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의학석사 학위논문

**Inter-eye differences in myopic  
patients with unilateral normal-  
tension glaucoma**

단안 정상안압녹내장을 가진  
근시 환자에서 양안간의 차이

2014 년 2 월

서울대학교 대학원  
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**A thesis of the Degree of Master**

**Inter-eye differences in myopic  
patients with unilateral normal-  
tension glaucoma**

**February 2014**

**The Department of Ophthalmology,  
Seoul National University  
College of Medicine  
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# Inter-eye differences in myopic patients with unilateral normal-tension glaucoma

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이 논문을 의학석사 학위논문으로 제출함  
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**Inter-eye differences in myopic  
patients with unilateral normal-  
tension glaucoma**

**by**

**Won Hyuk Oh**

**A thesis submitted to the Department of Medicine in  
partial fulfillment of the requirements for the Degree of  
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논문제목 : Inter-eye differences in myopic patients with unilateral normal-tension glaucoma

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## Abstract

# Inter-eye differences in myopic patients with unilateral normal-tension glaucoma

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**Purpose:** To compare the extent of myopia and axial length (AL) along with other ocular risk factors for the development of open-angle glaucoma between two eyes in bilaterally myopic patients with unilateral normal-tension glaucoma (NTG).

**Methods:** Bilaterally myopic patients with unilateral NTG were consecutively enrolled for this study. Comparison between 2 eyes was performed with regard to intraocular pressure (IOP), mean deviation (MD) and pattern standard deviation (PSD) of the visual field (VF), spectral-domain optical coherence tomography parameters (circumpapillary retinal nerve fiber layer [cpRNFL] thickness, disc area,  $\beta$ -zone parapapillary atrophy [PPA] area),

refractive error, and AL.

**Results:** Thirty-six bilaterally myopic patients with unilateral NTG (21 men and 15 women,  $41.6 \pm 9.3$  years) were included. Untreated mean and highest IOP in NTG eyes were not significantly different from those in contralateral non-glaucomatous eyes. VF parameters were worse in NTG eyes than in contralateral non-glaucomatous eyes. The average, superior and inferior quadrants of cpRNFL thickness in NTG eyes were thinner than those in contralateral non-glaucomatous eyes. Compared with contralateral non-glaucomatous eyes, the disc area in NTG eyes was smaller ( $1.91 \pm 0.54 \text{ mm}^2$  vs.  $2.02 \pm 0.50 \text{ mm}^2$ ,  $p = 0.040$ ), but the  $\beta$ -zone PPA area in NTG eyes was larger ( $1.40 \pm 0.75 \text{ mm}^2$  vs.  $0.98 \pm 0.56 \text{ mm}^2$ ,  $p < 0.001$ ). NTG eyes had more myopic refractive error and longer AL than contralateral non-glaucomatous eyes ( $-5.73 \pm 1.87 \text{ D}$  vs.  $-4.92 \pm 2.01 \text{ D}$ ,  $p < 0.001$ ;  $26.42 \pm 1.04 \text{ mm}$  vs.  $26.08 \pm 1.11 \text{ mm}$ ,  $p < 0.001$ ).

**Conclusions:** In bilaterally myopic individuals, NTG eyes had more myopic refractive error, longer AL, and larger  $\beta$ -zone PPA areas than contralateral non-glaucomatous eyes. These inter-eye differences in the levels of risk factors for open-angle glaucoma may have contributed to the development of unilateral NTG in myopes.

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**Keywords:** Normal-tension glaucoma, Myopia, Axial length,  $\beta$ -zone parapapillary atrophy

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# Introduction

Several epidemiologic studies have shown that myopia is one of the established risk factors for the development of open-angle glaucoma<sup>1-7</sup> and that higher levels of myopia increase the risk of open-angle glaucoma.<sup>1, 2, 4-7</sup> Compared with other ocular components such as the cornea and the crystalline lens, axial length (AL) is typically regarded as the primary determinant of refractive error.<sup>8</sup> Recent studies<sup>6, 7</sup> have found that longer AL is associated with open-angle glaucoma. Myopic eyes have longer AL, and an elongated eyeball induces stress on the parapapillary sclera/laminar cribrosa, which may increase optic nerve susceptibility to glaucomatous damage.<sup>9, 10</sup>

While open-angle glaucoma generally affects both eyes, the severity of optic nerve damage can be asymmetric between eyes.<sup>11</sup> Unilateral open-angle glaucoma, nonetheless, is relatively rare. As mentioned above, myopia is a risk factor for developing open-angle glaucoma. Some myopic patients had glaucomatous optic nerve damage in one eye only. Both eyes of each individual are expected to be equally influenced by various systemic diseases, some of which are known to be associated with open-angle glaucoma, such as hypertension<sup>12</sup>, diabetes<sup>13</sup>, thyroid disease<sup>14</sup>, cardiovascular disease<sup>15</sup>, migraine<sup>16</sup>, sleep apnea<sup>17</sup>, and Raynaud's phenomenon<sup>18</sup>. The aim of this study was to compare the extent of myopia and AL along with other ocular risk factors for the development of open-angle glaucoma such as central corneal thickness (CCT)<sup>19</sup>, mean and highest untreated intraocular pressure (IOP)<sup>20, 21</sup>,  $\beta$ -zone parapapillary atrophy (PPA) area<sup>22</sup>, and disc hemorrhage<sup>23</sup> between

two eyes in bilaterally myopic patients with unilateral normal-tension glaucoma (NTG).

## Materials and Methods

Patients with unilateral NTG who visited Kong Eye Clinic, Seoul, Korea between December 2012 and January 2013 were consecutively enrolled. Among them, patients with bilateral myopia on manifest refraction were selected for our study. Myopia was defined as SE of the eye  $\leq -1.0$  diopter (D). This study was approved by the Institutional Review Board and Ethics Committee of Inje University Sanggye Paik Hospital. All investigations conformed to the tenets of the Declaration of Helsinki.

