



Prevalence of transforming growth factor β -induced gene corneal dystrophies in Chinese refractive surgery candidates

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Purpose: To determine the prevalence of the transforming growth factor (TGF) β -induced gene corneal dystrophies in refractive surgery candidates in China.

Setting: Five hospitals in China.

Design: Prospective case series.

Method: Refractive surgical candidates from 5 preselected eye hospitals/centers in China were recruited after providing informed consent. All patients had slitlamp biomicroscopy and collection of a buccal swab as a source of DNA for screening of the TGF β -induced gene for the 5 most common mutations associated with Reis-Bückler corneal dystrophy, Thiel-Behnke corneal dystrophy, granular corneal dystrophy type 1, granular corneal dystrophy type 2, and lattice corneal dystrophy type 1.

Results: Of the 2068 refractive surgery candidates analyzed, 4 had corneal opacities in both eyes on slitlamp examination.

Screening for the TGF β -induced gene found the heterozygous p.R124H mutation associated with granular corneal dystrophy type 2 in each of the 4 individuals with corneal opacities as well as in a fifth individual who did not have any corneal opacities, for a prevalence of 0.24%. Exacerbation of dystrophic corneal deposition developed after laser refractive surgery in 2 individuals who did not have preoperative TGF β -induced gene screening.

Conclusions: The prevalence of the TGF β -induced gene corneal dystrophies in Chinese refractive surgery candidates was estimated to be approximately 0.24%. Genetic testing is recommended to identify and exclude from candidacy all individuals with a TGF β -induced gene dystrophy before elective keratorefractive surgery to avoid causing accelerated postoperative dystrophic deposition.

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Corneal dystrophies are a group of inherited bilateral noninflammatory corneal disorders without any relationship to environmental or systemic factors.^{1,2} The accumulation of opacities in the cornea leads to significant impairment of corneal transparency and refraction. The advent of modern molecular genotyping technology has made it possible to classify these corneal dystrophies using accurate genetic information, and they are now separated by both the layer of the cornea in which the

dystrophic opacities appear and the identity of the causative gene.¹ More than 60 mutations in the transforming growth factor (TGF) β -induced gene (OMIM601692, formerly called TGF β -induced gene H3) have been associated with a variety of phenotypically distinct corneal dystrophies.³ Of these, 5 more commonly occurring distinctive heterozygous mutations have been found to be associated with 5 specific phenotypes; they are p.R124L in Reis-Bückler corneal dystrophy, p.R555Q in

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Thiel-Behnke corneal dystrophy, p.R555W in granular corneal dystrophy type 1, p.R124H in granular corneal dystrophy type 2, and p.R124C in lattice corneal dystrophy type 1. Because the majority of the TGF β -induced gene protein is produced by the corneal epithelium, even though deposition of the dystrophic protein occurs in the Bowman layer and stroma, the TGF β -induced gene dystrophies have been renamed the epithelial-stromal TGF β -induced gene dystrophies by the International Committee for the Classification of the Corneal Dystrophies.¹

Although the TGF β -induced gene dystrophies typically present in affected individuals in the first or second decade of life, the early manifestations of these dystrophies can be subtle and can differ from the classic phenotype, leading to the potential for the opacities to be missed or misdiagnosed. Granular corneal dystrophy type 2 is typically associated with the latest appearance of dystrophic corneal deposits and is thus commonly diagnosed during the teens or early adulthood. Because individuals as young as 18 years are eligible for keratorefractive surgery, the dystrophic deposits might be few in number, small in size, and not resemble characteristic dystrophic deposits in young adults with a TGF β -induced gene dystrophy, in particular granular corneal dystrophy type 2, leading to the diagnosis of a TGF β -induced gene dystrophy not being made during a keratorefractive surgery screening examination. Because the failure to diagnose a TGF β -induced gene dystrophy before keratorefractive surgery could lead to an exacerbation of the dystrophic deposits and loss of vision, it is imperative for refractive surgeons to identify individuals at risk for this complication before refractive surgery.⁴⁻⁷ More than 1 million refractive surgeries are performed in China annually; thus, it is of great importance for ophthalmic surgeons to exclude these high-risk patients from elective refractive surgery procedures.⁸

