• Investigation •

A recognition survey of granular corneal dystrophy type 2 genetic detection in China

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Abstract

● **AIM:** To evaluate the feasibility of promoting genetic detection for granular corneal dystrophy type 2 (GCD_2) by a questionnaire conducted among citizens in five cities in China.

● **METHODS:** The data were collected by questionnaire, and analyzed by Chi-square test and one-tailed *t* test in IBM SPSS statistics.

● **RESULTS:** Based on the survey data on the awareness of GCD_2 genetic detection in this study and the positive predictive analysis report of the citizens in five cities in China, the vast majority (84.2%) of respondents had never heard of it and did not know that GCD_2 patients have been prohibited from performing excimer surgery that can deteriorate GCD_2 patients' condition even leading to blindness. Though 3.4% of patients understood GCD_2 very much, they have no idea that GCD_2 could not be 100% accuracy diagnosed by the conventional inspection methods.

● **CONCLUSION:** It is feasible and necessary to use GCD_2 genetic detection as an excimer preoperative examination project. In order to promote the development of detection project, a few improvements should be carried out in terms of the promoting efforts, costs, and research progress.

● **KEYWORDS:** granular corneal dystrophy type 2; corneal opacity; excimer laser surgery

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INTRODUCTION

Myopia is a condition in which the focusing power (refraction) of the eye is greater than that required for clear distance vision. It was estimated that the prevalence of myopia increased from 22.9% of the world population in 2000 to 49.8% of the world population in 2050, and that of high myopia increased from 2.7% to 9.8%, respectively[1]. In China, the prevalence of myopia was estimated around 80% in 18-year-old school children and 17% in adults aged 40y and older[2-5]. At present, there are two main types of surgical correction for from moderate to high myopia, excimer laser and phakic intraocular lenses (IOLs) respectively. Excimer laser refractive surgery for myopia works by removing corneal stroma to lessen the refractive power of the cornea and to bring the image of a viewed object into focus onto the retina rather than in front of it[1]. Among of the excimer laser refractive surgery candidates, many cases of granular corneal dystrophy type 2 (GCD_2) post-laser surgery exacerbation have been reported worldwide[1,6].

GCD_2 (OMIM 607541) is also known as combined granular-lattice corneal dystrophy or avellino corneal dystrophy. The name "Avellino corneal dystrophy" (ACD) was coined in a report of three related Italian-American families affected with the disease whose origin was Avellino, Italy[7-8]. It is characterized clinically by the coexistence of granular deposits and histological amyloidal opacities that are shaped like snowflakes, discs, stars, and rings in the cornea, but its periphery shows no opacities. In advanced age, this disease also presents additionally diffuse anterior stromal opacity[9]. GCD_2 is a kind of hereditary disease which is inherited by autosomal dominant corneal dystrophy with the R124H mutation of the *TGFBI* gene[9]. There were some estimation around 0.24% in the prevalence of the patients with GCD_2 in

China, while 18.3% in refractive surgery candidates and in all of patients with TGF-β-induced gene corneal dystrophies[10-11]. In Korea, the overall prevalence (combining heterozygotes and homozygotes) of GCD_2 was at least 8.25 affected people per 10 000 people and the corrected GCD_2 prevalence was 11.5 per 10 000 people[12]. As for the age of GCD_2 onset, homozygous patients have earlier onset with dystrophy diagnosed, as early as 3 years of age, compared with heterozygotes ones, who may be diagnosed as early as the age of 8y. The most of GCD_2 ones are diagnosed during teens or early adulthood[13].

It is known that patients with GCD_2 are prohibited from performing laser cornea surgeries including in laser *in situ* keratomileusis (LASIK), laser epithelial keratomileusis (LASEK), photorefractive keratectomy (PRK) and phototherapeutic keratectomy (PTK). Otherwise, the corneal opacity of GCD_2 patient will be accelerated through these surgeries, further leading to the deterioration of their condition and even blindness[6,14-15]. In the conventional inspection methods, a medical slit lamp biomicroscopy is usually used to confirm whether there are white opacities in corneas of patients, but this inspection cannot reach 100% accuracy about diagnosing GCD_2. In addition, as for patients who do not develop disease (without white speckle-like lesions on the cornea but carrying GCD_2 gene), their visions are not affected and their corneas are transparent by an examination of a slit lamp biomicroscopy. If this group of people are being performed laser cornea surgeries and their corneas are cut, it will result in poor vision even blindness[16]. At this point, relying on DNA detection can confirm whether the patient carries GCD_2 mutated gene more precisely, which can achieve nearly 100% confirmation. Therefore, genetic detection 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[17]. In South Korea, Japan, and other western developed countries, GCD_2 genetic detection is a mandatory item for excimer laser surgery[12,18-22]. On the contrary, there is few GCD_2 detection for preoperative examination of most ophthalmic surgeries in China, where the number of patients receiving GCD_2 before surgery is extremely small[23-24].