Each patient underwent a comprehensive ophthalmic examination, including refraction, slit-lamp biomicroscopy, Goldmann applanation tonometry, gonioscopy, optic disc photography, red-free retinal nerve fiber layer (RNFL) photography (Cannon CF-CUD, Cannon, Tokyo, Japan), automated static perimetry using the 30-2 Swedish Interactive Threshold Algorithm (Humphrey Visual Field Analyzer; Carl Zeiss Meditec, Dublin, CA, USA), ultrasound pachymetry (Pocket-II, Quantel Medical, Bozeman, MT, USA) for the measurement of CCT, IOLMaster (Carl Zeiss Meditec, Jena, Germany) for the measurement of AL, and spectral domain optical coherence tomography (SD-OCT; RS3000, Nidek, Gamagori, Japan) for the measurement of circumpapillary retinal nerve fiber layer (cpRNFL) thickness, disc area, and  $\beta$ -zone PPA area.

Unilateral NTG was defined as follows: untreated IOP  $\leq 21$  mmHg with no history of increased IOP, open angle on gonioscopy, and glaucomatous optic disc changes in one eye only. IOP measurements were obtained at least 3

times per patient prior to treatment at different daytime hours. Glaucomatous optic disc changes were characterized as focal or diffuse neuroretinal rim thinning, disc hemorrhage or RNFL defects on red-free RNFL photographs with corresponding optic disc changes. Glaucomatous visual field defects were defined as the presence of a cluster of  $\geq 3$  non-edge points on the pattern deviation plot with a probability of occurring in  $< 5\%$  of the normal population, and one of these points having the probability of occurring in  $< 1\%$  of the normal population; a pattern standard deviation (PSD) with  $p < 5\%$ , or outside normal limits based on a glaucoma hemifield test. These visual field defects had to be repeatable on 2 or more subsequent tests.

Each contralateral non-glaucomatous eye had an untreated IOP  $\leq 21$  mmHg with no history of increased IOP, open angle on gonioscopy, no glaucomatous optic disc changes, no visible RNFL defect on red-free RNFL photographs, and a normal visual field by automated static perimetry. Normal visual field indices were defined as mean deviation (MD) and PSD within 95% confidence limits and a glaucoma hemifield test result within normal limits.

Patients were excluded if they had best-corrected visual acuity worse than 20/40, cylinder correction of more than 3.0 D, visually significant nuclear lens opacity that could cause lens-induced myopia, clinical evidences of any retinal or neurologic disease, and poor reliability indices on the visual field test ( $>20\%$  fixation loss,  $>15\%$  false-positive or  $>15\%$  false-negative errors). Patients with poor OCT images (signal strength index score  $< 6$ ) or RNFL photographs of poor quality were also excluded.

Raster scanning over a  $6 \times 6$  mm square area (volume scan) centered on the optic disc center was conducted with a scan density of 512 A-scans (horizontal)  $\times$  128 B-scans (vertical) for the measurement of cpRNFL thickness, disc area, and  $\beta$ -zone PPA area. The cpRNFL thickness of the average, 4 quadrants, and 12 clock-hour segments were calculated using each volume scan image at the circle of 3.45 mm (256 A-scans) in diameter, which was centered automatically to the optic disc center. Left eye data were converted into right eye format. This device can automatically measure the area of the optic disc and cup, and provide tools with which users can redefine the boundaries of the optic disc and cup. It also provides tools that can correct the magnification effect of the OCT itself as well as the ocular optical system by inputting AL or refractive error. For the measurement of  $\beta$ -zone PPA area, one of the authors (W.H.O) drew one set of contour lines to include the  $\beta$ -zone PPA and optic disc (area A), and an additional set of contour lines to include the optic disc (area B), based on optic disc photographs without knowing clinical information. Then,  $\beta$ -zone PPA area was quantified by subtracting area B from area A.

Variables (refractive error, IOP, CCT, visual field parameters, AL, and OCT parameters) were compared between eyes using the paired *t*-test and Wilcoxon signed-rank test. A pilot study of 15 bilaterally myopic patients with unilateral NTG revealed that there was a statistically significant inter-eye difference in refractive error, AL, and  $\beta$ -zone PPA area. By inputting the mean, the standard deviation of refractive error, AL, and the  $\beta$ -zone PPA area of each group (NTG eyes, contralateral myopic non-glaucomatous eyes) and correlation

coefficients of each pair into G\*Power software (version 3.1.6; Universität Kiel Dusseldorf, Germany), the required sample sizes were calculated with a power of 80% and  $\alpha = 0.05$ . The results showed that at least 21, 27 and 19 patients would be required to detect inter-eye differences in refractive error, AL, and  $\beta$ -zone PPA area respectively.

The trend of the appearance of glaucomatous optic neuropathy with increasing inter-eye differences in AL was evaluated using linear-by-linear association. Pearson's correlations were performed to quantify the association between AL and the extent of myopia, disc area,  $\beta$ -zone PPA area, and the  $\beta$ -zone PPA-to-disc area ratio. To determine the effect of various factors on the  $\beta$ -zone PPA area, multivariate linear regression analysis was performed. A two-sided  $p < 0.05$  was considered to be statistically significant for all analyses. These statistical analyses were performed using a commercially available statistical software package (PASW 18.0; SPSS Inc., Chicago, IL, USA).

## Results

Thirty-six bilaterally myopic patients with unilateral NTG were included in this study. The mean age in this group of 36 patients (21 men and 15 women) was  $41.6 \pm 9.3$  years (range, 26–58 years). These patients were followed up for  $19.2 \pm 18.0$  months (median, 15 months; range, 1–77 months). The untreated mean and highest IOP in NTG eyes were not different from those in contralateral non-glaucomatous eyes. The CCT in NTG eyes was similar to that in contralateral non-glaucomatous eyes. MD and PSD values in NTG eyes were significantly worse than those in contralateral non-glaucomatous eyes ( $p < 0.001$ ,  $p < 0.001$ , respectively, Wilcoxon signed-rank test). NTG eyes were more myopic than contralateral non-glaucomatous eyes ( $-5.73 \pm 1.87$  D vs.  $-4.92 \pm 2.01$  D,  $p < 0.001$ , paired  $t$ -test), and the AL in NTG eyes was longer than that in contralateral non-glaucomatous eyes ( $26.42 \pm 1.04$  mm vs.  $26.08 \pm 1.11$  mm,  $p < 0.001$ , paired  $t$ -test) (Table 1).