The purpose of this study was to estimate the frequency of the TGF β -induced gene corneal dystrophies in a refractive surgery population in China as well as to determine the feasibility of performing preoperative genetic testing to identify individuals at risk for developing an exacerbation of a TGF β -induced gene dystrophy after keratorefractive surgery.

PATIENTS AND METHODS

Patients enrolled in this study were refractive candidates who received preoperative evaluations in 1 of the 5 hospitals or eye centers in China. The 5 preselected eye hospitals were Beijing Tongren Hospital of Capital Medical University; Peking University Third Hospital, Beijing; Eye and ENT Hospital, Fudan University, Shanghai; Eye Hospital, Wenzhou Medical University, Zhejiang Eye Hospital, Wenzhou; and West China Hospital, Sichuan University, Chengdu. Ethics committee approvals were obtained from these 5 hospitals or eye centers in China. Written informed consent was obtained from all patients before the initiation of examinations. The multicenter research conformed to the tenets of the Declaration of Helsinki.

Ophthalmologic Examinations of Patients with Corneal Dystrophies

Slitlamp Biomicroscopy The cornea of each patient was assessed by slitlamp biomicroscopy after the examinations of binocular

uncorrected distance visual acuity and corrected distance visual acuity. Digital photography with the Visupac video system and 130 SL-M slitlamp (Carl Zeiss Meditec AG) ($\times 6$ to $\times 10$ white-light direct illumination) was performed on corneas that showed abnormal opacities.

Anterior Segment Optical Coherence Tomography A spectral-domain optical coherence tomography (OCT) device fitted with an anterior segment module (Optovue, Inc.) was used to detect and assess the depth of the corneal deposits.

Genomic DNA Collection and Molecular Genetic Analysis Buccal samples were collected from all study patients using dry cotton or rayon swabs without preservatives (sample collection kit, Avellino Lab USA, Inc.). At least 10 swipes were taken from the inside of each cheek to obtain an adequate amount of buccal epithelial cells. Genomic DNA was extracted using a DNA Extract All Reagents Kit (Life Technologies). Taqman real-time polymerase chain reaction (PCR) amplification was performed using GTXpress Master Mix (Life Technologies Corp.) and custom primers and probes (Life Technologies Corp.). The amplification reaction and result analysis were performed using the Applied Biosystems 7500 FAST Real-Time PCR System (Life Technologies Corp.). The TGF β -induced gene exon 4 was analyzed for mutations at codon 124, and the TGF β -induced gene exon 12 was analyzed for mutations at codon 555. Nucleotide sequences were compared with the published TGF β -induced gene cDNA sequence (GenBank accession no. NM_000358).

RESULTS

Ophthalmologic Examinations of Patients With Corneal Dystrophies

Of the 2068 patients analyzed in this study, 973 were men and 1095 women. The age of the patients ranged from 17 to 48 years. Most patients were Han Chinese, except 2 who were Tibetan, 2 who were Mongolian, 2 who were Manchu, 2 who were Yi minority people, 2 who were Tujia minority people, 2 who were Hui minority people, 2 who were Hmong people, and 1 who was Korean.

Four of the 2068 patients had corneal opacities in both eyes, diagnosed in each case as dystrophic corneal deposits based on the clinical appearance, a family history, or both. They included a 39-year-old woman without a family history whose 5-year-old son did not show an opacity in either cornea (Figure 1), a 20-year-old man (Figure 2) and his 55-year-old mother (Figure 3), and 2 unrelated individuals, a 23-year-old woman and a 31-year-old woman who both had a family history of an undiagnosed corneal disorder. In addition, exacerbation of dystrophic corneal deposition developed after laser refractive surgery in a 22-year-old woman (Figure 4) and a 36-year-old woman (Figure 5) who did not have preoperative TGF β -induced gene screening.

