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Clinical and Genetic Features of Gelatinous Drop-Like Corneal Dystrophy: First Cohort from Türkiye with a Novel *TACSTD2* Mutation

Gelatinöz Damla Benzeri Kornea Distrofisinin Klinik ve Genetik Özellikleri: Yeni Bir *TACSTD2* Mutasyonu ile Türkiye'den İlk Kohort

Fulya Yaylacıoğlu Tuncay[1], Hasan Diker[2], Ahmet Yücel Üçgül[2], Mehmet Cüneyt Özmen[2], Bahri Aydın[2]

[1]Department of Medical Biology, University of Health Sciences, Gülhane Faculty of Medicine, Ankara, Türkiye
[2]Department of Ophthalmology, Gazi University Faculty of Medicine, Ankara, Türkiye

ABSTRACT

Objective: To describe the clinical and genetic findings, as well as treatment outcomes, in patients with gelatinous drop-like corneal dystrophy (GDLD) from a single center in Türkiye.

Methods: In this retrospective study, 10 patients from five families who were clinically diagnosed with GDLD at the Ophthalmology Department of Gazi University Medical Faculty were included. Genetic analysis was performed using Sanger sequencing of the coding regions of the tumor-associated calcium signal transducer 2 (*TACSTD2*) gene and of exons 4 and 12 of the transforming growth factor-beta-induced (*TGFBI*) gene. Clinical findings, treatment modalities, and follow-up outcomes were documented.

Results: One novel *TACSTD2* mutation (c.779del, p.Tyr260SerfsTer11) and two previously reported *TACSTD2* mutations, c.355T>A (p.C119S) and c.341T>G (p.F114C), were identified in three families. In one family, no disease-associated variants were detected in either *TGFBI* or *TACSTD2*. The most common initial symptoms were photophobia, corneal pain, and blurred vision, and the mean age at onset was 11.3 years. The follow-up duration ranged from 2 to 21 years, and seven patients required repeated surgical interventions. Epithelial debridement followed by diamond burr polishing (ED-DBP) was performed in seven patients, resulting in symptomatic improvement and delaying the need for keratoplasty.

Conclusion: This is the first report of the clinical and genetic characteristics of GDLD patients from Central Anatolia, and it expands the *TACSTD2* mutational spectrum with a novel variant. ED-DBP is

ÖZ

Amaç: Bu çalışmanın amacı, Türkiye'de tek bir merkezden gelatinöz damla benzeri kornea distrofisi (GDLD) tanısı alan hastalarda klinik ve genetik bulgular ile tedavi sonuçlarını tanımlamaktır.

Yöntemler: Bu retrospektif çalışmaya, Gazi Üniversitesi Tıp Fakültesi Göz Hastalıkları Anabilim Dalı'nda klinik olarak GDLD tanısı konulan beş aileden 10 hasta dâhil edildi. Genetik analiz, tümörle ilişkili kalsiyum sinyal transdüseri 2 (*TACSTD2*) geninin kodlayıcı bölgeleri ile transforming growth factor-beta-induced (*TGFBI*) geninin 4. ve 12. ekzonlarının Sanger dizilemesi ile gerçekleştirildi. Klinik bulgular, uygulanan tedavi yöntemleri ve takip sonuçları kaydedildi.

Bulgular: Üç ailede, biri yeni (c.779del, p.Tyr260SerfsTer11) ve ikisi daha önce bildirilmiş c.355T>A (p.C119S) ve c.341T>G (p.F114C) üç *TACSTD2* mutasyonu saptandı. Bir ailede ise ne *TGFBI* ne de *TACSTD2* genlerinde hastalıkla ilişkili herhangi bir varyant tespit edilmedi. En sık görülen başlangıç semptomları fotofobi, kornea ağrısı ve bulanık görme olup, ortalama başlangıç yaşı 11,3 yıl idi. Takip süresi 2 ile 21 yıl arasında değişmekteydi ve yedi hastada tekrarlayan cerrahi girişimler gerekmişti. Yedi hastaya epitel debridmanı sonrası elmas freze ile polisaj (ED-DBP) uygulanmış; bu işlem semptomatik iyileşme sağlamış ve keratoplasti gereksinimini geciktirmiştir.

Sonuç: Bu çalışma, Orta Anadolu'dan bildirilen GDLD hastalarının klinik ve genetik özelliklerine ilişkin ilk rapor olup, *TACSTD2* mutasyon spektrumunu yeni bir varyant ile genişletmektedir. ED-DBP, GDLD için bir tedavi seçeneği olarak önerilmektedir; hastalığın ilerlemesini

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Address for Correspondence/Yazışma Adresi: Fulya Yaylacıoğlu Tuncay, MD, PhD, FEBO, Department of Medical Biology, University of Health Sciences, Gülhane Faculty of Medicine, Ankara, Türkiye
E-mail / E-posta: drfulyatuncay@gmail.com
ORCID ID: orcid.org/0000-0002-2088-3416

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ABSTRACT

proposed as a treatment modality for GDLD; it may not halt disease progression but can alleviate corneal discomfort, temporarily improve vision, and postpone corneal transplantation.