While the magnitude of the inter-eye AL difference (dAL) increased, there was a tendency such that longer eyes were more likely to have glaucomatous optic nerve damage ( $p = 0.003$ , linear by linear association for trend, Table 2). The dAL ranged between 0.02 mm and 1.69 mm, and was not normally distributed ( $p < 0.001$ , Shapiro–Wilk test). Figure 1 showed 4 outliers (1.23, 1.45, 1.49, and 1.69 mm), which could distort the results of statistical analysis, so we excluded data of these 4 patients from additional statistical analysis to avoid misleading results (dAL range: 0.02–0.94 mm). The myopic NTG eyes had, nonetheless, more myopic refractive error and longer AL than

contralateral non-glaucomatous eyes ( $-5.62 \pm 1.83$  D vs.  $-5.07 \pm 2.02$  D,  $p < 0.001$ , paired  $t$ -test;  $26.41 \pm 1.09$  mm vs.  $26.21 \pm 1.10$  mm,  $p = 0.001$ , paired  $t$ -test). The trend wherein much longer eyes had glaucomatous optic nerve damage with increased dAL was also observed after excluding 4 outliers ( $p = 0.008$ , linear by linear association for trend, Table 2).

The average cpRNFL thickness in NTG eyes was statistically thinner than that in contralateral non-glaucomatous eyes, and regional differences were also observed at inferior (5, 6, and 7 o'clock segments) and superior (11, 12, and 1 o'clock segments) quadrants. The disc areas in NTG eyes were smaller than those in contralateral non-glaucomatous eyes, but the  $\beta$ -zone PPA areas in NTG eyes were larger than those of contralateral non-glaucomatous eyes. The  $\beta$ -zone PPA-to-disc area ratio in NTG eyes was greater than that in contralateral non-glaucomatous eyes (Table 3).

Multivariate linear regression analysis of the effect of AL and disc area on  $\beta$ -zone PPA area is shown in Table 4. In both NTG eyes and contralateral non-glaucomatous eyes,  $\beta$ -zone PPA areas could be determined by measuring AL and disc area.

AL was strongly correlated with the extent of myopia (correlation coefficient  $r = -0.653$ ,  $p < 0.001$  in NTG eyes;  $r = -0.712$ ,  $p < 0.001$  in contralateral non-glaucomatous eyes) (Figure 2). AL was not significantly correlated with disc area ( $r = -0.292$ ,  $p = 0.084$  in NTG eyes;  $r = -0.289$ ,  $p = 0.087$  in contralateral non-glaucomatous eyes) (Figure 3). In NTG eyes, AL was not significantly correlated with  $\beta$ -zone PPA area ( $r = 0.289$ ,  $p = 0.087$ ), but was significantly correlated with the  $\beta$ -zone PPA-to-disc area ratio ( $r =$

0.405,  $p = 0.014$ ). In contralateral non-glaucomatous eyes, however, AL was significantly correlated with  $\beta$ -zone PPA area and the  $\beta$ -zone PPA-to-disc area ratio ( $r = 0.345$ ,  $p = 0.039$ ;  $r = 0.464$ ,  $p = 0.004$ , respectively) (Figures 4, 5).

Disc hemorrhages were observed in eighteen eyes with NTG (18 of 36, 50%), but not in any contralateral non-glaucomatous eye (0%) ( $p < 0.001$ , Fisher's exact test).

Table 1. Demographic and Clinical Characteristics of Subjects

|                              | NTGEyes              | Contralateral<br>Non-glaucomatous<br>Eyes | Pvalue                       |
|------------------------------|----------------------|---|------------------------------|
| Age(year)                    | 41.6 ± 9.3 (26 - 58) |   |                              |
| Gender (male/female)         | 21/15                |   |                              |
| Refraction (Diopter)         | -5.73 ± 1.87         | -4.92 ± 2.01                              | <b>&lt;0.001*</b>            |
| Untreated mean IOP (mmHg)    | 15.4 ± 2.1           | 15.4 ± 2.4                                | 0.837*                       |
| Untreated highest IOP (mmHg) | 16.9 ± 2.0           | 16.9 ± 2.6                                | 0.908 <sup>†</sup>           |
| CCT (µm)                     | 538 ± 40             | 538 ± 38                                  | 0.884*                       |
| MD (dB)                      | -3.83 ± 3.88         | -1.26 ± 1.28                              | <b>&lt;0.001<sup>†</sup></b> |
| PSD (dB)                     | 4.74 ± 3.75          | 1.74 ± 0.35                               | <b>&lt;0.001<sup>†</sup></b> |
| Axial Length (mm)            | 26.42 ± 1.04         | 26.08 ± 1.11                              | <b>&lt;0.001*</b>            |

NTG = normal-tension glaucoma  
IOP = intraocular pressure; CCT = central corneal thickness  
MD = mean deviation; PSD = pattern standard deviation  
\* Comparison was performed using the paired *t*-test  
<sup>†</sup> Comparison was performed using Wilcoxon signed-rank test  
Significant p-values are in bold type.

Table 2. The Relationship between the Inter-eye Difference in Axial Length and Glaucomatous Optic Nerve Damage

|                             | dAL (mm)       |                  |                               | P value  |
|-----------------------------|----------------|------------------|-------------------------------|--|
|                             | < 0.16         | 0.16 – 0.32      | > 0.32                        |  |
| <b>Longer Eyes with NTG</b> | 33.3%<br>(3/9) | 84.6%<br>(11/13) | 92.9% [90%]<br>(13/14) [9/10] | <b><i>p=0.003*</i></b><br><b>[<i>p=0.008</i>]*</b> |

dAL = The magnitude of inter-eye difference in axial length (absolute values)

NTG = normal-tension glaucoma

[ ] Excluding 4 outliers

\* Trend estimated by linear-by-linear association. Significant p-values are in bold type.