In response to the inconsistency between Chinese huge market requirement and its market gap[23-24], and also in order to improve the safety and reliability of excimer laser surgery, the purpose of this study was to provide data for the promotion feasibility of GCD_2 detection by conducting a questionnaire of citizens in five cities in north and south China and to understand the GCD_2 detection program, the market acceptable price range, and in-depth analysis of GCD_2 detection implementation direction.

SUBJECTS AND METHODS

Ethical Approval The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from the investigators on behalf of themselves. The questionnaires were approved by the Ethics Committee of Fujian Medical University.

Investigation Method In the form of questionnaire, the questionnaire consisted of 15 single-choice questions and 1 multiple-choice question and was distributed, filled out and collected on the spot. In addition, the GCD_2 related knowledge was also introduced in the questionnaire to ensure that the respondents distinguished GCD_2 from other similar ophthalmic diseases, and each question is independent of another, as a result of individual respondents' refusal to answer individual questions will not affect the integrity of the questionnaire. For the group of people who needed to consult or be performed the excimer laser surgery, questions were intended to provide information about personal situation of the myopic population interviewed, acceptance of excimer laser surgery, and awareness degree of GCD_2 genetic detection.

Questionnaire Description In order to reduce the unreliability of the survey results caused by the lack of knowledge of GCD_2 genetic detection among the respondents, the principles of GCD_2 genetic detection and the necessity of preoperative detection are attached to the questionnaire.

Statistical Analysis Statistical analyses were performed by using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp, Armonk, New York) as indicated in the text. All variables involved in the study were semi-continuous or discrete. Statistical analysis used Chi-square test and one-tailed *t* test, with a significance level of 5% and expressed as $P<0.05$, respectively. All differences were regarded as statistically significant at $P<0.05$.

RESULTS

Main Personal Circumstances of the Respondents The survey was directed to people group for the need to consult or be performed the excimer laser surgery. First, understanding the diopter of myopia in the eyes of the respondents, and further their awareness, ideas and needs for GCD_2 were performed. As any other voluntary surveys, that is a self-selected subset that chose to complete it. Although its overall response rate was 100% (n=318), only 91% (n=289 of 318) survey respondents have completed questionnaire. In this survey, the remaining incomplete questionnaires have been counted together for statistical purposes, since each question was not relevant and could be grouped to maximize data integrity. Therefore, the data such as 317, 289, and 309, that appears later, represented the total number of respondents corresponding in the group question.

Of note the location selected in this questionnaire was mainly based on the ophthalmic hospitals, and targeted surveys were conducted to ask people who were receiving excimer laser surgery. For gender, women accounted for more than half of the response rate (58.5%, *n*=186 of 317). The age of the respondents was mainly 18-25 years old, accounting for 70.0% *(n*=222 of 317) of the total, which was consistent with the data from the primary population for laser surgery. Among the myopic respondents, 75.8% (*n*=219 of 289) of them had myopia of more than 2.00 diopters, which was generally higher (Table 1).

Understanding and Idea of People Aiming at Excimer Laser Surgery In the field of refractive surgery, only 27% (*n*=86 of 318) of respondents thought that laser surgery was necessary, and 35.8% (*n*=114 of 318) of respondents were unwilling to undergo it, which was not much different from "I have no idea" group (Table 2). The reason ''why people are unwilling to undergo surgery'' accounting for 44.3% (*n*=137 of 309) was mainly to worry about the sequelae after surgery. There were differences and misunderstandings in the overall understanding of concept and recognition of excimer laser surgery (pearson χ^2 test, P<0.001; Figure 1 and Table 3). For preoperative examinations, 71.1% (*n*=226 of 318) of the population considered it necessary to have a preoperative examination, which should include more detailed examinations such as genetic detection (Table 2).