Keywords: Gelatinous drop-like corneal dystrophy, Epithelial debridement with diamond burr polishing, *TACSTD2*, Sanger sequencing, keratoplasty

ÖZ

durdurmasa da korneal rahatsızlığı azaltabilir, görmeyi geçici olarak iyileştirebilir ve kornea transplantasyonunu erteleyebilir.

Anahtar Sözcükler: Gelatinöz damla benzeri kornea distrofisi, elmas freze ile epitel debridmanı, *TACSTD2*, Sanger dizileme, keratoplasti

INTRODUCTION

Gelatinous drop-like corneal dystrophy (GDLD) is a rare inherited corneal disorder (OMIM 2014870) characterized by subepithelial and stromal deposition of amyloid. GDLD has been most frequently reported in Japan, where its prevalence is estimated at 1 in 33,000 (1,2). However, cases have also been described in other countries (3-10). Because the disease follows an autosomal recessive inheritance pattern, consanguineous marriages are more common among families affected by GDLD (11).

GDLD typically presents during the first or second decade of life and affects both sexes equally. The most common initial symptoms include foreign body sensation, photophobia, and visual impairment, depending on the location and severity of the corneal deposits (12). In the early stages, deposits usually appear in the subepithelial central cornea. As the disease progresses, these deposits increase in number and depth, extend peripherally, and coalesce (13). In advanced stages, superficial and deep corneal vascularization often accompany the corneal deposits (13). Four clinical subtypes of GDLD have been described based on the appearance of corneal deposits: 1. Typical mulberry type: observed in early stages, characterized by white-grayish gelatinous deposits; 2. Band-keratopathy type: also seen in early stages, featuring band-shaped amyloid deposits in the subepithelial space; 3. Stromal opacity type: found in advanced stages, in which deposits extend into the deeper stromal layers; 4. Kumquat-like type: an advanced form characterized by yellow-white, widespread deposits with neovascularization (14). Treatment strategies for GDLD include removal of the superficial corneal layer via photoablation or keratectomy in early stages, and corneal transplantation using DALK or penetrating keratoplasty (PKP) in advanced cases (12). In addition, limbal stem cell transplantation (LSCT) and the Boston keratoprosthesis have been reported as treatment options for patients with GDLD (15-17). Recurrence of amyloid deposits remains the main challenge during follow-up, and repeated interventions are often required (12).

Mutations in the tumor-associated calcium signal transducer 2 (*TACSTD2*) gene are responsible for the majority of GDLD cases (18,19). *TACSTD2*, located on chromosome 1p32, encodes a transmembrane glycoprotein consisting of 323 amino acids. The non-sense variant p.Gln118Ter (Q118X) has been reported in up to 90% of Japanese GDLD cases (18). Nevertheless, the Human Genome Mutation Database (HGMD) lists more than 30 distinct *TACSTD2* mutations across different populations. Loss-of-function mutations in *TACSTD2* alter the expression of key cell-junction proteins, disrupting cell-to-cell and cell-to-substrate adhesion in the corneal epithelium, thereby increasing epithelial permeability (20, 21). This abnormal permeability facilitates protein leakage—such as lactoferrin—into the cornea, resulting in amyloid deposition (22). In the early stages of disease, the basal lamina, Bowman's membrane (BM), and stroma remain intact in corneas with GDLD (23). However, with disease progression, BM destruction occurs, and amyloid deposits extend into the deeper stromal layers (23,24). Corneal vascularization and mechanical stress have also been shown to exacerbate deposit formation (25).

To date, two siblings from a Turkish family have been clinically and genetically characterized by Uhlig et al. (25) no additional cases have been reported from Türkiye (26). Furthermore, there are few studies describing long-term follow-up of GDLD patients, and none have reported the use of epithelial debridement with diamond burr polishing (ED-DBP) as a treatment modality (25,27). In this study, we present the clinical characteristics, treatment modalities, and long-term outcomes of 10 patients with GDLD from five Turkish families and identify three disease-causing *TACSTD2* variants in three of those families, one of which is novel.

MATERIALS AND METHODS

Ethical Approval

This retrospective study was approved by the Institutional Ethics Review Board of Gazi University (approval number: 2025–405/04, date: 11.03.2025) and conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants and/or their legal guardians.