Table 3. Circumpapillary Retinal Nerve Fiber Layer Thickness, Disc Area and  $\beta$ -zone Parapapillary Atrophy Area, and the  $\beta$ -zone Parapapillary Atrophy-to-Disc Area Ratio

|   | NTG Eyes         | Contralateral<br>Non-glaucomatous<br>Eyes | Pvalue                       |
|---|------------------|---|------------------------------|
| RNFL Thickness (um)   |                  |   |                              |
| Average   | 86.2 $\pm$ 12.5  | 100.4 $\pm$ 9.8                           | <b>0.000*</b>                |
| Quadrant  |                  |   |                              |
| Superior  | 105.8 $\pm$ 20.8 | 121.5 $\pm$ 18.0                          | <b>&lt;0.001*</b>            |
| Temporal  | 75.6 $\pm$ 12.9  | 78.7 $\pm$ 14.8                           | 0.186 <sup>†</sup>           |
| Inferior  | 88.6 $\pm$ 26.0  | 121.2 $\pm$ 14.5                          | <b>&lt;0.001*</b>            |
| Nasal   | 72.1 $\pm$ 11.5  | 77.1 $\pm$ 16.0                           | 0.086*                       |
| Clock-hour  |                  |   |                              |
| 12 Superior   | 98.8 $\pm$ 27.2  | 114.8 $\pm$ 30.5                          | <b>0.004*</b>                |
| 11  | 117.6 $\pm$ 33.5 | 139.4 $\pm$ 18.9                          | <b>0.001*</b>                |
| 10  | 90.3 $\pm$ 20.7  | 88.6 $\pm$ 15.7                           | 0.575*                       |
| 9 Temporal  | 64.7 $\pm$ 14.9  | 61.7 $\pm$ 16.5                           | 0.343 <sup>†</sup>           |
| 8   | 68.7 $\pm$ 20.7  | 82.3 $\pm$ 18.4                           | <b>0.002<sup>†</sup></b>     |
| 7   | 91.7 $\pm$ 41.0  | 148.7 $\pm$ 20.6                          | <b>&lt;0.001*</b>            |
| 6 Inferior  | 89.9 $\pm$ 34.1  | 117.7 $\pm$ 23.5                          | <b>&lt;0.001*</b>            |
| 5   | 79.6 $\pm$ 18.2  | 90.9 $\pm$ 16.8                           | <b>0.003*</b>                |
| 4   | 63.2 $\pm$ 18.4  | 70.3 $\pm$ 17.2                           | 0.050*                       |
| 3 Nasal   | 68.4 $\pm$ 13.3  | 73.7 $\pm$ 16.3                           | 0.098*                       |
| 2   | 81.3 $\pm$ 14.5  | 83.8 $\pm$ 23.0                           | 0.606*                       |
| 1   | 95.7 $\pm$ 21.8  | 105.0 $\pm$ 27.0                          | <b>0.018*</b>                |
| Area (mm <sup>2</sup> )   |                  |   |                              |
| Disc  | 1.91 $\pm$ 0.54  | 2.02 $\pm$ 0.50                           | <b>0.040*</b>                |
| $\beta$ -zone PPA   | 1.40 $\pm$ 0.75  | 0.98 $\pm$ 0.56                           | <b>&lt;0.001<sup>†</sup></b> |
| $\beta$ -zone PPA/Disc  | 0.76 $\pm$ 0.36  | 0.51 $\pm$ 0.27                           | <b>&lt;0.001*</b>            |
| NTG = normal-tension glaucoma   |                  |   |                              |
| PPA = parapapillary atrophy   |                  |   |                              |
| * Comparison was performed using the paired <i>t</i> -test            |                  |   |                              |
| <sup>†</sup> Comparison was performed using Wilcoxon signed-rank test |                  |   |                              |
| Significant p-values are in bold type.                                |                  |   |                              |

Table 4. Multivariate Linear Regression Analysis of the Effect of AL and Disc Area on  $\beta$ -zone Parapapillary Atrophy Area

|              | NTG eyes <sup>a</sup> |              | Contralateral non-glaucomatous eyes <sup>b</sup> |              |
|--------------|-----------------------|--------------|--|--------------|
|              | $\beta$ (SE)          | P value      | $\beta$ (SE)                                     | P value      |
| Disc area    | 0.487 (0.216)         | <b>0.003</b> | 0.325 (0.182)                                    | 0.055        |
| Axial length | 0.439 (0.113)         | <b>0.007</b> | 0.428 (0.083)                                    | <b>0.013</b> |

<sup>a</sup>R<sup>2</sup> = 0.264, *p* = **0.003**  
<sup>b</sup>R<sup>2</sup> = 0.165, *p* = **0.021**  
 NTG = normal-tension glaucoma  
 Significant p-values are in bold type.

