• Letter to the Editor •

Characteristics of classical Ehlers-Danlos syndrome by clinical manifestations of the eyes: two cases report

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Dear Editor,

Ehlers-Danlos syndrome (EDS) comprises a heterogeneous group of inherited connective tissue disorders characterized by defects in collagen synthesis and structural integrity. Classical EDS (cEDS), most commonly associated with *COL5A1* or *COL5A2* mutations, typically presents with skin hyperextensibility, atrophic scarring, and joint hypermobility. However, ocular manifestations are often underrecognized and may precede systemic features, leading to delayed or missed diagnosis in clinical practice[1-3].

We report a familial case of cEDS in a mother and daughter, who presented predominantly with extreme corneal thinning and no other typical ocular manifestations, and lacked classic systemic features. This case highlights the diagnostic value of ophthalmic evaluation in identifying underlying connective tissue disorders.

Ethical Approval This study was conducted in accordance with the Declaration of Helsinki and approved by the Science and Technology Ethics Committee of Xi'an People's Hospital (Xi'an Fourth Hospital; Approval Number: KJLL-Z-K-2023001). Written informed consent was obtained from both patients (the mother and her daughter) for participation in this study and for publication of this report.

Case Presentation A 40-year-old woman was referred for refractive surgery evaluation due to high myopia. Pentacam examination revealed markedly reduced central corneal thickness (CCT) of 359 μm in the right eye and 358 μm in the left eye. Best-corrected visual acuity (BCVA) was 0.6 bilaterally, and intraocular pressure was within normal limits. Slit-lamp examination showed no apparent anterior segment abnormalities. However, corneal biomechanical assessment demonstrated increased corneal deformability [tomographic and biomechanical index (TBI): 0.97–1.00], suggesting compromised structural integrity. *In vivo* confocal microscopy revealed disorganized subepithelial nerve fibers and stromal abnormalities, while optical coherence tomography identified bilateral peripapillary retinoschisis, indicating posterior segment involvement (Figure 1).

Her daughter exhibited normal BCVA (1.0 in both eyes), similarly reduced CCT (350–355 μm), and abnormal corneal biomechanics (TBI: 1.0 bilaterally), with no additional ocular findings. She had a history of congenital spina bifida and had undergone multiple hip surgeries, and no family history of hereditary connective tissue diseases was reported. The concordance of corneal phenotypes within the family, combined with the daughter's systemic orthopedic history, raised strong suspicion of an inherited connective tissue disorder (Figure 2; Table 1).

Given these atypical findings, trio whole-exome sequencing was performed and identified a novel heterozygous frameshift mutation in *COL5A1* (c.1390_1397delGGCATGCTinsAGA; p.Gly464Argfs*150) in both patients. This variant is predicted to introduce a premature termination codon, resulting in truncated protein production and loss of normal collagen V function. According to American College of Medical Genetics and Genomics guidelines, it was classified as likely pathogenic. Notably, this mutation has not been reported in existing genomic

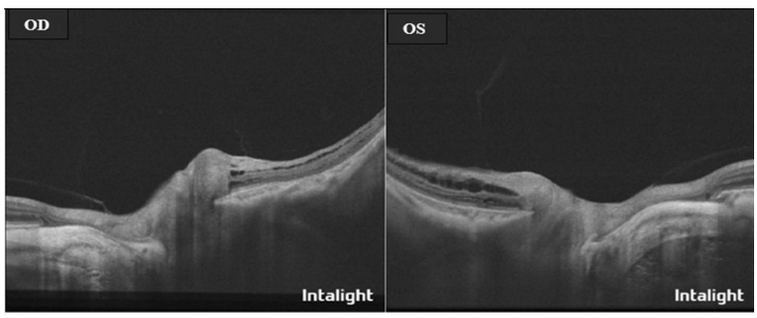


Figure 1 Optical coherence tomography images of the patient showing bilateral peripapillary retinoschisis OD: *Oculus dexter*; OS: *Oculus sinister*.