Participants and Clinical Evaluation

Patients clinically diagnosed with GDLD and followed at the Department of Ophthalmology Gazi University Faculty of Medicine between January 2004 and January 2025 were included in the study. A detailed medical history was obtained from all patients, including information on ethnicity, family history, parental consanguinity, history of ocular trauma, exposure to chemicals, drug use, systemic diseases, and previous treatments.

Comprehensive ophthalmic evaluations were performed, including best-corrected visual acuity (BCVA), intraocular pressure measurement, slit-lamp biomicroscopy, and, when feasible depending on the degree of corneal opacity or photophobia, fundus examination. In cases where fundus visualization was limited, ultrasonography was performed. Treatment modalities, treatment outcomes, and follow-up durations were also recorded. Interocular asymmetry in BCVA was evaluated in patients and defined as a difference of more than two lines between the eyes.

Genetic Analyses

Peripheral blood samples (5 mL) were collected from patients, when available, their parents for DNA extraction and molecular analysis. DNA isolation was performed using a spin-column-based nucleic acid purification method (MN Macherey-Nagel, Düren, Germany). The coding regions and exon–intron boundaries of *TACSTD2*, as well as exons 4 and 12 of *TGFBI*, were amplified by polymerase chain reaction using primers designed with Primer3 (Table 1).

Bidirectional Sanger sequencing was conducted using the BigDye Terminator Mix v3.1 (Applied Biosystems, Foster City, CA, USA) and analyzed on an ABI-3100 Genetic Analyzer (Applied Biosystems). Chromatograms were reviewed using ChromasPro v1.7.7 (Technelysium, South Brisbane, Australia), and obtained sequences were compared with reference gene sequences in the National Center for Biotechnology Information database. Familial segregation of the novel variant was confirmed by sequencing the parents of the probands.

Identified variants were classified according to the 2015 ACMG/AMP guidelines for sequence variant interpretation. Population allele frequencies were obtained from the Genome Aggregation Database (gnomAD v4.1.0; https://gnomad.broadinstitute.org/). Variant pathogenicity was evaluated using the Ensembl Variant Effect Predictor (VEP; https://useast.ensembl.org/Tools/VEP) and Franklin (https://franklin.genoox.com/). Additional data on variant function and associated phenotypes were retrieved from the Human Gene Mutation Database (Professional 2025.1), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), and the relevant published literature.

RESULTS

Demographic and Clinical Findings

Ten patients from five unrelated families were included in the present study. All families consisted of sibling groups. The demographic and clinical characteristics of the patients are summarized in Table 2. The mean age at the first ophthalmological examination (AE) at our center was 28.3 years (range, 8–42 years). The sex distribution was equal for males and females. The mean age of onset (AO) of the first ocular symptoms or signs was 11.3 years (range, 6–17 years). All participants self-identified as Turkish and originated from the Central Anatolia region. Parental consanguinity was present in all families, with marriages between first cousins reported in three of them. Participants with Systemic diseases, a history of drug use, or ocular trauma that could lead to corneal amyloid deposition were excluded based on detailed medical history. The most common presenting symptoms were photophobia, corneal pain, and blurred vision (Table 2).

At the first examination, the BCVA ranged from hand motion (HM) to 0.8. Slit-lamp examination revealed central and paracentral mulberry-like, transparent or whitish nodular corneal elevations; band keratopathy; corneal scarring; widespread yellow-white deposits; recurrent nodular lesions in the graft; and opaque corneal grafts (Figure 1). Corneal neovascularization was present in four patients at baseline and was subsequently observed in five patients during follow-up (Table 2, Figure 1).

Patients from the same family exhibited similar phenotypes, including anterior segment findings, BCVA, and AO. Notable interocular asymmetry was observed only in patient 8, particularly in BCVA and anterior segment findings (Tables 2 and 3).

Treatment Modalities and Outcomes

The mean follow-up duration of the patients was 9.4 years, ranging from 2 to 21 years (Table 3). Surgical interventions performed during follow-up included ED-DBP photorefractive keratectomy (PRK), deep anterior lamellar keratoplasty (DALK), and PKP (Table 3). In addition to surgical procedures, bandage contact lenses and medical therapy were administered as needed for symptomatic relief. Between the first and last visits, BCVA increased in 7 eyes, remained stable in 5 eyes, and decreased in 8 eyes (Table 3). In the better-seeing eye, BCVA was at least 0.1 in seven of 10 patients and at least 0.5 in four (Table 3).