Genomic DNA Collection and Molecular Genetic Analysis

Screening of TGF β -induced gene in each of the 2068 refractive surgery candidates found the p.R124H mutation associated with granular corneal dystrophy type 2 in 5 individuals (heterozygous in each), each of the 4 individuals with corneal opacities and a fifth individual, a 30-year-old man who had a family history of a corneal disorder but who did not show any corneal opacities. In addition, both of the individuals who did not have preoperative TGF β -induced gene screening and developed an exacerbation

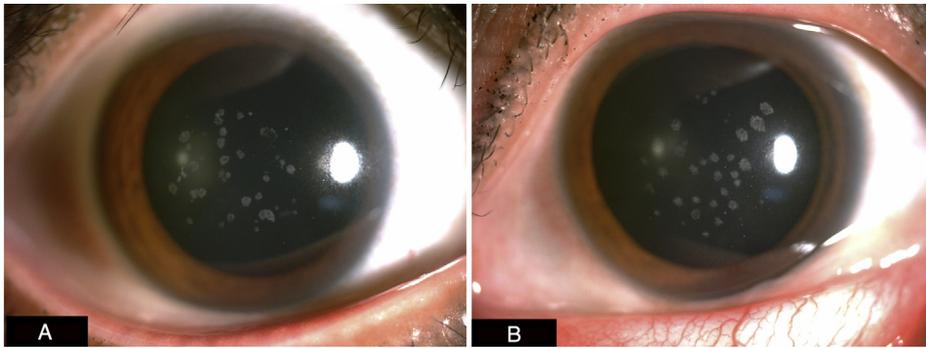


Figure 1. Slitlamp biomicroscopy images of the right (A) and left (B) eyes of a 39-year-old woman refractive surgery candidate with no known family history of corneal dystrophy. Grayish-white central granular opacities with clear intervening stroma are seen in each cornea.

of dystrophic corneal deposition after laser refractive surgery had the p.R124H mutation in the heterozygous state. None of the other 4 most common pathogenic mutations associated with the TGF β -induced gene dystrophies was identified. Therefore, the prevalence of the TGF β -induced gene corneal dystrophies in this Chinese refractive surgery candidate population was 0.24% (5 of 2068 individuals).

DISCUSSION

To our knowledge, this study is the first to estimate the frequency of any of the corneal dystrophies in a Chinese population, although Chinese individuals with a variety of corneal dystrophies have been included in a number of case reports and case series.^{9–13} The 5 hospitals and eye centers in this study were located in different regions across China, with the majority of the patients being from the Han ethnic group. Because approximately 91.6% of the Chinese population are Han, the study population is representative of the Chinese population as a whole.¹⁴ Five individuals heterozygous for the mutation that causes granular corneal dystrophy type 2 were identified in a refractive surgical candidate population of 2068 individuals (0.24%). Cases of granular corneal dystrophy type 2 have been reported globally in various ethnic origins.^{15–17} Codon 124 is a mutation hotspot in the TGF

β -induced gene, and granular corneal dystrophy type 2 caused by the heterozygous p.R124H mutation in the TGF β -induced gene appears to be the most common TGF β -induced gene corneal dystrophy in China, as it is in Taiwanese, South Korean, and Japanese populations.^{9,18–22} A conservative estimate of the frequency of granular corneal dystrophy type 2 in Korea is 11.5/10 000.²³ Extrapolating from the number of cases detected in this study, the frequency of granular corneal dystrophy type 2 in Chinese refractive surgical candidates is approximately 24.1/10 000, which is higher than the prevalence of granular corneal dystrophy type 2 in Korea. This difference might be the result of the different methods of calculation and estimation. What we report here is the frequency of granular corneal dystrophy type 2 in Chinese refractive surgery candidates, and the limited age range (17 to 48 years) might not be representative of the prevalence in the entire Chinese population.