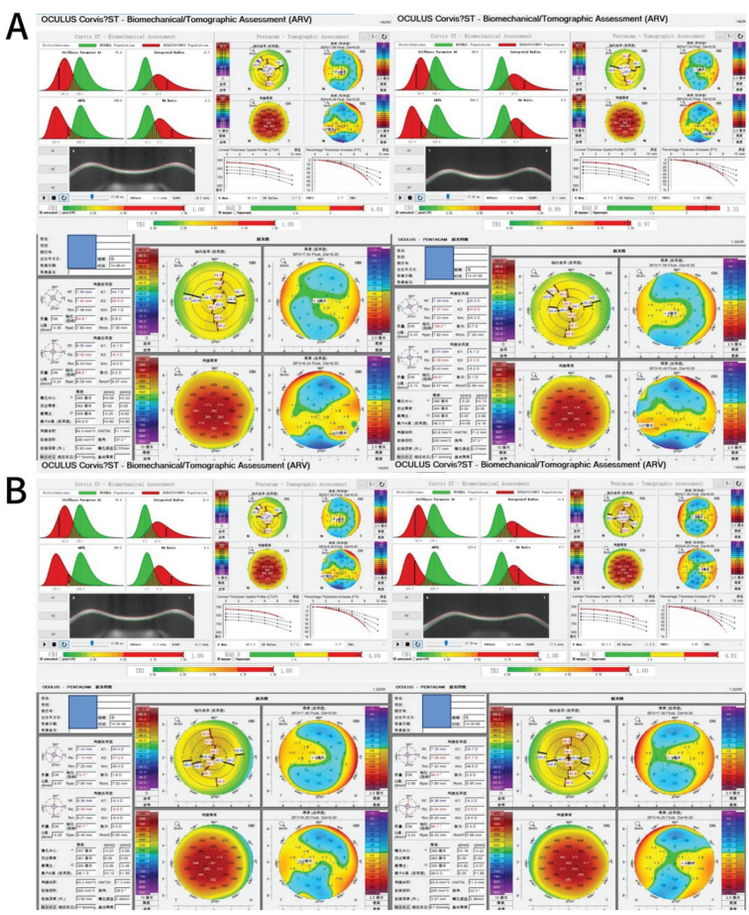


Figure 2 Corvis ST images and Pentacam maps of the patient and her daughter A: The patient, showing bilateral corneal softening and extreme thinning (TBI: 0.97/1.00; CCT: 359/358 μm); B: The daughter, with markedly thin central corneal thickness (TBI: 1.00/1.00; CCT: 350/355 μm). TBI: Tomographic and Biomechanical Index; CCT: Central corneal thickness.

databases, suggesting it represents a previously unrecognized pathogenic variant associated with cEDS (Figure 3).

Based on the clinical and genetic findings, a diagnosis of cEDS was established[4]. Corneal thinning is more commonly associated with brittle cornea syndrome; however, the absence of blue sclera, hearing impairment, and pathogenic variants in *ZNF469* or *PRDM5* excluded this diagnosis. Other connective tissue disorders, including Marfan syndrome and osteogenesis imperfecta, were also ruled out based on systemic evaluation and clinical features[5-7].

From a mechanistic perspective, type V collagen plays a critical regulatory role in collagen fibrillogenesis by controlling fibril diameter and spatial organization. Haploinsufficiency or structural abnormalities of *COL5A1* can disrupt stromal collagen architecture, resulting in reduced corneal thickness and biomechanical instability. This may explain the pronounced corneal thinning observed in both patients, even in the absence of overt systemic manifestations[8-9]. Our findings suggest that isolated or predominant ocular phenotypes may represent an early clinical expression of cEDS, particularly in patients with atypical presentations.

