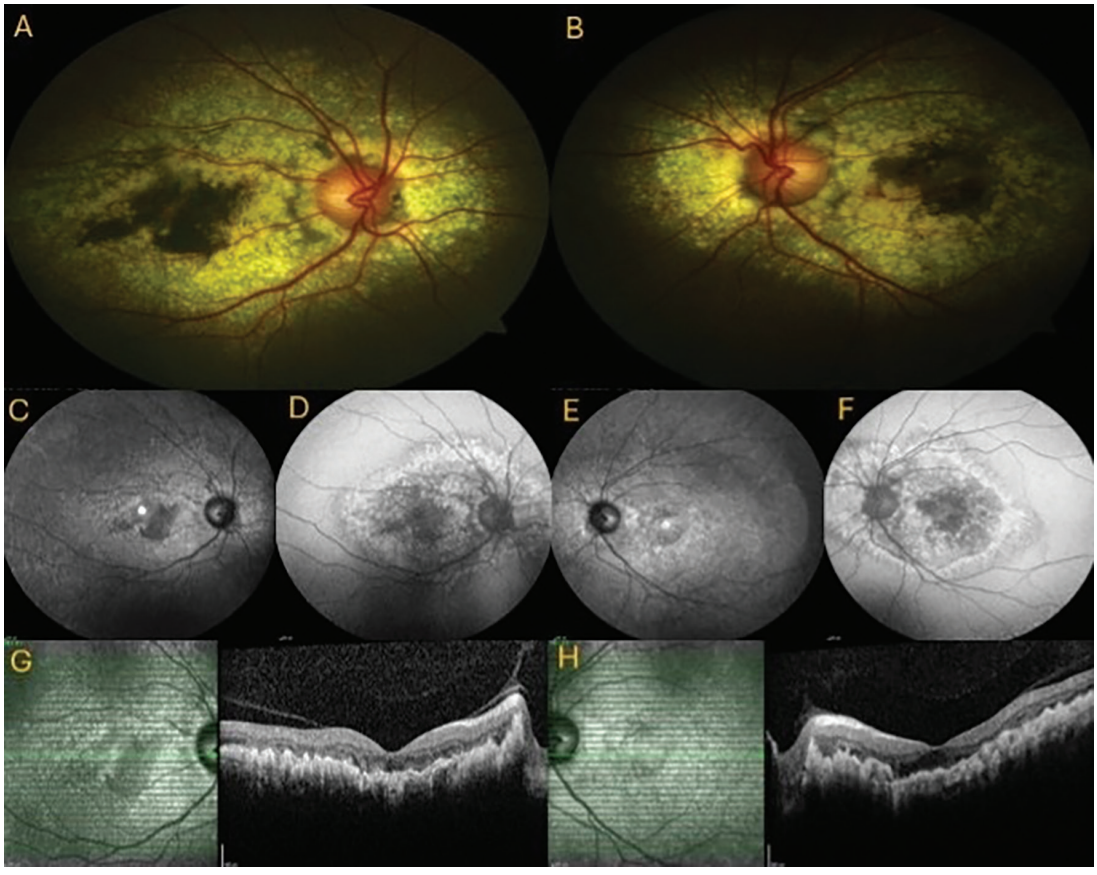

Figure 4. Color fundus examination of Case 3 demonstrates numerous drusen in the macular and peripapillary regions of the right (A) and left (B) eyes, arranged in a radial pattern with a tendency to coalesce. Fundus autofluorescence imaging shows extensive hyperautofluorescent areas in both the right (C, D) and left (E, F) eyes. Optical coherence tomography reveals widespread sub-retinal pigment epithelium deposits in both eyes, along with disrupted ellipsoid zone integrity (G, H)
RPE: Retinal pigment epithelium