Although researchers have been working on the pathogenic mechanism underlying corneal dystrophies, effective therapies to ameliorate or cure these corneal disorders have not been achieved.^{24–26} The depth and extension of corneal opacities tend to worsen as the dystrophies progress. The opacities increase in number and spread to deeper layers of the stroma over years, as observed in the patients and their offspring in our study. In some cases, although the

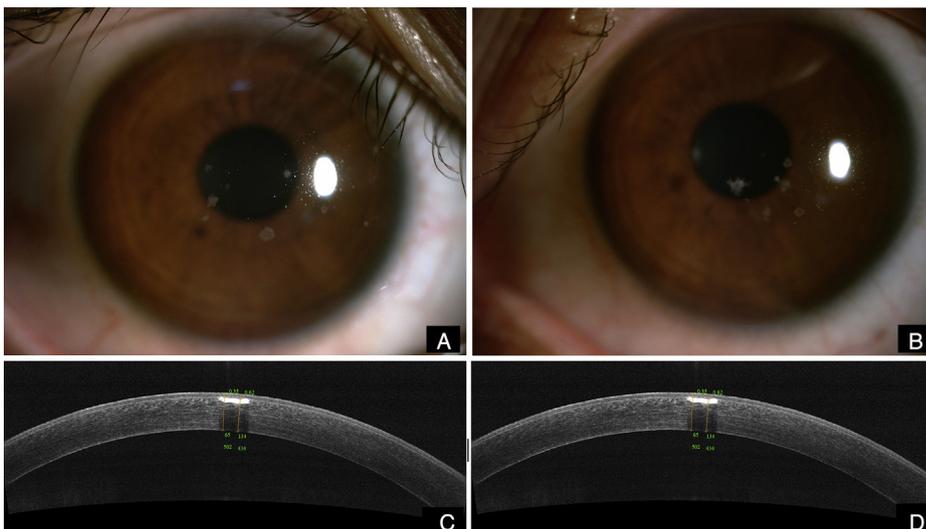


Figure 2. Slitlamp biomicroscopy images of the right (A) and left (B) eyes of a 20-year-old man refractive surgery candidate. Several pleomorphic semitransparent deposits are scattered throughout both corneas. Anterior segment OCT shows deposits located at a depth of approximately 65 μ m to approximately 134 μ m from the corneal surface in the right (C) and left (D) eyes.