To remove the superficial corneal layer, ED-DBP or PRK was performed. During ED-DBP, the corneal epithelium surrounding the lesions was removed to Bowman's layer, followed by diamond-burr polishing of the entire corneal surface. A handheld, battery-powered ophthalmic burr with a 3.3-mm diamond-dusted spherical tip was used to polish the corneal surface for approximately 10–15 seconds (Figure 2a). At the end of the procedure, a soft bandage contact lens was applied. Postoperatively, patients received topical corticosteroids, antibiotics, and artificial tears, each administered four times daily for one month. The bandage lens was removed on the fifth postoperative day. ED-DBP was performed as the initial surgical step in 7 eyes (5 patients) and as a secondary procedure following keratoplasty in 2 eyes (2 patients) (Table 3). Recurrent ED-DBP was applied to 3 eyes of 2 patients during follow-up; in one eye, a stromal anti-VEGF injection was co-administered. All patients reported significant symptomatic relief following ED-DBP, with

Table 1. Primer List of *TACSTD2* and *TGFBI* genes.

TACSTD2	Sequences of primers (5'-3')	Tm (°C)	PCR product (bp)
Primer_1	F: CCTGCAGACCATCCCAGAC R: CAGGAAGCGTGACTCACTTG	59	1140
TGFBI	Sequences of primers (5'-3')	Tm (°C)	PCR product (bp)
Exon 4	F: TCGTCCTCTCCACCTGTAGA R: AACATGTTCTCAGCCCTCGT	59.0	548
Exon 12	F: AACCAAGGTGTGTGCATTCC R: TTTAGTCCCGCCCACTCTTT	59.0	415

TACSTD2: Tumor-associated calcium signal transducer 2, *TGFBI*: Transforming growth factor-beta-induced, PCR: Polymerase chain reaction.

Table 2. Demographic, clinical and genetic findings of Turkish GDLD patients.

Patient no	Sex	AE	AO	Initial symptom	Anterior segment findings	Genetic test	Gene	Nucleotide change	Amino acid change	Zygosity
1[1]	M	33	10	Vision loss	OD: typical yellow-white nodules, vascularization OS: corneal scar, vascularization	Yes	TACSTD2	c.355T>A	p.C119S	Homozygous
2[1]	M	32	8	Vision loss	OD: corneal scar, vascularization OS: typical yellow-white nodules, vascularization	Yes	*TACSTD2*	c.355T>A	p.C119S	Homozygous
3[2]	M	26	12	Corneal pain	OD: yellow-white nodules OS: yellow-white nodules, band keratopathy	Yes	TACSTD2	c.341T>G	p.F114C	Homozygous
4[2]	M	33	16	Corneal pain	OD: typical yellow-white nodules OS: typical yellow-white nodules	No	NA	NA	NA	NA
5[3]	F	42	15	Vision loss	OD: opaque graft with vascularization OS: opaque graft with vascularization	Yes	TACSTD2	c.779delT*	p.Tyr260SerfsTer11	Homozygous
6[3]	F	32	10	Vision loss	OD: widespread nodules OS: widespread nodules, vascularization	Yes	TACSTD2	c.779delT*	p.Tyr260SerfsTer11	Homozygous
7[4]	F	42	17	Vision loss	OD: corneal scar with vascularization OS: widespread nodules	No	NA	NA	NA	NA
8[4]	F	18	6	Vision loss	OD: few corneal deposits OS: corneal scar	No	NA	NA	NA	NA
9[5]	F	8	8	Photophobia	OD: typical yellow-white nodules OS: typical yellow-white nodules	Yes	Negative	NA	NA	NA
10[5]	M	17	11	Corneal pain	OD: typical yellow-white nodules OS: typical yellow-white nodules	Yes	Negative	NA	NA	NA

*Denotes novel variant, [1, 2, 3, 4, 5]denotes family numbers.
M: Male; F: Female; AO: Age of onset, AE: Age at exam, OD: Right eye; OS: Left eye, NA: Non-available, GDLD: Gelatinous drop-like corneal dystrophy

improvement lasting for at least 12 months during follow-up (Figure 2b). Three eyes of three patients underwent PRK, including one eye that received intraoperative mitomycin-C. In two patients, PRK was performed as a secondary procedure following ED-DBP.

For corneal transplantation, either DALK or PKP was performed. Six eyes in four patients underwent PKP as a second-step procedure following ED-DBP during the follow-up period; one patient received PKP as the primary surgical treatment. Two eyes of one patient initially underwent DALK; however, one of these later required PKP as a second surgery (Figure 2c). The interval between ED-DBP and keratoplasty ranged from 12 to 38 months (Table 3). Following DALK or PKP, BCVA improved further in treated eyes. However, Patient 1 developed retinal detachment in the left eye during follow-up, resulting in permanent vision loss. Additionally, recurrence of corneal deposits within the graft led to a decrease in BCVA during late postoperative visits and necessitated repeated keratoplasties in six eyes of six patients, as shown in Table 3.

