Post-LASIK exacerbation of granular corneal dystrophy type 2 in members of a Chinese family

Abstract

Purpose The post-LASIK exacerbation of corneal dystrophy, otherwise asymptomatic, is almost exclusively associated with the TGFBI gene mutations at codon 124 in exon 4 and codon 555 in exon 12. It is our intention to demonstrate that the pre-operative genetic screening for TGFBI mutations should be mandatory for refractive surgery candidates.

Patients and Methods In this study, we reviewed the proband’s post-LASIK slit-lamp and in vivo confocal microscopy images and genetic testing results, and performed genetic testing on eleven additional members of the family to investigate the penetrance of corneal dystrophy in asymptomatic members who carry the mutation.

Results The proband demonstrated a post-LASIK exacerbation of Granular Corneal Dystrophy type 2 (GCD2), identified as a TGFBI R124H mutation. Three of the 11 family members tested positive for the same R124H mutation as the proband.

Conclusion The lesson learned from this case is that the genetic screening of TGFBI mutations must be incorporated into the pre-operative screening procedures to prevent exacerbation and recurrence, which eventually could lead to the need for a corneal transplant.

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Introduction

As the first report of autosomal-dominant Granular Corneal Dystrophy type 2 (GCD2) in individuals from Avellino, Italy in 1988, many cases of post-laser surgery exacerbation have been reported worldwide. Inherited corneal dystrophy exacerbation is characterized by bilateral opacity in anterior corneal stroma leading to a severe decrease of the best corrected visual acuity (BCVA) and ultimately to surgical treatment.

The Avellino Universal Test examines the five most common TGFBI corneal dystrophies, each triggered by different mutations in exons 4 and 12 of the TGFBI gene, located on chromosome 5q31.1. Purified DNA is extracted from oral epithelial cells collected by buccal swabs and the genotype of the LASIK candidate obtained by amplifying the targeted DNA point mutations (Table 1).

Herein, we report the results of ophthalmic and genetic examination of an individual with post-LASIK GCD2 and his family from Jiangsu province, China.

Case series

Case 1

The proband is a 29-year-old Chinese male who underwent bilateral LASIK surgery in 2006. The post-operative uncorrected visual acuity (UCVA) in both eyes was 20/20. He had an uneventful post-operative course and did not have regular follow-up examinations after the surgery. In July 2016, 10 years after LASIK surgery, he was referred to Shanghai First People’s Hospital for evaluation of dryness, foreign body sensation, and mildly decreased vision acuity in both eyes. The findings were opacities in both of his corneas. Slit-lamp examination was conducted (Figure 1a and b). His UCVA was 16/20 in the right eye and 12/20 in the left eye. The manifest refraction was −1.00 diopters cylinder...
Table 1 The five most common TGFBI corneal dystrophies are GDC2, LCD1, RBCD, GCD1, and TBCD

| Corneal dystrophy name                          | Exon location | Nucleotide change | Sequence change | Amino-acid change |
|------------------------------------------------|---------------|-------------------|-----------------|-------------------|
| Granular corneal dystrophy, type 2             | 4             | c.418G>A          | CGC>CAC         | p.R124H           |
| Lattice corneal dystrophy, type 1              | 4             | c.417C>T          | CCC>TGC         | p.R124C           |
| Reis-Buckler corneal dystrophy                 | 4             | c.418G>T          | CGC>CAC         | p.R124L           |
| Granular corneal dystrophy, type 1             | 12            | c.1663C>T         | CGG>TGC         | p.R555W           |
| Thiel-Behnke corneal dystrophy                 | 12            | c.1664G>A         | CGG>CAG         | p.R555Q           |

The respective exon locations, nucleotide changes, and amino-acid changes of their causative mutations are listed (Nucleotide change and Sequence change information is from HGMD by Qiagen, Hilden, Germany). A sterile Copan buccal swab (Copan, Brescia, Italy) was used for collecting oral epithelial cells. The swabs were then sent to Avellino Labs China for testing using the Universal Test, which detects the five most common TGFBI corneal dystrophies. The laboratory performed a DNA extraction from the swab using the DNA Extract All Reagents kit (Thermo Fisher Scientific Inc., Waltham, MA, USA). The purified DNA was then amplified by the TaqMan GTXpress Master Mix (Thermo Fisher Scientific Inc.) with Life Technology’s 7500 FAST real-time PCR system (Thermo Fisher Scientific Inc.). Through a series cycle of denaturing, annealing and extension, the 7500 instrument collects the amplification fluorescence signals of the targets and generates a result from which the genotype may be inferred.