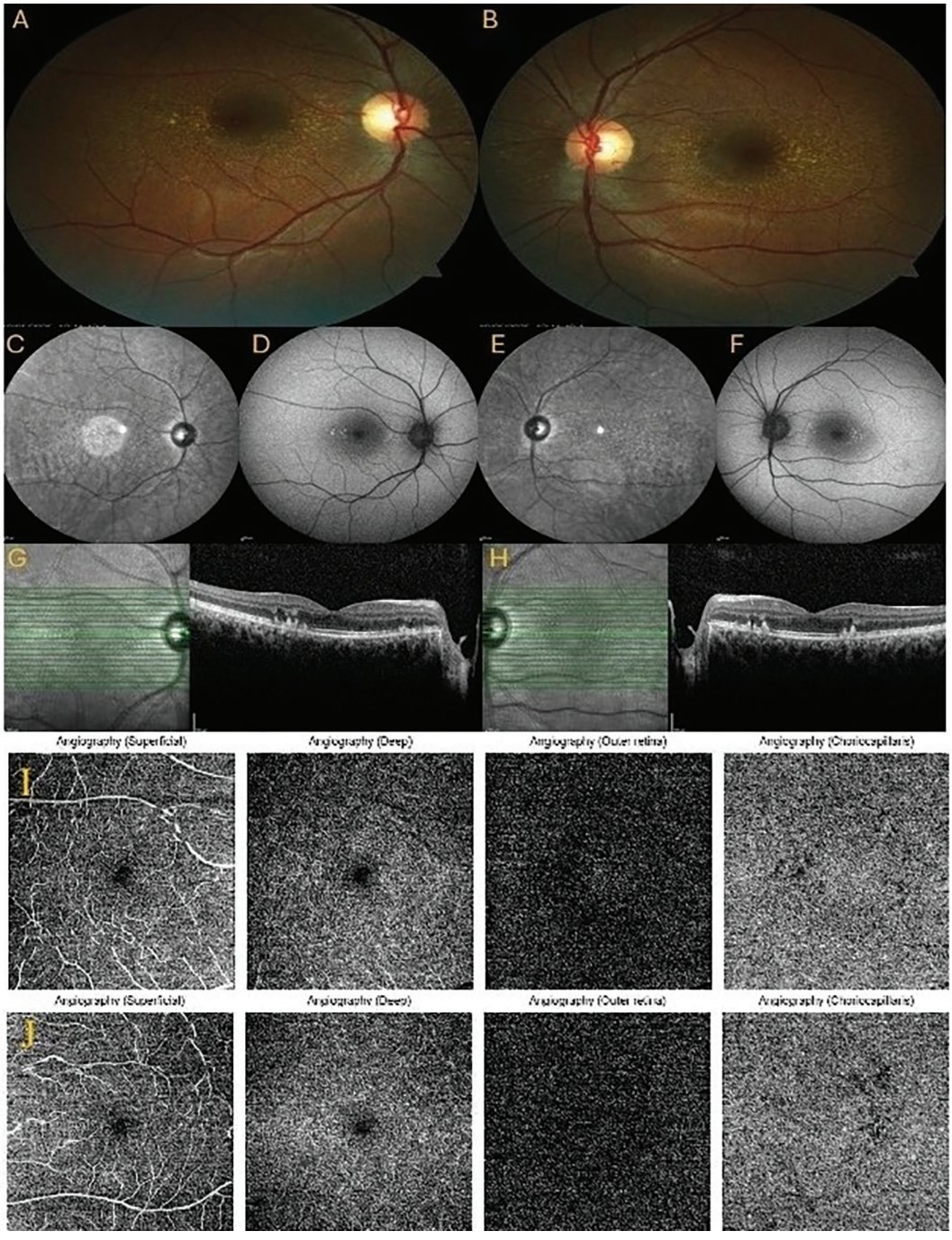

Figure 5. Color fundus photographs of Case 4 show a small number of small, radially arranged drusen in the macular region, along with a few small drusen located nasal to the optic disc in both the right (A) and left (B) eyes. Fundus autofluorescence images of the right (C, D) and left (E, F) eyes demonstrate a few small hyperautofluorescent areas in the parafoveal region. Optical coherence tomography images of the right (G) and left eyes (H) reveal a small number of drusen located in the parafoveal region bilaterally. Optical coherence tomography angiography images of the right (I) and left eyes (J) show a preserved foveal avascular zone in both the superficial and deep capillary plexuses, with mild microvascular irregularities in the perifoveal region. The deep capillary plexus appears largely unremarkable. At the level of the choriocapillaris, focal flow deficits and mild heterogeneity are observed, which are more limited and less pronounced compared to the index case. No abnormal vascular network suggestive of macular neovascularization is detected

Table 2. Clinical comparison of Malattia Leventinese/Doyne honeycomb retinal dystrophy and age-related macular degeneration

Clinical presentation	Malattia Leventinese	Age-related macular degeneration
Age at onset	Usually the 3rd-4th decade	Advanced age (>50 years)
Inheritance pattern	Autosomal dominant	Multifactorial/Sporadic
Genetic basis	Strong association with the *EFEMP1* p.Arg345Trp mutation	Polygenic (e.g., *CFH*, *ARMS2*, *HTRA1*)
Drusen morphology	Presence of drusen located nasal to the optic disc Presence of drusen in the macula exhibiting a typical radial arrangement Drusen can become large, dense, and confluent in advanced stages, frequently accompanied by juxtapapillary nodular drusenoid lesions	A drusen pattern where both hard and soft drusen can be seen together; soft drusen are generally large, confluent, and prominent in the macula
Multimodal imaging	FAF: Hyper/hypoautofluorescent areas corresponding to drusen located in the macula and around the optic disc OCT: Sub-RPE deposits FFA: Large central drusen have poorly defined borders and a hypofluorescent appearance, whereas small radial drusen are well-defined and prominently hyperfluorescent OCTA: Relatively preserved superficial and deep capillary plexuses, mild perifoveal microvascular irregularities, and a heterogeneous mottled appearance with focal flow deficits at the choriocapillaris level. MNV is not common in the early stage	FAF: Irregular autofluorescence patterns, hypoautofluorescent areas in regions of atrophy OCT: Drusen, RPE irregularities, geographic atrophy, subretinal and intraretinal fluid FFA: Early hyperfluorescence in drusen, leakage in the presence of MNV OCTA: Decreased choriocapillaris density, focal flow deficits, and MNV (type 1, 2, 3)
Macular neovascularization	Can develop with varying frequency (6-24%)	Common (especially in the neovascular type)
Progression pattern	Slow onset, with atrophy and/or MNV in the advanced stage	Progressive; progression from dry type to neovascular type or geographic atrophy