Variants in TACSTD2 and TGFBI

Sanger sequencing was successfully performed in seven patients from four families (Table 1). In two families, previously reported disease-associated homozygous missense variants were detected: c.355T>A (p.C119S) and c.341T>G (p.F114C) (Table 2). Both variants were classified as likely pathogenic according to the ACMG

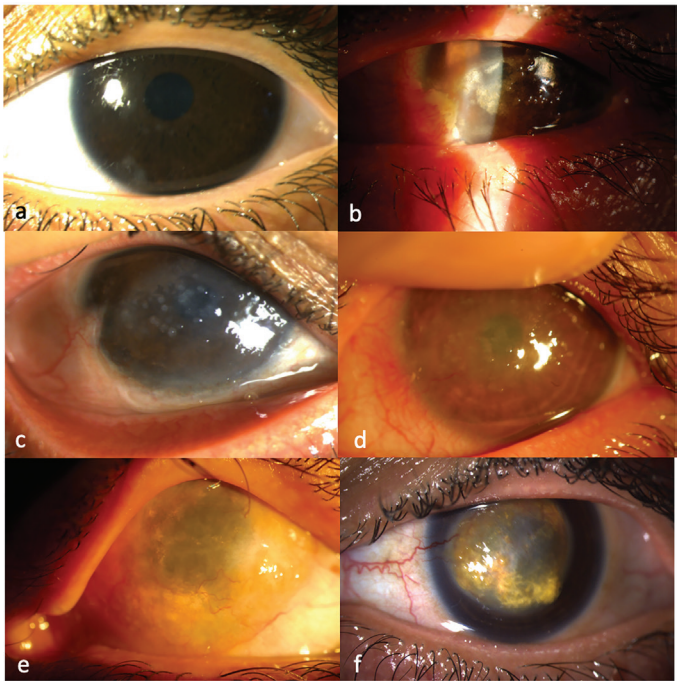

Figure 1. Anterior segment images of representative Gelatinous drop-like corneal dystrophy patients at first visit. (a) Youngest patient in the cohort (Patient 9) with few corneal deposits; (b) Patient 4 with yellow-white nodules and band keratopathy; (c) One of the sibling pair, Patient 1, with typical central whitish mulberry-like nodular corneal elevations; (d) The other sibling, Patient 2, with a similar pattern of corneal deposits with his brother; (e) Opaque corneal graft with corneal vascularization in Patient 5; (f) Central severe corneal deposits and vascularization in Patient 6.

guidelines. In one family, no disease-associated variant was detected in *TACSTD2*. No disease-associated variants were identified in exons 4 or 12 of the *TGFBI* gene in any of the patients.

In Family 3, a novel biallelic frameshift variant was identified: c.779del (p.Tyr260SerfsTer11) (Figure 3). The allele frequency of this variant has been reported as 8.477×10^{-7} in populations of European ancestry, and this variant has not been reported in the homozygous state in any database. This variant has not been described in HGMD, LOVD, or ClinVar, nor has it been reported in association with GDLD in the literature or in the Turkish Genome Project Data Sharing Portal. Given its predicted loss-of-function effect and extremely low frequency in population databases, this variant was classified as likely pathogenic under ACMG criteria (Pathogenic very strong 1_PVS1, Pathogenic moderate 2_PM2). Segregation analysis revealed heterozygosity in both parents, who were second-degree cousins and exhibited no corneal abnormalities. Family 3 included two affected female siblings diagnosed at ages 10 and 15 years. Their initial symptom was visual loss. Patient 5 underwent PKP in both eyes in her twenties at another hospital. At her first visit to our center, both corneal grafts were opaque and vascularized, and ultrasonography detected chronic retinal detachment in the left eye (Table 2, Figure 1e). Slit-lamp examination of patient 6 revealed central, severe, yellowish corneal deposits in both eyes, with peripheral corneal vascularization in the left eye. In both siblings, BCVA at diagnosis was HM in the right eye and 0.05 in the left eye. Patient 5 underwent recurrent PKP on the right eye at our center in 2016 and 2025. The right eye of patient 6 underwent ED-DBP as the first intervention, followed by PKP on subsequent follow-up, whereas the left eye underwent PRK as the first intervention, followed by DALK on subsequent follow-up.

The clinical findings of patients with the frameshift variant regarding AO, BCVA, anterior segment findings, and the need for and timing of corneal transplantation tended to be more severe than those in patients with missense variants (Tables 2 and 3).

DISCUSSION

In this study, we investigated the clinical findings of five pairs of siblings with GDLD from Türkiye. Three disease-associated *TACSTD2* variants were identified in three families; one variant was novel. A follow-up period of up to 21 years was documented, including treatment modalities and patient outcomes.