From a clinical standpoint, this case has important implications. First, it underscores the need for heightened vigilance during refractive surgery screening, as patients with undiagnosed

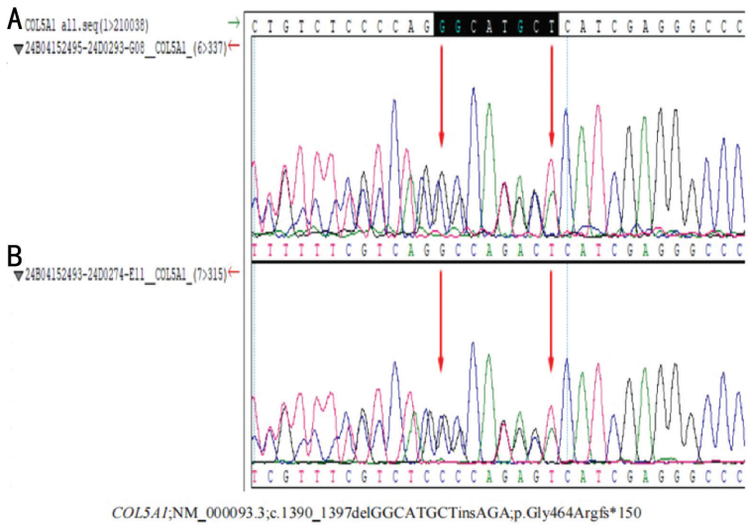


Figure 3 Sanger sequencing chromatograms of COL5A1 showing the heterozygous deletion–insertion frameshift variant (c.1390_1397delGGCATGCTinsAGA, p.Gly464Argfs*150) in exon 10, shared by the patient (B) and her daughter (A) Red arrows indicate the breakpoints of the deletion–insertion; overlapping heterozygous peaks downstream of the breakpoint reflect the two haplotypes generated by the frameshift. The genetic change in both individuals is COL5A1; NM_000093.3; c.1390_1397delGGCATGCTinsAGA; p.Gly464Argfs*150, present in the heterozygous state.

Table 1 Ocular characteristics of the mother and daughter

Characteristics	Mother	Daughter
BCVA	OD: 0.6; OS: 0.6	OD: 1.0; OS: 1.0
Intraocular pressures, mm Hg	OD: 9.6; OS: 11.9	OD: 9.1; OS: 10.0
Corneal endothelial cell count, cells/mm²	OD: 1577; OS: not measurable	OD: 2820; OS: 2476

BCVA: Best corrected visual acuity; OD: *Oculus dexter*; OS: *Oculus sinister*.

connective tissue disorders may present solely with abnormal corneal parameters. Second, it highlights the importance of integrating advanced ophthalmic imaging with genetic testing to achieve an accurate diagnosis. Finally, it emphasizes that ocular findings should not be interpreted in isolation, but rather as potential indicators of systemic disease.

Management in this case focused on preventing corneal complications, including strict avoidance of refractive surgery, implementation of protective strategies to reduce the risk of corneal trauma, and regular longitudinal follow-up. Genetic counseling was also recommended to address familial risk and guide future reproductive decisions[4,10].

This report expands the phenotypic and genotypic spectrum of cEDS in several ways. It demonstrates that extreme corneal thinning can serve as the initial and predominant manifestation of cEDS, and identifies a novel *COL5A1* frameshift mutation that may contribute to this phenotype. These findings provide new insights into genotype–phenotype correlations and broaden the clinical spectrum of the disease.

In conclusion, this case highlights the importance of a diagnostic paradigm that progresses from localized ocular abnormalities to systemic disease recognition. The identification of a previously unreported *COL5A1* mutation further underscores the genetic heterogeneity of cEDS and its potential ocular presentations. Clinicians should adopt a multidisciplinary approach, integrating ophthalmology, genetics, and systemic evaluation, when encountering unexplained corneal thinning. Such an approach may facilitate early diagnosis, prevent inappropriate interventions such as refractive surgery, and reduce the risk of severe complications including corneal rupture.

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