Recognition of GCD_2 Genetic Detection In terms of GCD_2 genetic detection, the vast majority (84.2%, *n*=267 of 317) of respondents had never heard of it and even did not know that GCD_2 patients were prohibited from performing excimer surgery and GCD_2 could not be confirmed by this kind of routine surgery. On the contrary, only 5.0% (*n*=16 of 317) of respondents had heard that patient with GCD_2 was prohibited from performing excimer surgery and knew that GCD_2 could not be completely diagnosed only by routine testing (Figure 2 and Table 4).

Possibility of Adding GCD_2 Genetic Detection to Preoperative Examination of Laser Surgery In the questionnaire, there was some information about the results of patients with GCD_2 who were undergoing excimer surgery to give patients advanced or worsened conditions. After a preliminary understanding of GCD_2, 77.0% (*n*=244 of 317) of respondents considered it necessary to add GCD_2 genetic detection before laser surgery (Table 5). Since this test was not popular, the remaining 23.0% (*n*=73 of 317) of respondents believed that the occurrence probability of GCD_2 was not high and it would not happen to themselves (Table 5). One part of reason was that the market was not comprehensive, so they (25.0%, *n*=18 of 72 of 317) thought they were not aware of the project and had reservations, which was the same number of respondents

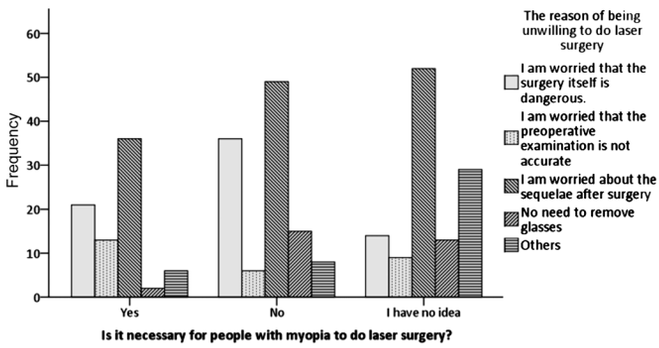

Figure 1 The understanding and concept of people aiming at excimer laser surgery.

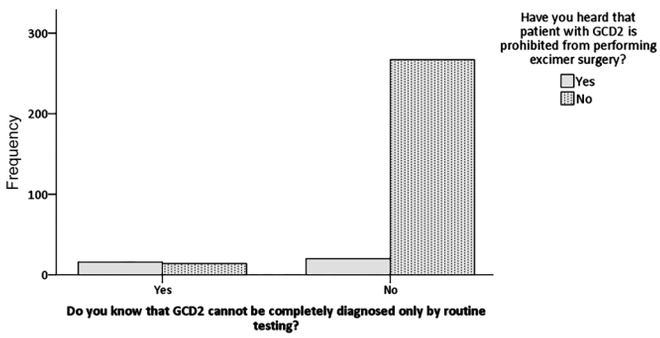

Figure 2 The recognition of GCD_2 genetic detection.

Table 1 Characteristics of respondents surveys

Characteristics	Frequency	Valid percent
Gender (*n*=318)		
Male	132	41.5
Female	186	58.5
Age (y, *n*=317)		
<18	22	6.9
18-25	222	70.0
25-35	44	13.9
35-45	19	6.0
>45	10	3.2
Ocular diopter (D, *n*=289)		
>-2.00	70	24.2
-2.00 to -4.00	107	37.0
-4.00 to -6.00	77	26.6
<-6.00	35	12.1

D: Diopter.

who thought the price of detection was too high to bear. The 34.7% (*n*=25 of 72 of 317) of respondents considered GCD_2 genetic detection was untrustworthy or could not become the state of the art for technical degree reasons, and 15.3% (*n*=11 of 72 of 317) of respondents receiving this test now did not think they need it (Figure 3; Table 6).