The novel *TACSTD2* variant identified in our cohort, c.779del (p.Tyr260SerfsTer11), is a frameshift variant predicted to cause premature truncation of the protein, resulting in the loss of the transmembrane and PIP_2-binding domains. A previously reported truncating mutation located near this site, c.798del (p.Lys267SerfsTer4), has been shown to be deleterious in HeLa cells, leading to loss of function and impaired trafficking of claudin-1 and claudin-7 from the cytoplasm to the plasma membrane (28). In our cohort, patients carrying this truncating variant (Patients 5 and 6) exhibited a more severe phenotype than those with missense variants (Tables 2 and 3). However, previous studies have reported conflicting results regarding the relationship between mutation type and disease severity 6,14,29.

Previously reported *TACSTD2* missense variants, c.355T>A (p.C119S) and c.341T>G (p.F114C), were identified in two families in our study. Both p.C119S and p.F114C affect the thyroglobulin-like repeat domain, a region crucial for protein stability and epithelial cell adhesion, and have been described in patients from Tunisia, Saudi Arabia, and Iran 6,10,30. A Sudanese patient carrying the p.C119S variant experienced recurrent keratoplasties, similar to patient 1 in our cohort (30). In contrast, the Iranian patient with the p.F114C variant exhibited earlier disease onset and a more severe phenotype than patient 3 in our series (6). Although previous reports from Japan and Iran have highlighted phenotypic heterogeneity both within families and among patients carrying the same *TACSTD2* variant, the siblings in our cohort exhibited remarkably similar clinical findings (Tables 2 and 3) 6,31. Nevertheless, interocular differences were evident in patients 1, 7, and 8. Interocular asymmetry and even unilateral cases have previously been reported in GDLD (6,32). These observations support the concept that loss of *TACSTD2* function is essential for GDLD development; however, it is unlikely to be the sole determinant of disease severity. The variability in clinical expression may depend on factors such as tear film composition, epithelial microtrauma, eyelid structure, glandular function, systemic conditions, and other genetic or epigenetic modifiers (8,10).

The only previously reported Turkish GDLD family in the literature consisted of two siblings who carried a different *TACSTD2* truncating mutation, c.653delA, which was not detected in our cohort (9). The 15-year follow-up of that family showed a clinical course comparable to that of our patients with truncating *TACSTD2* variants, as repeated PKP were required because of recurrent corneal deposits (25).

Table 3. Treatment modalities and treatment outcomes of patients of GDLD patients.

Patient no/eye	Tx_1/Year	Tx_2/Year	Tx_3/Year	Tx_4/Year	BCVA at first visit/year	BCVA at last visit/year
1/OD	ED-DBP+anti-VEGF/2015	ED-DBP/2019	ED-DBP/2023	PRK/2025	0.2/2004	0.1/2025
1/OS	PPK/2004	PPK+PPV/2013	_	_	0.05/2004	HM/2025
2/OD	PPK/2004	ED-DBP/2018	PRK+MMC/2022	_	HM/2004	0.05/2022
2/OS	ED-DBP/2015	_	_	_	0.05/2004	0.05/2022
3/OD	ED-DBP/2013	_	_	_	0.4/2013	0.6/2020
3/OS	ED-DBP/2014	_	_	_	0.3/2013	0.5/2020
4/OD	ED-DBP/2014	ED-DBP/2021	ED-DBP/2023	ED-DBP+/2025	0.4/2014	0.2/2025
4/OS	ED-DBP/2014	ED-DBP/2021	ED-DBP/2023	_	0.6/2014	0.2/2025
5/OD	PPK/1996*	PPK/2016	PPK/2025	_	HM/2016	0.05/2025
5/OS	PPK/2000*	_	_	_	0.05/2016	HM/2025
6/OD	ED-DBP/2016	PPK/2017	PPK/2025	_	HM/2016	0.05/2025
6/OS	PRK/2020	DALK/2025	_	_	0.05/2016	0.05/2025
7/OD	DALK/2023	Cataract surgery/2024	_	_	HM/2017	0.5/2024
7/OS	DALK/2017	Cataract surgery /2020	ED-DBP/2023	PPK/2024	0.2/2017	0.1/2024
8/OD	_	_	_	_	0.8/2017	0.8/2024
8/OS	PPK/2007	PPK/2017	_	_	HM/2017	0.2/2024
9/OD	_	_	_	_	0.7/2021	0.7/2023
9/OS	_	_	_	_	0.5/2021	0.4/2023
10/OD	_	_	_	_	0.4/2020	0.3/2023
10/OS	_	_	_	_	0.3/2020	0.3/2023

*Denotes treatment applied in another center.
OD: Right eye, OS: Left eye, ED-DBP: Epithelial debridement with diamond burr polishing, PPV: Pars plana vitrectomy, PRK: Photorefractive keratectomy, DALK: Deep anterior lamellar keratoplasty, PPK: Partial penetrating keratoplasty, BCVA: Best-corrected visual acuity, HM: Hand motion, MMC: Mitomycin-C, Anti-VEGF: Anti-vascular endothelial growth factor, BCVA: Best-corrected visual acuity.