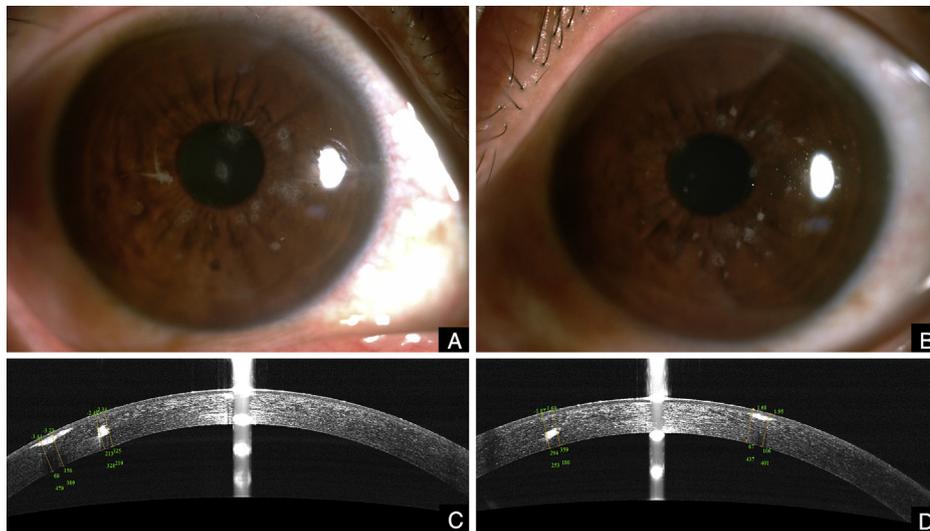


Figure 3. Slitlamp biomicroscopy images of the right (A) and left (B) eyes of the 55-year-old mother of case 2. Granular snowflake-like and lattice-like opacities were scattered in the corneas. Anterior segment OCT shows some deposits that are much deeper than those in her son's corneas, with the deepest deposits at approximately 294 μm to approximately 359 μm from the corneal surface in the right (C) and left (D) eyes.

dystrophic deposits might gradually progress to involve the deep stroma, the patients still had good visual acuity into their 50s and 60s. However, keratorefractive surgery is well known to increase the rate of TGF β -induced gene protein deposition in the cornea and adversely affect vision in

individuals with granular corneal dystrophy type 2.^{7,9,27–28} This was shown by the significantly greater number of dystrophic deposits and associated worse vision in the 22-year-old woman 2 years after laser in situ keratomileusis (LASIK) surgery compared with her 56-year-old mother,