FAF: Fundus autofluorescence imaging, OCT: Optical coherence tomography, RPE: Retinal pigment epithelium FFA: Fundus fluorescein angiography, OCTA: OCT angiography, MNV: Macular neovascularization

early stages, as in our fourth case, but vision loss becomes pronounced in the advanced stages. The primary causes of this loss are drusen confluence, RPE atrophy, and MNV development.[9] Regular OCTA imaging is recommended during follow-up for the early detection of MNV.[10] OCTA was performed in all of our cases, but MNV was not detected in any of the patients. MNV and subretinal hemorrhage are rarely seen in ML/DHRD, and when they do develop, they are the most important complications that can lead to severe vision loss.[12,13,14] Although anti-vascular endothelial growth factor (anti-VEGF) therapy has been reported to be effective in cases developing MNV in the literature, there is no specific treatment for the macular atrophy that develops over time. In cases where MNV is not detected, the treatment approach is directed toward visual rehabilitation and preservation of functional vision.[12,15] In contrast, another study examining inherited macular diseases reported that despite consecutive intravitreal anti-VEGF injections in an ML/DHRD patient that developed MNV, there was no significant change in the MNV on OCTA measurements, and their visual acuity continued to decline.[16]

Our cases highlight the distinctive importance of multimodal imaging findings in the diagnosis of ML/DHRD. This disease can easily be confused with AMD and other dystrophies. In the advanced stages of ML/DHRD, drusen coalesce to form a homogeneous area, and atrophy develops in these regions. This differs from the lifecycle of drusen in AMD, which mostly disappear with outer retinal atrophy.[17] A comparison of the clinical findings of ML/DHRD and AMD is summarized in Table 2.[5,10,14,18,19,20,21,22] Sorsby retinal dystrophy generally presents with reticular drusen and is characterized by hypoautofluorescence on FAF and deposits above the RPE on OCT.[23] Pattern dystrophy is characterized by typical hyperautofluorescent lesions in the center of the macula

and subretinal hyperreflective deposits on OCT, and it is among the retinal dystrophies requiring differential diagnosis from ML/DHRD.[24] The radially arranged and honeycomb-like drusen appearance in ML/DHRD serves as a distinguishing feature.[14] The p.Arg345Trp variant identified in this study is the classic *EFEMP1* mutation most frequently associated with ML/DHRD and forms the molecular basis of the disease. The independent reporting of this variant in different populations in the literature supports its strong causal relationship with the disease. This demonstrates a high genotype-phenotype correlation, increasing the diagnostic value of targeted genetic analyses in cases where ML/DHRD is suspected clinically.

Apart from the ML/DHRD diagnosed in our cases, *EFEMP1* gene mutations have also been associated with juvenile open-angle glaucoma, sporadic cuticular drusen, and myopia. Furthermore, *EFEMP1* was reported to make polygenic contributions to common ophthalmic diseases such as primary open-angle glaucoma, and *EFEMP1*-related signaling pathways have been linked to AMD. However, despite the available evidence, it is not yet fully understood how *EFEMP1* is involved in this broad spectrum of clinically distinct diseases.[25]

ML/DHRD should be kept in mind for young patients presenting with drusen. Anti-VEGF injections and regular follow-ups are important for patients who develop MNV. NV was not detected in any of our cases, demonstrating that family screening is of critical importance in the diagnosis of this rare and sight-threatening disease. This study documents the first ML/DHRD cases in Türkiye diagnosed through both clinical and genetic analyses. This rare disease must be considered in the differential diagnosis of patients with drusen at a young age, as well as older patients who present with fundus and OCT images distinct from the typical AMD drusen pattern.

Ethics

Informed Consent: Informed consent was obtained from all participants in the study.

Declarations

Authorship Contributions

Surgical and Medical Practices: A.İ., M.K., A.O.Ç., Ö.K., Z.A., A.O.S., Concept: A.İ., A.O.Ç., Ö.K., Z.A., A.O.S., Design: A.İ., A.O.Ç., Ö.K., Z.A., A.O.S., Data Collection or Processing: A.İ., M.K., A.O.Ç., Ö.K., A.O.S., Analysis or Interpretation: A.İ., M.K., A.O.Ç., Ö.K., A.O.S., Literature Search: A.İ., M.K., A.O.Ç., Ö.K., A.O.S., Writing: A.İ., M.K., A.O.Ç., Ö.K., A.O.S.

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