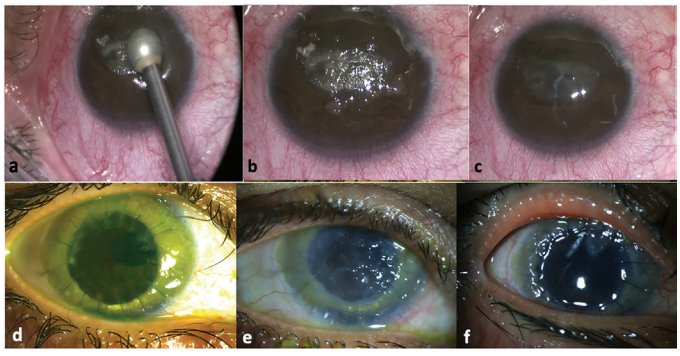

Figure 2. Anterior segment images of representative Gelatinous drop-like corneal dystrophy patients during follow-up regarding treatment modalities and outcomes. (a) Intraoperative image of Epithelial debridement with diamond burr polishing in the left eye of Patient 2; (b) Preoperative image of the left eye of Patient 2; (c) Postoperative image of the left eye of Patient 2; (d) Right eye of Patient 7 in 2018 after deep anterior lamellar keratoplasty; (e) Right eye of Patient 7 in 2024 showing recurrence of deposits in the graft; (f) Right eye of Patient 7 in 2025 after partial penetrating keratoplasty.

There was one family without any disease-associated *TACSTD2* variants in our cohort. Sequencing of exons 4 and 12 of *TGFBI* also did not reveal any variants. In the literature, GDLD patients without variants in the *TACSTD2* gene have been reported (10,33,34). A detailed investigation, by next-generation sequencing, of the non-coding regions of the *TACSTD2* gene or of other genes may reveal the responsible genetic variant in these patients.

The surgical management of GDLD primarily aims to remove the superficial corneal layers during the early stages of deposit formation, thereby improving vision, alleviating discomfort, and delaying the need for corneal transplantation. Among these procedures, phototherapeutic keratectomy (PTK) is one of the most frequently performed treatments in reported cases. In our cohort, ED-DBP was applied as the first surgical intervention to seven eyes of five patients and found to improve visual acuity, reduce corneal discomfort, and effectively postpone corneal transplantation, as anticipated. To the best of our knowledge, this is the first report describing the use of ED-DBP in patients with GDLD. ED-DBP has been demonstrated to be an effective treatment modality for recurrent corneal erosion and epithelial basement membrane dystrophy and is considered a safe, convenient, and cost-effective approach for managing

