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## Trauma-induced exacerbation of epithelial-stromal *TGFBI* lattice corneal dystrophy



Several heritable diseases of the cornea known as corneal dystrophies are caused by mutations within the human genome. With the advent of genetic sequencing, it is possible to link most corneal dystrophies to a specific gene mutation.<sup>1</sup> While Transforming Growth Factor Beta 1 (*TGFBI*) is the most studied gene, with over 60 documented single point mutations,<sup>2</sup> without sequencing the patient's DNA it is difficult to determine if mutations within *TGFBI* are causal when a patient has symptoms of the disease. In symptomatic cases where the genotype of the individual is unknown, a DNA sequencing method such as next-generation sequencing (NGS) can provide the clinician with a genetic diagnosis. Furthermore, NGS can be used to distinguish which *TGFBI* mutation the patient may have or if other mutations in other genes that are known to cause other types of corneal dystrophy are present.<sup>1</sup>

Classic lattice corneal dystrophy (LCD), one of the *TGFBI* corneal dystrophies caused by the R124C mutation,<sup>1</sup> commonly presents as radially oriented linear opacities in the anterior stroma corresponding to amyloid accumulation.<sup>3</sup> It is often referred to as LCD type 1. In

addition to type 1, there exist several different subtypes of LCD linked to mutations within *TGFBI*.<sup>1</sup> We present two cases of LCD in a mother and son, both with a rare *TGFBI* variant mutation. The underlying LCD was discovered during a LASIK procedure, and trauma from a tree branch, in the mother and son respectively. To our knowledge, these are among the first reported cases of lattice dystrophy to be revealed by trauma. In order to uncover the underlying genetic mutation that was causal for this mother and son pair, we sequenced the patients' entire exome utilizing a NGS platform.

## MATERIALS AND METHODS

Institutional review board approval was waived for this retrospective case series, and permission to publish clinical findings was obtained from both patients. The two patients underwent full ophthalmic examination. Genetic testing was conducted on epithelial cells collected from the inner cheeks with an iSWAB collection kit (Mawi DNA Technologies, Hayward, Calif, USA). Genomic DNA was extracted with a QIAGEN QIAamp® DNA blood mini kit (Hilden, Germany), and whole-exome sequencing was carried out with the ACE platform™ (Personalis Inc., Menlo Park, Calif, USA) on a HiSeq 2000 (Illumina Inc., San Diego, Calif, USA). Real-time PCR (RT-PCR) was carried out on a 7500 FAST PCR System (Thermo Fisher

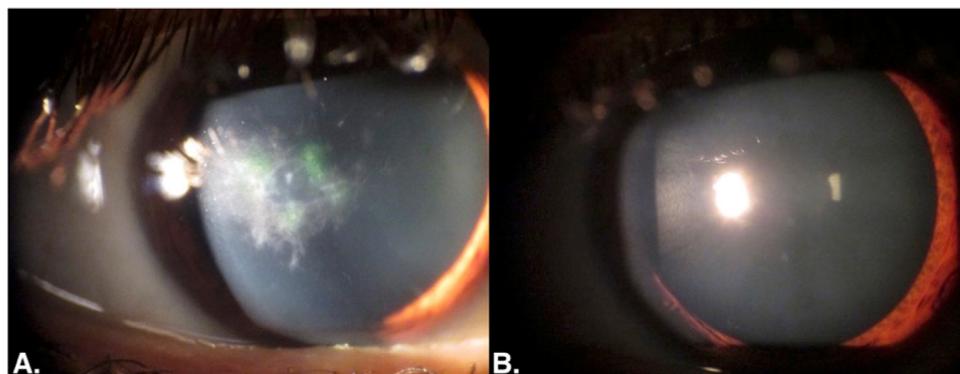


Fig. 1—Slit lamp photograph of the son. (A) Three epithelial defects within an area of lattice-like changes were found in the right eye. (B) A clear cornea with no lattice-like changes was found in the left eye.

Scientific, Waltham, Mass, USA) by Avellino Lab USA, Inc., (Menlo Park, Calif, USA).