Promotion of GCD_2 Genetic Detection For the promotion of GCD_2 genetic detection, less than half of respondents (44.7%, *n*=142 of 318) expressed a willingness to pay higher testing costs. Nearly half of the respondents (49.7%, *n*=153 of 308) viewed the hospital as more reliable (Table 7), based

Table 2 The understanding and concept of people aiming at excimer laser surgery

Questions	Frequency	Valid percent
Is it necessary for the myope to receive laser surgery? (*n*=318)		
Yes	86	27.0
No	114	35.8
I have no idea.	118	37.1
The reason of being unwilling to receive laser surgery (*n*=309)		
I am worried that the surgery itself is dangerous.	71	23.0
I am worried that the preoperative examination is not accurate enough.	28	9.1
I am worried about the sequelae after surgery.	137	44.3
No need to remove glasses.	30	9.7
Others	43	13.9
How to treat preoperative detection of laser surgery? (*n*=318)		
It is very necessary that the project should be more detailed and specific, such as genetic detection.	226	71.1
It is necessary, but the current test is sufficient.	58	18.2
This is unnecessary and wasteful.	34	10.7

Table 3 The understanding and concept of people aiming at excimer laser surgery[a] *n* (%)

The reason of being unwilling to do laser surgery	Is it necessary for people with myopia to do laser surgery?			Total
	Yes	No	I have no idea	
I am worried that the surgery itself is dangerous.	21 (6.8)	36 (11.7)	14 (4.5)	71 (23.0)
I am worried that the preoperative examination is not accurate.	13 (4.2)	6 (1.9)	9 (2.9)	28 (9.1)
I am worried about the sequelae after surgery.	36 (11.7)	49 (15.9)	52 (16.8)	137 (44.3)
No need to remove glasses.	2 (0.6)	15 (4.9)	13 (4.2)	30 (9.7)
Others	6 (1.9)	8 (2.6)	29 (9.4)	43 (13.9)
Total	78 (25.2)	114 (36.9)	117 (37.9)	309 (100.0)

[a]Pearson χ^2 test confirms that there was a difference in the overall understanding of concept and recognition of excimer laser surgery, χ^2=39.254, P<0.001.

Table 4 The recognition of GCD_2 genetic detection[a,b] *n* (%)

Have you heard that patient with GCD_2 is prohibited from performing excimer surgery?	Do you know that GCD_2 cannot be completely diagnosed only by routine testing?		Total
	Yes	No	
Yes	16 (5.0)	20 (6.3)	36 (11.4)
No	14 (4.4)	267 (84.2)	281 (88.6)
Total	30 (9.5)	287 (90.5)	317 (100.0)

[a]Continuity correction χ^2 test confirms that there was a difference in the overall understanding of the recognition from network and knowledge of GCD_2 genetic detection, χ^2=58.000, P<0.001; [b]Computed only for a 2×2 table.

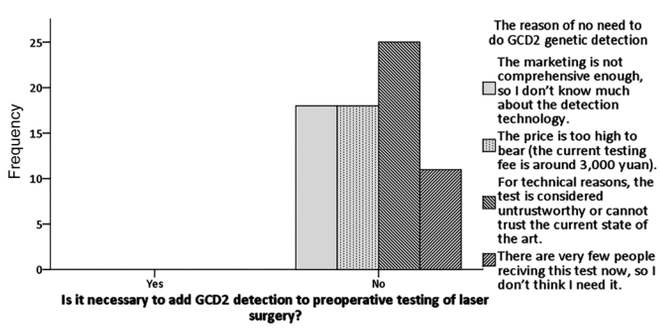

Figure 3 The reason of no need to do GCD_2 genetic detection.

on access to the GCD_2 genetic testing program. At present, most hospitals in China do not have GCD_2 genetic detection technology, and the GCD_2 genetic detection kit is provided by the *in vitro* diagnostic kit company, which is tested in the hospital to ensure the reliability of the test results[23]. In promoting this project, publicists should carry out marketing and publicity. When the price and technology of the test reach maturity, there will be more respondents, accounting for 82.5% (*n*=259 of 314) of the total number, willing to accept GCD_2 genetic detection (Table 7).