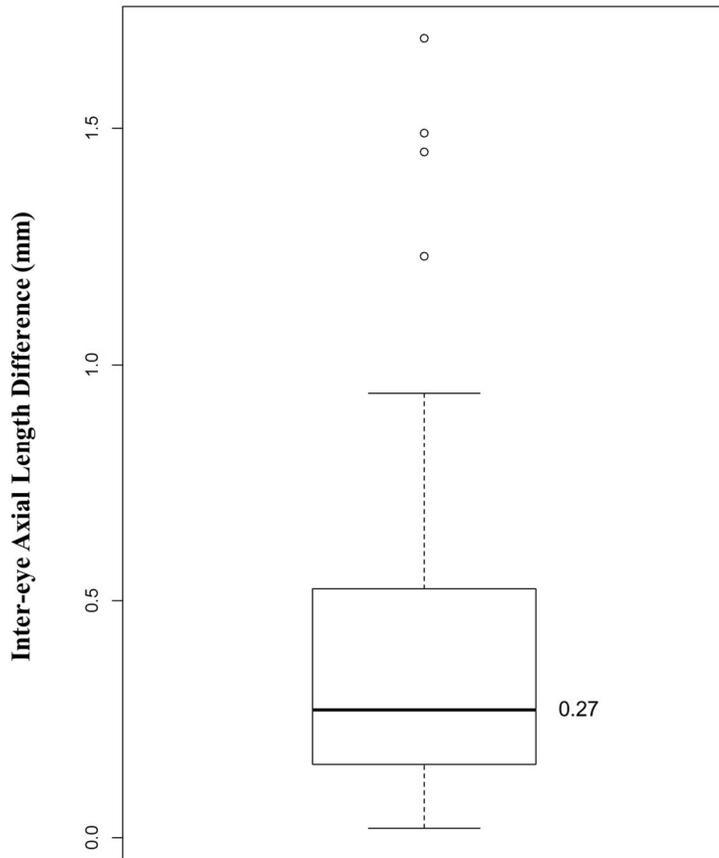


Figure 1. The distribution of the inter-eye difference in axial length (median 0.27 mm).  $\circ$  indicates outliers.

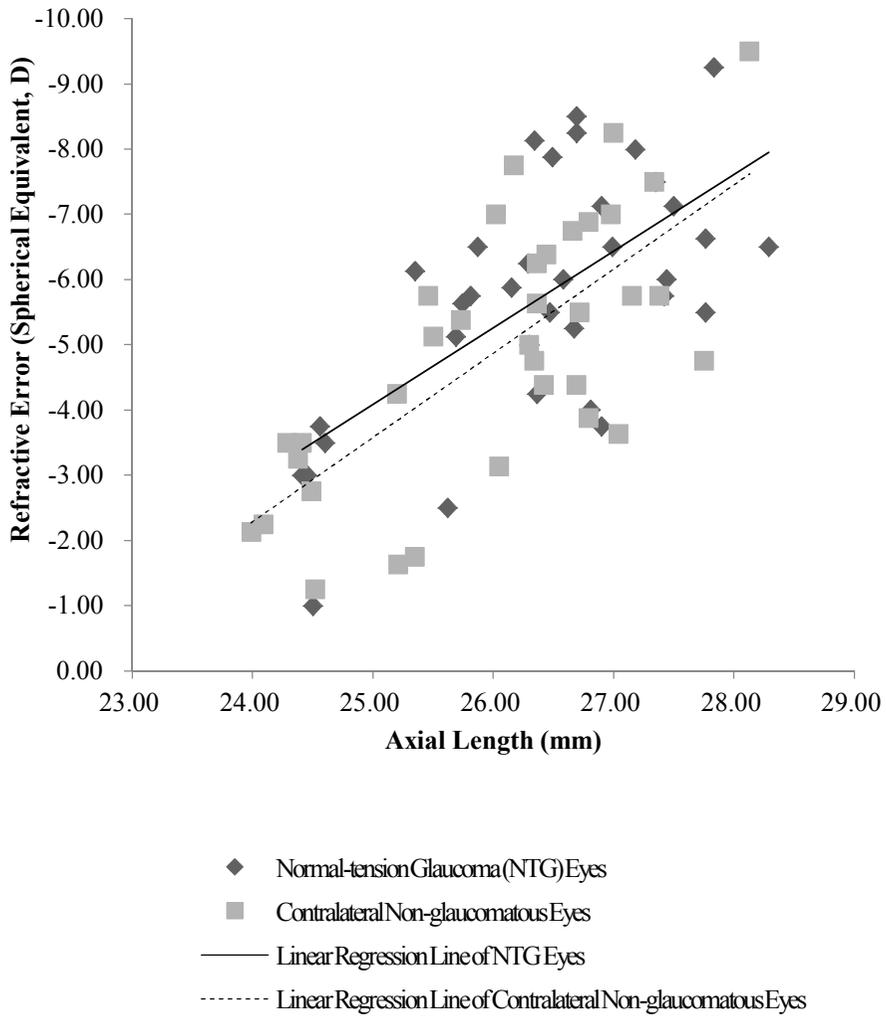


Figure 2. Scatterplot showing the correlation between axial length and extent of myopia. The correlation is statistically significant ( $r = -0.653$ ,  $p < 0.001$  in myopic normal-tension glaucoma eyes;  $r = -0.712$ ,  $p < 0.001$  in contralateral myopic non-glaucomatous eyes).