## RESULTS

### Case 1

A 26-year-old male presented with symptoms of recurrent corneal erosions in his right eye 4 years after a tree branch injury. His family history was significant for LCD on the maternal side, including two relatives who had had corneal transplants. Best corrected visual acuity was 20/25 bilaterally. He had 3 epithelial defects within an area of lattice-like changes in his right eye (Fig. 1A). His left eye was unremarkable (Fig. 1B). He had mild Meibomian gland dysfunction and rosacea facies. He was treated with a bandage contact lens, preservative-free hyaluronic acid eye drops 6 times daily, and was started on Doxycycline 100mg daily. Genetic testing revealed a sequence variation (H626R c.1877A>G) in exon 14 of the *TGFBI* gene.<sup>4</sup> RT-PCR analysis confirmed the presence of the H626R variant.

### Case 2

The patient's 62-year-old mother was in attendance with him at consultation. In view of the findings and family history, she was examined. Her best corrected visual

acuity was 20/20 OD and 20/70 OS. She had bilateral LASIK performed in 2003, with central lattice-like changes at the flap interface in the right eye (Fig. 2A) and diffuse interface lattice-like changes in the left eye (Fig. 2B). She did not report to have had known corneal pathology before the LASIK procedure. The remainder of her eye exam was normal. Genetic testing as described above confirmed the same mutation in the *TGFBI* gene as her son.

## DISCUSSION

LCD is a common epithelial-stromal corneal dystrophy.<sup>5</sup> It is most often associated with a mutation in *TGFBI* on chromosome 5q31.<sup>1,6</sup> Typically, lesions are thin branching lines and/or subepithelial whitish ovoid dots and involve the central cornea with peripheral and posterior corneal sparing.<sup>1</sup> Patients are prone to recurrent corneal erosions and vision loss due to irregular astigmatism, and eventually confluence of the lesions. Treatment involves management of the recurrent erosions through traditional methods and visual rehabilitation through phototherapeutic keratectomy,<sup>7</sup> contact lenses, and ultimately corneal transplantation, if necessary.

The mutation identified in our patients has been associated with a late-onset (fourth to fifth decade) form of LCD that

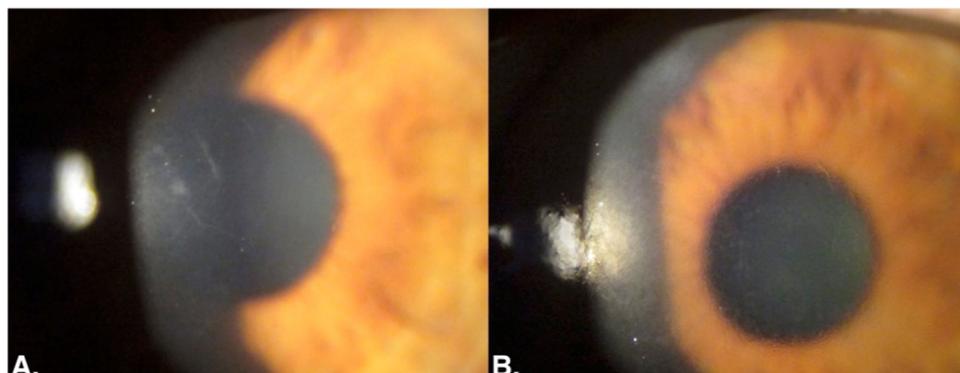


Fig. 2—Slit lamp photograph of the mother. (A) Lattice lines were noted in the center of the LASIK flap in the right eye. (B) Diffuse interface lattice-like changes were noted in the left eye.

was asymmetric in manifestation and possibly linked to minor corneal trauma in one case.<sup>8</sup> The patients in our series were asymptomatic until they sustained trauma to their eyes, and the son had an earlier unilateral presentation. In a patient where a significant family history of transplantation without known cause is present, genetic testing may be warranted. Given the late onset of this subtype of lattice dystrophy, genetic testing of the mother may have dissuaded her surgeon from performing LASIK.

## CONCLUSIONS

Whilst there have been a number of cases of granular/mixed granular dystrophy reported to have been exacerbated by LASIK or trauma,<sup>9,10</sup> we believe these to be the among the first cases of lattice dystrophy to follow a similar course. The use of genetic analysis in these patients was critical in diagnosing a rare type of LCD and will guide future therapy and disease monitoring. Identifying the specific type of LCD that a patient is genetically susceptible to may help clinicians predict the age of onset, any potentiating factors, and/or the histology and severity of any corneal depositions; however, such associations have yet to be fully elucidated. Additionally, our cases illustrate the role of genetic screening in refractive laser surgery candidates who have a family history of corneal transplantation of known or unknown cause. Prospective studies may clarify the role of genetic screening in such patients in the future.

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