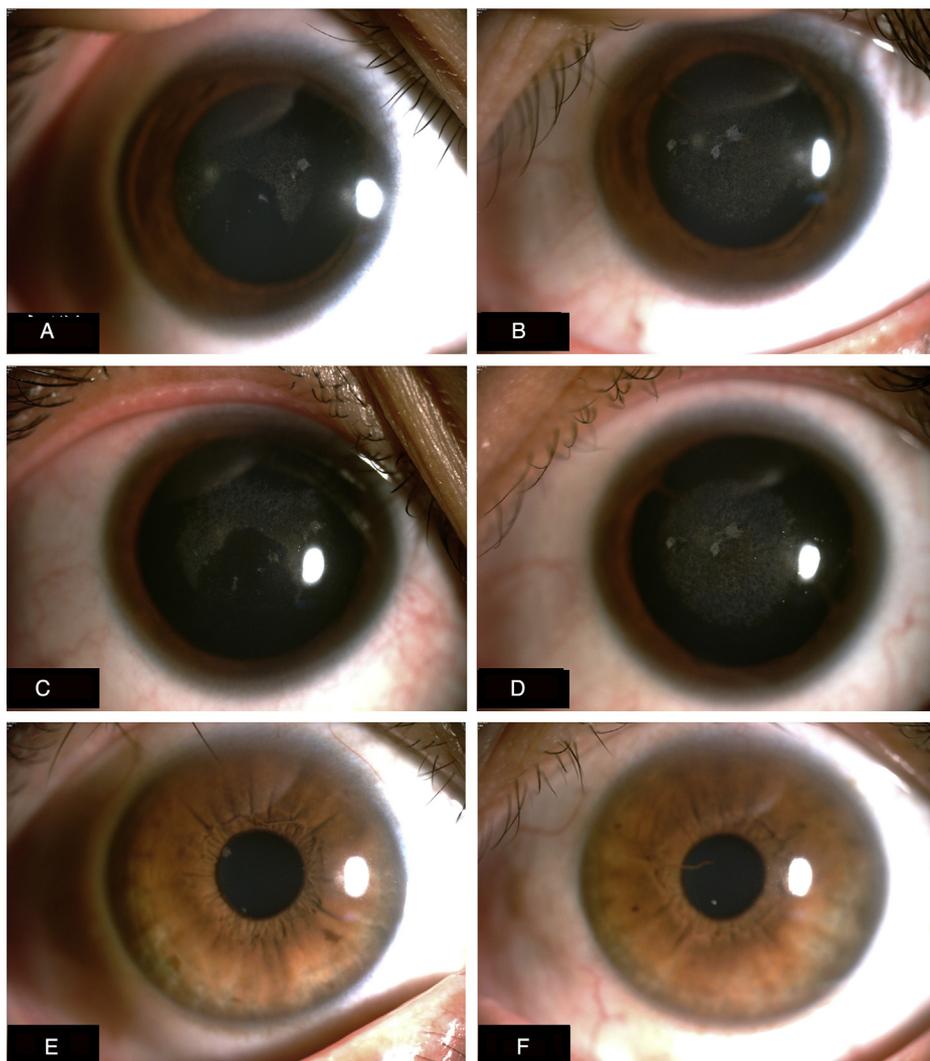


Figure 4. Slitlamp biomicroscopy images of the corneas of a 22-year-old woman after femtosecond laser-assisted LASIK surgery. The ophthalmic examinations performed before refractive surgery did not document any corneal opacities. A large number of subtle and fine sand-like opacities were observed in the interface between the flap and the residual stromal bed 18 months after surgery in both the right (A) and left (B) eyes. Continued accelerated collection of interface opacities was observed 24 months after surgery in both the right (C) and left (D) eyes. Slitlamp biomicroscopy images of the cornea of the woman's 56-year-old mother show a paucity of granular corneal opacities in both the right (E) and left (F) eyes.

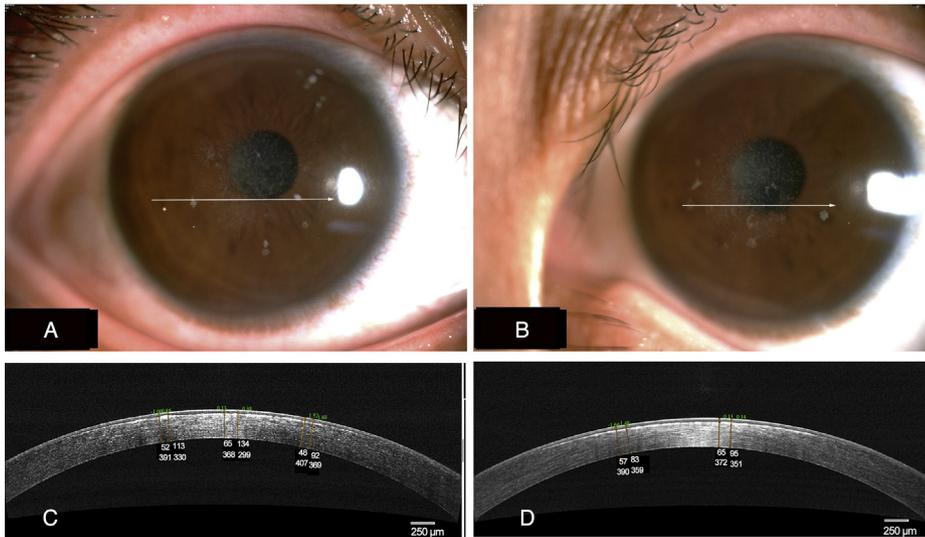


Figure 5. Slitlamp biomicroscopy images of the corneas of a 36-year-old woman after femtosecond laser-assisted LASIK surgery. Several discrete granular opacities and a layer of diffuse fine opacities are localized on the LASIK flap interface in the right (A) and left (B) eyes. The locations scanned by AS-OCT in the right (C) and left (D) eyes are marked with the white arrows in the slitlamp biomicroscopy images (A and B). The deposit depths (*top numbers below the cornea*) and residual stromal bed thickness (*bottom numbers below the cornea*) are annotated in the AS-OCT images, which confirmed that the deposits were localized to the LASIK flap interface in the right (C) and left (D) eyes.

who had not had previous corneal surgery but shared the same p.R124H mutation associated with granular corneal dystrophy type 2. The excimer laser ablation activates production of TGF β -1, which plays a key role in the healing process, and subsequently activates TGF β -induced gene protein production and accumulation in the cornea.^{4,27} Although all reported cases of exacerbation of a TGF β -induced gene dystrophy involve individuals with granular corneal dystrophy type 2, it is likely that a similar phenomenon would be observed in individuals with other TGF β -induced gene dystrophies as well. Because LASIK surgery stimulates TGF β -1-induced TGF β -induced gene protein expression, increased wild-type TGF β -induced gene protein expression is expected in individuals without a TGF β -induced gene dystrophy and increased mutant TGF β -induced gene protein expression and deposition is expected in individuals with any of the TGF β -induced gene dystrophies.