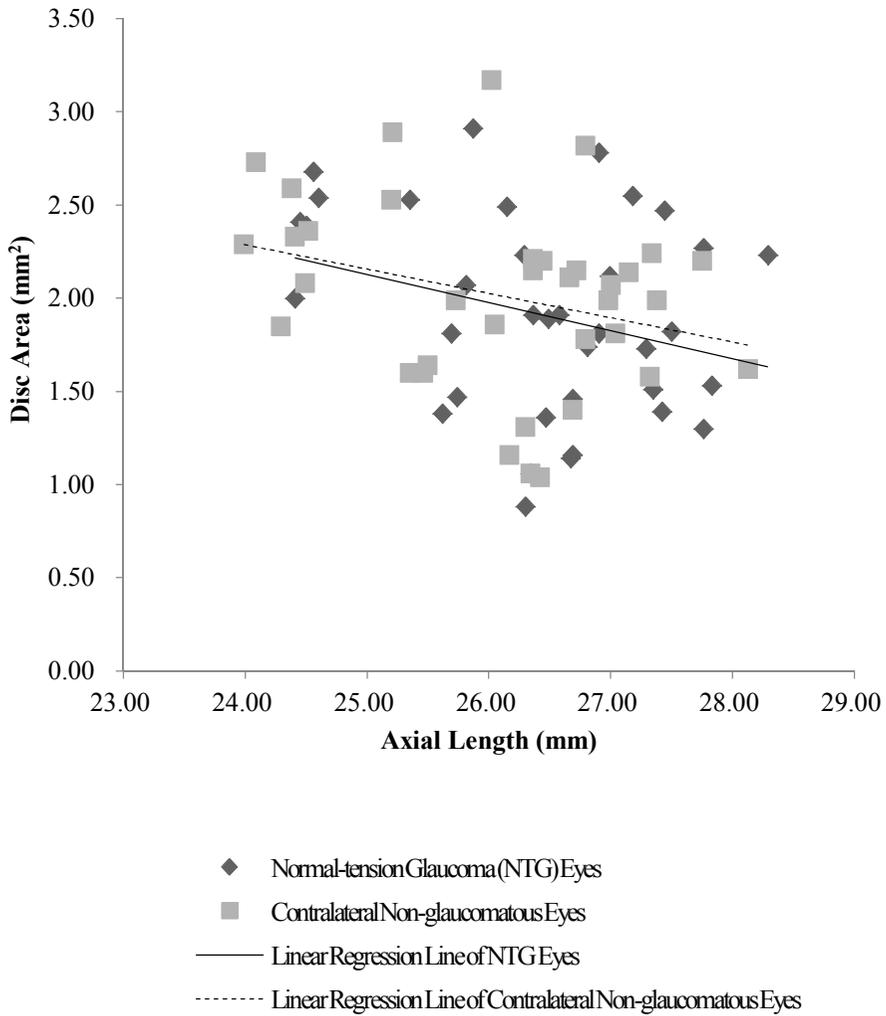


Figure 3. Scatterplot showing the correlation between axial length and disc area. The correlation is not statistically significant ( $r = -0.292$ ,  $p = 0.084$  in myopic normal-tension glaucoma eyes;  $r = -0.289$ ,  $p = 0.087$  in contralateral myopic non-glaucomatous eyes).

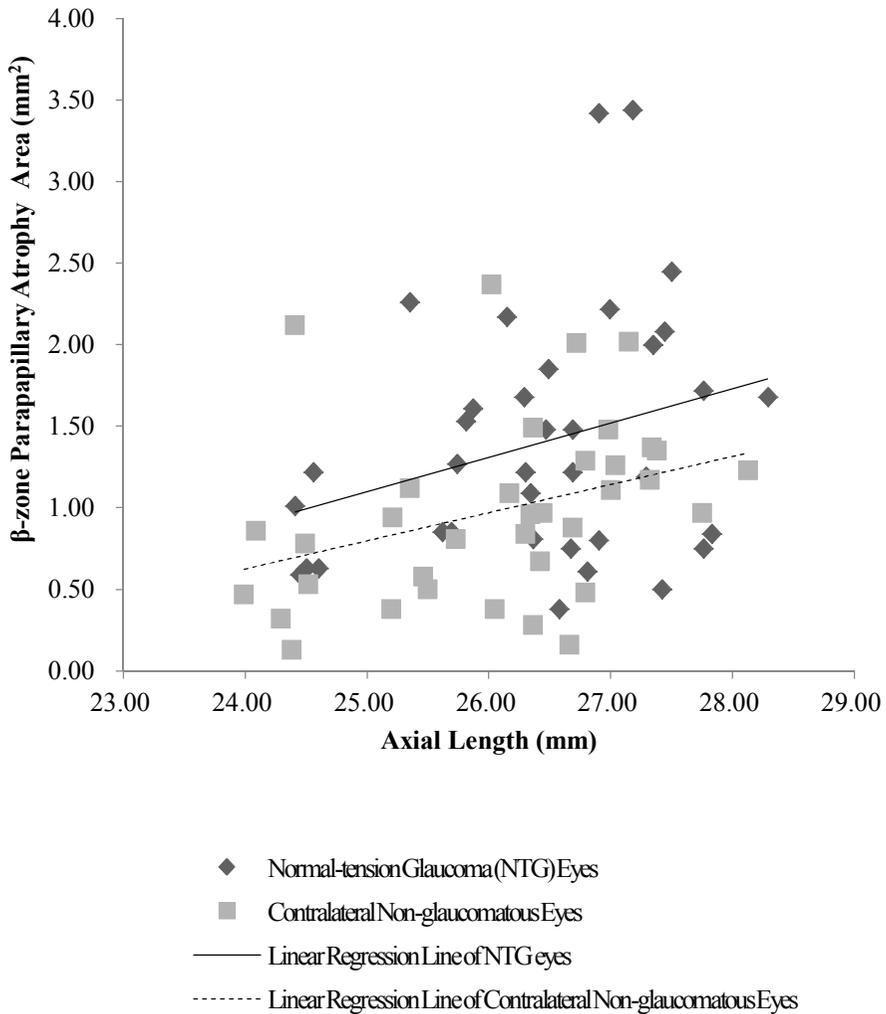


Figure 4. Scatterplot showing the correlation between axial length and  $\beta$ -zone parapapillary atrophy area. The correlation is statistically significant in contralateral myopic non-glaucomatous myopic eyes ( $r = 0.345$ ,  $p = 0.039$ ), but not in myopic normal-tension glaucoma eyes ( $r = 0.289$ ,  $p = 0.087$ ).