DISCUSSION

With the economic development, more and more people caring about their health are willing to spend money on it. Therefore, the GCD_2 genetic detection service has its huge market prospects[23]. It was found that only 3.4% of patients understood GCD_2 very much, presumably reflecting poor awareness of the disease and the psychological state characteristic of patients with this disease. In addition, the price and technology of

Table 5 The requirement to do GCD_2 genetic detection

Questions	Frequency	Valid percent
Is it necessary to add GCD_2 detection to preoperative testing of laser surgery? (*n*=317)		
Yes	244	77.0
No	73	23.0
The reason for objection to excimer laser surgery (*n*=72)		
The market is not mature enough, so I do not know much about the detection technology.	18	25.0
The price is too high to bear (the current testing fee is around 3000 RMB).	18	25.0
For technical reasons, the test is considered untrustworthy or cannot trust the state of the art.	25	34.7
There are few people receiving this test now, so I do not think I need it.	11	15.3

Table 6 The reason of no need to do GCD_2 genetic detection *n* (%)

The reason of no need to do GCD_2 genetic detection	Is it necessary to add GCD_2 detection to preoperative testing of laser surgery?	Total
	No	
The marketing is not comprehensive enough, so I do not know much about the detection technology.	18 (25.0)	18 (25.0)
The price is too high to bear (the current testing fee is around 3000 RMB).	18 (25.0)	18 (25.0)
For technical reasons, the test is considered untrustworthy or cannot trust the state of the art.	25 (34.7)	25 (34.7)
There are very few people receiving this test now, so I do not think I need it.	11 (15.3)	11 (15.3)
Total	72 (100.0)	72 (100.0)

Table 7 The awareness of GCD_2 promotion

Questions	Frequency	Valid percent
Are you willing to pay for the detection, which is higher than the surgery fee? (*n*=318)		
Yes	142	44.7
No	176	55.3
Where do you want to know more about GCD_2 detection? (*n*=308)		
Hospital	153	49.7
Kit company	18	5.8
Laboratory specializing in genetic detection	137	44.5
In the future, what do you most want to improve in GCD_2 genetic detection? (*n*=312)		
Cheaper price	66	34.2
More marketing promotion	127	65.8
When the price and technology of the test are at maturity, would you like to receive GCD_2 genetic detection when needed? (multiple-choice, *n*=314)		
Yes	259	82.5
No	55	17.5

GCD_2 detection technology have not yet reached the maturity stage. The above data indicated that the population of people undergoing excimer surgery was huge, but respondents still had concerns about its safety, especially that GCD_2 could not be diagnosed exactly by traditional preoperative examination. A little less than a quarter of (23.0%) people thought that it was not necessary to add GCD_2 detection before the laser surgery, which indicated that the detection technology could not be fully implemented. Nevertheless, most respondents believed that preoperative examination was particularly important and should be more specific to improve surgical safety.

From the data point of view, most respondents did not understand the significance of GCD_2 genetic detection, since no relevant literature case reports or references from the perspective of daily life had been reported. A few reasons are involved in the lack of the popularization of relevant knowledge, such as the publicity on GCD_2 genetic detection in the market, a media puffery for higher molecular surgery success rates, and few reports about GCD_2 patients having failed surgery, those of which make GCD_2 genetic detection project hard to carry out vigorously. However, there were still 76.7% of respondents who had hope for GCD_2 genetic

detection. It is feasible to use the GCD_2 genetic detection as a preoperative examination item of the excimer, though the market lacks the corresponding publicities of it and the market penetration rate of GCD_2 genetic detection is low, resulting in too little understanding of its necessity.

In order to promote the detection project, the following development proposals are proposed in this study. First of all, the promotion of GCD_2 genetic detection can be increased by speech and media publicities, such as television, news, internet, *etc*., and increase the exposure of negative and adverse effects of GCD_2 patients, so that more people realize that GCD_2 gene is an important safety hazard for excimer laser surgery. Based on the doctors' clinical research, listing the GCD_2 genetic detection as an excimer surgery preoperative examination item in several large hospitals and professional eye hospitals, and gradually carrying out in various hospitals, make it an easy-to-accept test. Second, in terms of testing costs, the traditional testing cost is about 200 RMB, and the GCD_2 genetic detection in the market needs between 2000 and 10 000 RMB, which price span is large, while the detection with high reliability and low price can make the patient more acceptable. Similarly, in terms of medical insurance, whether medical insurance can be reimbursed for GCD_2 genetic detection is also a way to consider implementation. Finally, the ophthalmology department of hospital can work with specialized laboratories or kit companies to further improve the materials and methods of the test kits, find ways to minimize the cost of testing, and ensure 100% confirmation of the test.

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