The 2 cases that we report of individuals who did not have TGF β -induced gene screening performed before LASIK surgery and subsequently developed a rapid acceleration of corneal opacities add to the growing number of reports of granular corneal dystrophy type 2 exacerbation after elective keratorefractive surgery.^{4,6} The induced deposits often appear in the flap interface and primarily within the ablation zone, which causes decreased visual acuity, photophobia, and glare.^{4,5} Although phototherapeutic keratectomy can be performed on the stromal bed to remove the deposits, removing the deposits on the underside of the LASIK flap is more problematic and might require flap amputation. Therefore, deep anterior lamellar keratoplasty or penetrating keratoplasty might be required to restore corneal clarity, although recurrence of the dystrophic deposits is of course expected.¹¹

Given that the majority of people seeking refractive surgery in China are in their 20s and 30s, preoperative detection is critical. In clinical practice, the diagnosis of corneal dystrophies is made based on a family history and

the location and morphology of corneal deposits using slitlamp biomicroscopy.^{29,30} However, it can be difficult to differentiate early dystrophic opacities from other non-dystrophic conditions with slitlamp biomicroscopy and it is impossible in younger patients with few, if any, corneal opacities at the time of presentation for a refractive surgery screening examination.

The appearance of corneal opacities does not and should not automatically exclude an individual from elective keratorefractive surgery. It is incumbent on the ophthalmologist to diagnose corneal opacities as being post-infectious, post-inflammatory, degenerative, dystrophic, and so forth and then determine whether the individual is a candidate for elective keratorefractive surgery. In the cases that we presented, as well as other cases that the authors are aware of, dystrophic opacities were misinterpreted as non-dystrophic and thus the individuals were determined to be candidates for elective keratorefractive surgery. This is why we advocate the use of molecular genetic analysis to provide a definitive means of differentiating between dystrophic and non-dystrophic corneal opacities. The collection of buccal epithelial cells using a cheek swab is an easy to perform method of DNA collection that provides refractive surgeons with the molecular diagnostic information necessary to identify individuals who should not have keratorefractive surgery.

In conclusion, granular corneal dystrophy type 2 was the most common TGF β -induced gene corneal dystrophy identified in Chinese refractive surgery candidates, with an observed prevalence higher than the population prevalence reported for other regions in Asia. Performing TGF β -induced gene screening as part of the preoperative evaluation of candidates with unexplained corneal opacities or a family history of a corneal disorder can prevent the exacerbation of granular corneal dystrophy type 2, and perhaps the other TGF β -induced gene dystrophies, after keratorefractive surgery in an affected, but clinically misdiagnosed individual.

WHAT WAS KNOWN

- Keratorefractive surgery in individuals with granular corneal dystrophy type 2 will lead to an exacerbation of the dystrophic deposits and loss of vision.
- It is imperative for refractive surgeons to identify individuals at risk for this complication before refractive surgery.

WHAT THIS PAPER ADDS

- Granular corneal dystrophy type 2 was the most common TGF β -induced gene corneal dystrophy identified in Chinese refractive surgery candidates, with a prevalence of 0.24%.
- The prevalence of the granular corneal dystrophy type 2 in Chinese refractive surgery candidates was higher than the prevalence reported in other Asian populations.
- Molecular genetic analysis provided a definitive means of diagnosing granular corneal dystrophy type 2 and the other TGF β -induced gene corneal dystrophies before elective keratorefractive surgery to prevent postoperative exacerbation.

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