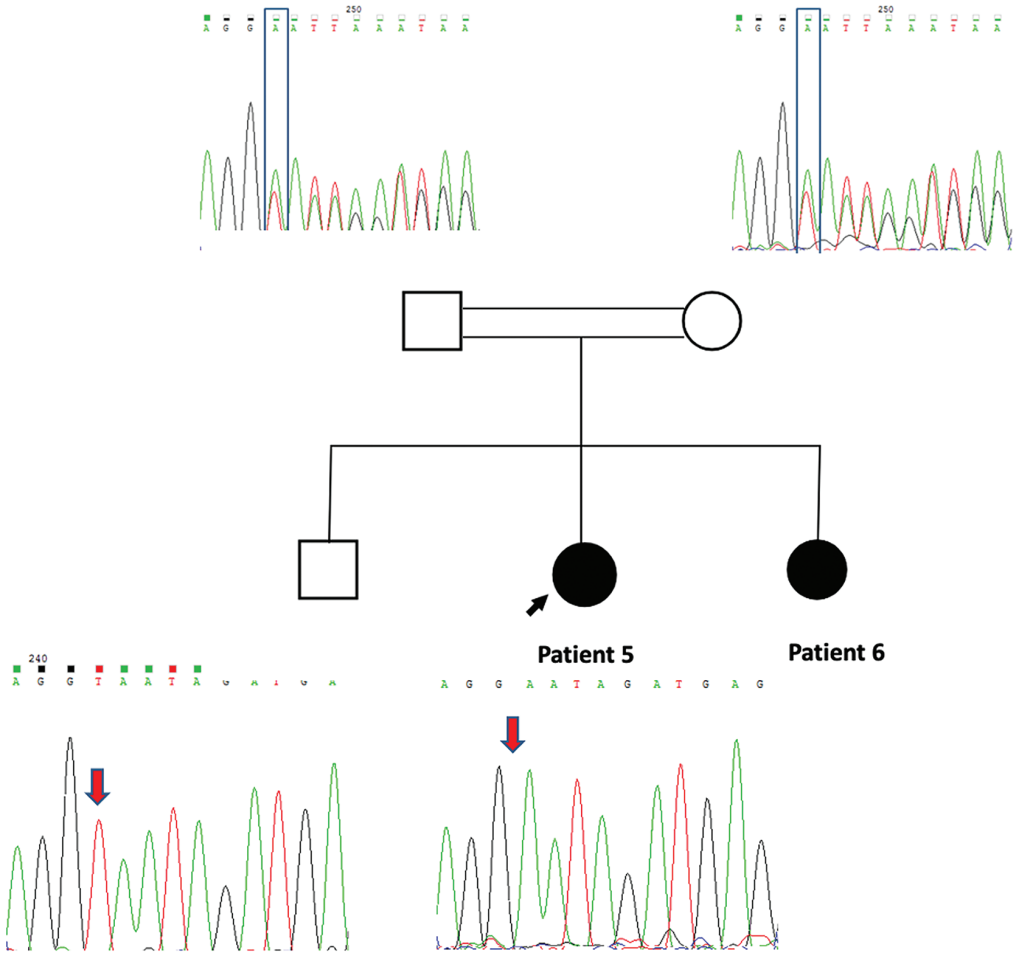

Figure 3. Pedigree of family 3 including Patient 5 and Patient 6 with homozygous novel frameshift variant, c.779del, p.Tyr260SerfsTer11, father and mother is heterozygous for this variant and the brother does not carry this variant and does not have any corneal signs or symptoms.

these pathologies (35-37). Furthermore, ED-DBP is reported to be technically simpler and less expensive than excimer laser PTK (38). Hieda et al. (39) reported that, after PTK combined with soft contact lens wear, the mean time to significant recurrence of GDLD was approximately 10 years. In contrast, Ozbek et al. (40) observed recurrence as early as two years after PTK without contact lens use, a recurrence interval comparable to that observed after ED-DBP in our cohort (Table 3).

Reports on long-term follow-up of GDLD patients are limited in the literature, and generally describe recurrent surgical interventions during the disease course. In our cohort, the longest follow-up period was 21 years, observed in patient 1, who underwent multiple ED-DBP procedures in the right eye and repeated PKPs in the left eye and had a BCVA of 0.1 in the better-seeing eye at the last visit. The longest follow-up reported in the literature is that of a Turkish patient, lasting 15 years, who required repeated PKPs and achieved a BCVA of 0.2 at the final examination (25). During follow-up, several of our GDLD patients required repeated keratoplasties, consistent with previous reports (Table 3). Recurrence rates after keratoplasty in GDLD have been reported as high as 50–70% within two years, and up to 97% within four years (1,12). To reduce recurrence, LSCT combined with keratoplasty has been reported to maintain corneal clarity and improve vision for up to two years 41,42. However, this technique has not gained routine clinical use due to complications such as severe glaucoma, the requirement for aggressive immunosuppression, and the need for repeat LSCT in failed cases (41,42). In the present study, LSCT was not performed on any of our GDLD patients.

Study Limitations

This study has several limitations. First, genetic testing could not be performed on all patients, and additional genetic analyses for those with negative Sanger sequencing results were unavailable. Second, histopathological evaluation of corneal specimens could not be performed on any patient. Third, statistical comparisons could not be performed due to the limited sample size. Finally, the pathogenicity of the novel variant was assessed only by *in silico* prediction methods.

CONCLUSION

In conclusion, this study represents the first report of GDLD patients from Central Anatolia and provides the most comprehensive clinical

and genetic characterization of Turkish GDLD patients to date. Our findings expand the mutational spectrum of *TACSTD2* in GDLD by identifying a novel variant and underscore the importance of genetic analyses of patients from diverse populations to better understand allelic and phenotypic heterogeneity. Furthermore, ED-DBP is proposed as a potential treatment modality for GDLD, particularly for cases with superficial deposits in both native corneas and grafts.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Institutional Ethics Review Board of Gazi University (approval number: 2025–405/04, date: 11.03.2025) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.Y.Ü., M.C.Ö., B.A., Concept: F.Y.T., H.D., A.Y.Ü., M.C.Ö., B.A., Design: F.Y.T., H.D., A.Y.Ü., M.C.Ö., B.A., Data Collection or Processing: F.Y.T., H.D., A.Y.Ü., Analysis or Interpretation: F.Y.T., A.Y.Ü., M.C.Ö., B.A., Literature Search: F.Y.T., Writing: F.Y.T.

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