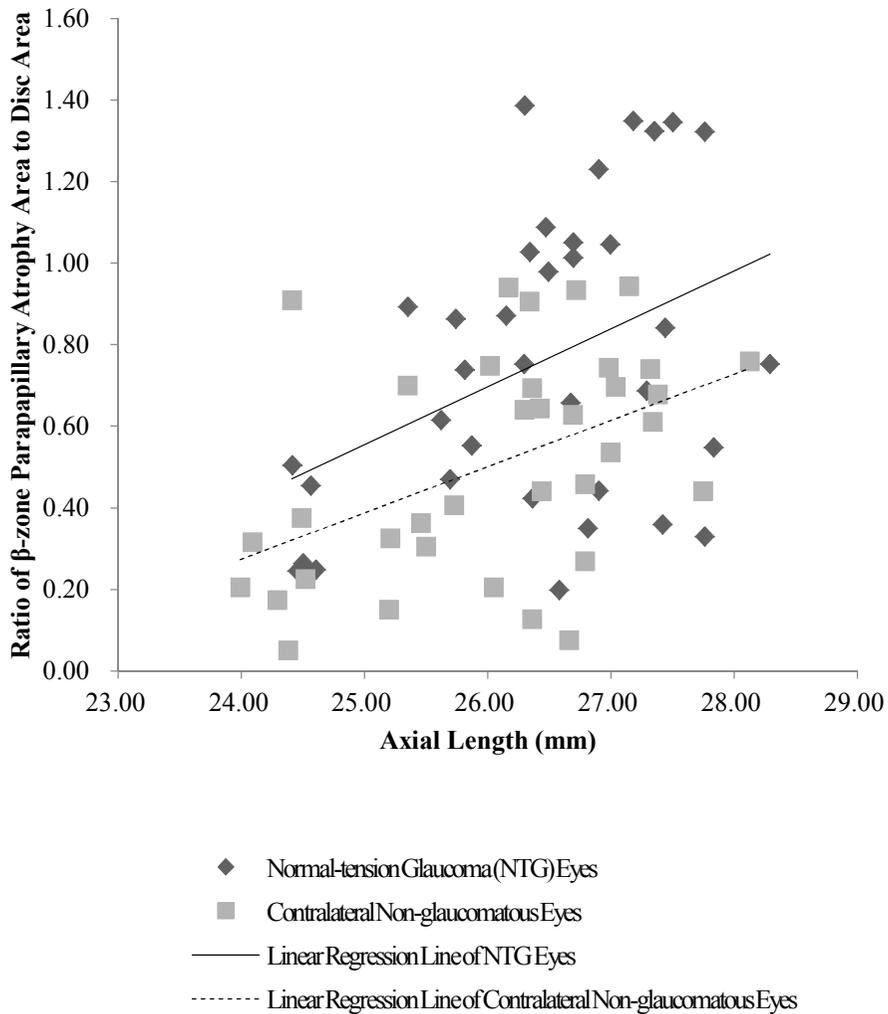


Figure 5. Scatterplot showing the correlation between axial length and  $\beta$ -zone parapapillary atrophy-to-disc area ratio. The correlation is statistically significant ( $r = 0.405$ ,  $p = 0.014$  in myopic normal-tension glaucoma eyes;  $r = 0.464$ ,  $p = 0.004$  in contralateral myopic non-glaucomatous myopic eyes).

## Discussion

The epidemiological relationships between myopia and open-angle glaucoma can be explained by several theories. Impaired retrobulbar<sup>24</sup>, retinal<sup>25</sup>, and choroidal<sup>26</sup> circulation were reported in patients with myopic open-angle glaucoma. Mechanical stretching of the parapapillary sclera/lamina cribrosa might increase optic nerve head susceptibility to glaucomatous damage in axial myopia. Distortions to optic nerve structure, particularly in the lamina cribrosa, could put stress on axons passing through the lamina pores.<sup>9,10</sup> Furthermore, the larger globe diameter and thinner sclera associated with axial myopia represent mechanical disadvantages when dealing with the stress of IOP.<sup>27,28</sup> During axial elongation, the optic nerve is pulled more laterally, because the choroid and retina are anchored nasally. This leads to the tilted discs and myopic crescents/PPA often seen in myopes.<sup>9,28</sup> PPA is classified into 2 categories,  $\alpha$ - and  $\beta$ -zone PPA.<sup>29</sup> The latter is thought to be closely associated with glaucoma.<sup>30</sup> The  $\beta$ -zone PPA is more frequently present and larger in patients with glaucoma than in normal individuals.<sup>22, 29, 31</sup> Moreover,  $\beta$ -zone PPA area in highly myopic eyes with glaucoma is larger than that of hyperopic or mildly to moderately myopic eyes with glaucoma.<sup>32</sup>

In this study, the NTG eyes were longer by 0.34 mm, which was beyond the range of interobserver variability (0.03–0.22 mm) of AL measurement with the IOLMaster.<sup>33</sup> The NTG eyes also exhibited  $\beta$ -zone PPA areas that were 0.41 mm<sup>2</sup> larger than those in contralateral non-glaucomatous eyes. Even after

excluding 4 outliers (patients with exceptionally large inter-eye AL differences), NTG eyes had more myopic refractive error, longer AL and larger  $\beta$ -zone PPA areas than contralateral non-glaucomatous eyes ( $-5.62 \pm 1.83$  D vs.  $-5.07 \pm 2.02$  D,  $p < 0.001$ , paired  $t$ -test;  $26.41 \pm 1.09$  mm vs.  $26.21 \pm 1.10$  mm,  $p = 0.001$ , paired  $t$ -test;  $1.34 \pm 0.71$  mm<sup>2</sup> vs.  $1.04 \pm 0.56$  mm<sup>2</sup>,  $p = 0.002$ , Wilcoxon signed-rank test). Moreover, our results showed that while the inter-eye AL difference (dAL) increased, there was a tendency for the much longer eyes to have glaucomatous optic nerve damage. Multivariate linear regression analysis revealed that AL and disc area were significant factors in determining  $\beta$ -zone PPA area in both NTG and contralateral non-glaucomatous eyes. In this sense, myopic  $\beta$ -zone PPA could be derived from scleral stretching associated with eyeball elongation, which might correspond to a new hypothesis of pathogenesis for  $\beta$ -zone PPA.<sup>35</sup> Asymmetric eyeball elongation, which was the cause and/or result of anisometropia ( $-0.80$  D), created a much larger  $\beta$ -zone PPA area, which has been regarded as a risk factor for developing glaucoma.<sup>34</sup>

If we can assume that ocular structural stiffness is the same in each individual, a longer eye may have more mechanical stress on the parapapillary sclera/lamina cribrosa than a shorter eye, which could explain why longer eyes in this study frequently developed glaucoma first. The results presented here showed that inter-eye AL differences, in terms of different levels of risk for open-angle glaucoma, may contribute to the development of unilateral NTG in myopes.

AL is strongly correlated with the extent of myopia. Disc area was

negatively correlated with AL, but this trend was not statistically significant. This result was coincident with a previous report<sup>9</sup> that the progression of myopia is associated with increases in PPA area and decreases in disc area. Whereas  $\beta$ -zone PPA areas in contralateral non-glaucomatous eyes exhibited a moderate and statistically significant correlation with AL,  $\beta$ -zone PPA areas in NTG eyes did not. This might be because the sample was too small to confer statistical significance. The  $\beta$ -zone PPA-to-disc area ratio, however, was significantly correlated with AL in both NTG and contralateral non-glaucomatous eyes.