Table 1 shows the five most common TGFBI corneal dystrophies are GDC2, LCD1, RBCD, GCD1, and TBCD. The respective exon locations, nucleotide changes, and amino-acid changes of their causative mutations are listed. The proband inherited the mutation. The mutation status of the proband’s grandparents was unknown. Since the proband’s aunt tested negative and the medical history of the deceased uncle is unknown, it is unclear whether the proband’s mother inherited the mutation or it arose de novo.

Discussion
Corneal dystrophies contraindicate refractive surgery due to the likelihood of recurrence and exacerbation. As they may be difficult to determine by family history and clinical examination alone, a genetic test to detect TGFBI mutations should be incorporated into standard practice as one of the prescreening tools for refractive surgeries. In Case 1, the patient displayed no clinical symptoms and passed the LASIK surgery prescreening examination. Ten years after surgery, he developed symptoms that affected his vision. A genetic test identified that most likely the cause of the stromal deposits was the TGFBI R124H heterozygous mutation. The proband’s 15-year-old nephew inherited the mutation from proband’s sister, who tested positive for the mutation without symptoms; however, the examination conducted after the testing revealed that she too had corneal stromal deposits. These two cases demonstrate that a lack of clinical signs does not mean the absence of corneal dystrophy-causing mutations. It is justified to test the asymptomatic refractive surgery candidates to rule out disease-causing mutations.

Corneal dystrophy is a disease with a low prevalence (US: 1:1115, Korea: 1:870, China: 1:416) and debilitating outcome, ultimately resulting in corneal transplant as a treatment. The recurrent nature of the disease can result in multiple corneal transplants. Therefore, prevention and prescreening with a genetic test to detect the mutations, in addition to a thorough clinical examination is key.
Figure 1  Slit-Lamp (Nikon Corporation, Tokyo, Japan) photographs of the proband revealed dense, fine, white granules in the central corneas of both eyes, located at the interface between the flap and stromal bed on the right (a) and left (b) eyes. *In vivo* confocal microscopy (IVCM) (Rostock Cornea Module of Retina Tomograph (HRT/RCM); Heidelberg Engineering GmbH, Heidelberg, Germany) images of the right (c) and left (d) anterior stroma with hyper-reflective extracellular deposits. *In vivo* confocal microscopy (IVCM) images of the right (e) and left (f) anterior stroma with hyper-reflective extracellular deposits observed in the corneas of the proband’s sister.
Summary

What was known before
- Post-LASIK exacerbation of corneal dystrophy is almost exclusively associated with TGFBI gene mutations.
- Some mutation carriers are asymptomatic.

What this study adds
- Genetic screening of TGFBI mutations must be incorporated into the pre-operative screening, especially for those who are asymptomatic.

Conflict of interest

John Marshall is a consultant to Avellino Lab USA, Inc., Frost Professor at Institute of Ophthalmology, University College of London, London, UK. Tara Moore is a consultant to Avellino Lab USA, Inc., Director of the Biomedical Sciences Research Institute and Professor of Personalized Medicine at University of Ulster, Coleraine, Northern Ireland, UK. M Andrew Nesbit is a Senior Lecturer at University of Ulster, Coleraine, Northern Ireland, UK. Rao Me is an Ophthalmologist and BL Ke is Professor of Ophthalmology at Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. Larry DeDionisio is an employee of Avellino Lab USA, Inc., Menlo Park, CA, USA. Connie Chao-Shern is a PhD student at University of Ulster, Coleraine, Northern Ireland, UK and an employee of Avellino Lab USA, Inc., Menlo Park, CA, USA. The authors declare no conflict of interests. The authors alone are responsible for the content and writing of this article.

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