Because myopia is a risk factor for glaucomatous optic nerve damage and NTG patients with unilateral visual field defects are at high risk of developing field damage in the eye with an initially normal visual field<sup>36</sup>, the contralateral non-glaucomatous eyes in this study are at risk of developing NTG. Moreover, as open-angle glaucoma is generally a bilateral disease and age is a risk factor for the development of open-angle glaucoma, many of our patients who had early disease (MD  $-3.83 \pm 3.88$  dB) and were relatively young would have bilateral disease in the future. Considering that longer and more myopic eyes had larger  $\beta$ -zone PPA areas and frequently develop glaucoma first, AL is likely to be a risk factor for the progression of glaucoma. This means that more elongated eyes may be the first to exceed individualized thresholds of resistance to glaucomatous optic nerve damage in myopes. As a risk factor for glaucoma progression, the effect of myopia on the progression of glaucoma has yet to be elucidated.<sup>37-41</sup> Our results support the opinion that the extent of myopia or AL influences the progression rate of glaucoma.

This study has several limitations. First, we could not verify the accuracy of the measurements of disc area and  $\beta$ -zone PPA area regarding magnification effects. A recent study showed that automated Cirrus SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA) measurements of disc area were not different from AL-corrected Cirrus measurements of disc area<sup>42</sup>, which could be applicable to our study. Second, the level of AL was identified with the extent of myopia. In fact, although AL is a major determinant of myopia, the powers of the cornea and lens also play a role. Third, the age of the study group was relatively young with respect to the average age of patients with NTG. It is also possible that our patients had optic neuropathy other than NTG. Doshi et al.<sup>43</sup> showed that young to middle-aged men of Chinese descent with ocular findings suggestive of glaucoma had no significant changes in optic nerve or visual field test throughout a 7-year follow-up and suggested that their patients simply had optic discs with glaucoma-like features, which were associated with myopia and tilted discs. Contrary to their report, our study included 16 women; furthermore, 18 patients had episodes of disc hemorrhage, which has been considered a risk factor for glaucoma progression<sup>44</sup> during the follow-up period.

## **Conclusions**

In conclusion, we showed that NTG eyes had significantly longer AL, more myopic refractive error and larger  $\beta$ -zone PPA areas compared to contralateral non-glaucomatous eyes in bilaterally myopic patients with unilateral NTG. These inter-eye differences in the levels of risk factors for open-angle glaucoma (extent of myopia, AL,  $\beta$ -zone PPA area) may have contributed to the development of unilateral NTG in myopes.

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## 국문초록

**목적:** 단안 정상안압녹내장이 있는 양안 근시 환자에서 정상안압녹내장안과 반대측 비녹내장안에서 양안간 개방각 녹내장 발병과 관련된 위험인자의 차이를 밝히고자 하였다.

**방법:** 단안 정상안압녹내장이 있는 양안 근시 환자를 연속적으로 수집하였다. 양안에서 안압 측정, 굴절검사, 안축장 측정 및 시야검사를 시행하였다. 또한 스펙트럼영역 공간섭촬영을 시행하여 양안의 시신경유두주위 망막신경섬유층의 두께, 시신경유두 면적 및  $\beta$  영역 시신경유두주위 위축의 면적을 측정하였다.

**결과:** 최종적으로 36명의 환자 (남자 21명, 여자 15명,  $41.6 \pm 9.3$ 세)가 본 연구에 포함되었다. 치료 전 평균 및 최고 안압은 정상안압녹내장안과 반대편 비녹내장안에서 통계적으로 유의한 차이가 없었다 (각각  $p = 0.837, p = 0.908$ ). 시야 검사 지표인 mean deviation (MD), pattern standard deviation (PSD)는 정상안압녹내장안에서 반대편 비녹내장안과 비교하였을 때 유의한 차이가 있었다 ( $-3.83 \pm 3.88$  dB vs.  $-1.26 \pm 1.28$  dB in MD,  $p < 0.001$ ;  $4.74 \pm 3.75$  dB vs.  $1.74 \pm 0.35$  dB in PSD,  $p < 0.001$ ). 평균, 상측 및 하측 사분면의 시신경유두주위 망막신경섬유층 두께는 통계적으로 유의하게

정상안압녹내장안에서 얇았다 (모두  $p < 0.001$ ).

정상안압녹내장안에서 반대편 비녹내장안과 비교하였을 때

시신경유두 면적은 더 좁았으나 ( $1.91 \pm 0.54 \text{ mm}^2$  vs.  $2.02 \pm 0.50 \text{ mm}^2$ ,  $p = 0.040$ ),  $\beta$  영역 시신경유두주위 위축의 면적은 더 넓었고 ( $1.40 \pm 0.75 \text{ mm}^2$  vs.  $0.98 \pm 0.56 \text{ mm}^2$ ,  $p < 0.001$ ), 근시 정도도 더 심했으며 ( $-5.73 \pm 1.87 \text{ D}$  vs.  $-4.92 \pm 2.01 \text{ D}$ ,  $p < 0.001$ ), 안축장도 더 길었다 ( $26.42 \pm 1.04 \text{ mm}$  vs.  $26.08 \pm 1.11 \text{ mm}$ ,  $p < 0.001$ ).

**결론:** 양안 근시가 있는 단안 정상안압녹내장 환자의 녹내장안에서 반대편 비녹내장안보다 더 근시가 더 심했고, 안축장은 더 길었고,  $\beta$  영역 시신경유두주위 위축의 면적도 더 넓었다. 이러한 양안간의 개방각 녹내장 발생의 위험인자 차이가 근시 환자에서 단안 정상안압녹내장 발생과 유의한 관련이 있을 가능성이 있다.

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**주요어:** 정상안압녹내장, 근시, 안축장,  $\beta$  영역 시신경유두주위 위축

**학번:** 2003-23812