

# Genetic Influences on Macular Thickness in Koreans: The Healthy Twin Study

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**PURPOSE.** To estimate genetic influences accounting for macular thickness in the Korean population.

**METHODS.** Study subjects were 830 healthy Korean adults (117 monozygotic twin pairs and 523 family members) from the Healthy Twin study. Macular thickness was measured with optical coherence tomography for nine subfields including the fovea, four inner quadrants (within 1 to 3 mm of the center), and four outer quadrants (within 3 to 6 mm of the center). Quantitative genetic analyses were performed to estimate the heritability of macular thickness with respect to familial correlations.

**RESULTS.** Macular thickness varied by subfield and was thinnest at the fovea and thickest at the inner superior area. Heritability of macular thickness at each subfield was 0.76, 0.73, 0.70, 0.56, 0.67, 0.70, 0.73, 0.29, and 0.36 at the fovea, inner superior area, inner inferior area, inner nasal area, inner temporal area, outer superior area, outer inferior area, outer nasal area, and outer temporal area, respectively.

**CONCLUSIONS.** Genetic factors play a significant role in determining macular thickness in the Korean population. (*Invest Ophthalmol Vis Sci.* 2011;52:9523-9526) DOI:10.1167/iovs.11-8521

Macular thickness is a valuable index in the diagnosis and treatment of macular edema and macular degeneration. It has been associated with visual prognosis in many retinopathies, and has provided critical information regarding the therapeutic effects of intravitreal drug injection or laser treatment for choroidal neovascularization or macular edema of various retinal pathologies.<sup>1-3</sup>

However, macular thickness has been found to vary significantly, even among healthy individuals, and little is known about the responsible factors, with the exceptions of age<sup>4-6</sup>

and ethnicity.<sup>7,8</sup> With regard to sex, macular thickness tended to be thicker in males than that in females in some studies,<sup>9-11</sup> whereas such differences were not evident in other studies.<sup>12,13</sup> Recently, genetic factors have been suggested to play an important role in accounting for the age-adjusted variance of macular thickness in twin studies.<sup>14,15</sup> Twin studies offer ideal opportunities to examine the extent of genetic and environmental contributions to a trait. The significantly greater intrapair correlation for monozygotic twins than that for dizygotic twins indicates the greater contributions of genetic factors than those of environmental factors. Elucidating the genetic component of a trait in the general population is very important because this may provide clues for effective gene searching. To date, there have been only two twin studies of macular thickness. One was an Australian study of 109 twin pairs of European descent (ranging in age from 50 to 80 years) in which correlations of retinal thickness within monozygotic twin pairs were greater than those within dizygotic twin pairs for foveal, inner, and outer macular regions.<sup>14</sup> Heritability in this sample was >80% in all macular regions.<sup>14</sup> The other such study was a British twin study of 155 female twin pairs (ranging in age from 17 to 50 years), which evaluated central retinal thickness.<sup>15</sup> The British study reported similar findings of greater correlations within monozygotic twin pairs than in dizygotic pairs; heritability was estimated at 90% in the study. However, the genetic contribution to macular thickness has never been studied in an East Asian population.

In the present study of healthy community-dwelling Korean twins and family members, we estimated the degree of genetic influence accounting for the variation in macular thickness.

## METHODS

The study subjects were participants in the Healthy Twin Study who underwent eye examinations in the Department of Ophthalmology at Samsung Medical Center between May 2007 and January 2009. Details of the study design and protocol of the Healthy Twin Study were published previously.<sup>16</sup> In brief, the Healthy Twin Study has been conducted in a community setting as part of the Korean Genome Epidemiology Study since 2005, and has recruited Korean adult twins and their family members through nationwide media advertisements and mailings without any ascertainment of baseline health status of the participants. The zygosity of participating twin pairs was identified by 16 short tandem repeat (STR) markers (15 autosomal markers and one sex-determining marker) in 67% of the twin pairs. For the remaining 33%, zygosity was determined based on a self-administered zygosity questionnaire, which was validated to be 94.3% accurate by an STR marker study.<sup>17</sup>

We measured macular thickness in each participant using optical coherence tomography (OCT; Stratus model, Carl Zeiss Meditec, Inc., Dublin, CA). OCT is a cross-sectional tomographic imaging technology and one of the most valuable noninvasive techniques for measuring retinal thickness with acceptable accuracy and reproducibility.<sup>18-21</sup> The introduction of OCT has enabled researchers and clinicians to

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reliably detect and measure small changes in macular thickness and to monitor a variety of macular diseases. We scanned both eyes of participants with a fast macular thickness map protocol using a 6-mm display diameter. We also used the retinal border detection algorithm contained in the commercial OCT software (Stratus OCT, Carl Zeiss Meditec). Macular thickness was automatically calculated as the distance between the vitreoretinal interface and the junction of inner and outer photoreceptor segments.<sup>22</sup>

A single well-trained operator screened all OCT scans during the scanning process. If the scans were too high or too low, scans with missing data, or any mismatch of retinal layer boundaries with the visible tissue contour were found, rescanning was done.

Quantitative thickness measurement of the macula was performed at several locations including the fovea, four inner quadrant subfields (within 1 to 3 mm of the center), and four outer quadrant subfields (within 3 to 6 mm of the center).

To identify any retinal pathology, digital retinal imaging (TRC-50IX; Topcon Corp., Tokyo, Japan) was performed for all participants and axial length was measured by corneal touch A-scan ultrasonography (Model 820; Allergan-Humphrey, San Leandro, CA).

OCT images of both eyes were obtained in 926 persons after pupil dilation. Among these 926 persons, a total of 169 persons were excluded for the following reasons: 1 was identified to be genetically unrelated to his or her family, 15 had low (<5) OCT signal strength in scans of both eyes, 6 exhibited highly skewed macular thickness caused by an unrecognized scanning error with motion artifact, 12 had either a history or evidence of pathologic features in the retina or treated retinal disease, 3 had glaucoma, 59 had known diabetes mellitus or a fasting glucose level higher than the cutoff level for diabetes mellitus (fasting serum glucose level  $\geq 7.0$  mmol/L), and 73 were missing for axial length data. As such, 757 persons were ultimately included in this analysis, with 117 pairs of monozygotic twins, 356 sibling, and 167 parents.

All participants provided written informed consent. The study protocol was approved by the institutional review board of the Samsung Medical Center and adhered to the tenets of the Declaration of Helsinki.

## Statistical Analysis

Because age, sex, and axial length may be closely associated with macular thickness,<sup>5,10,23-25</sup> the residual variance of each OCT measurement was estimated after adjusting for these variables using a linear regression model. Next, OCT intraclass correlation coefficients were calculated within monozygotic twin pairs, sibling pairs, and parent-child pairs after inverse normal transformation of the residual variances. For this intraclass correlation estimation, dizygotic twins were combined with siblings to avoid random variation due to the small numbers.

To estimate the heritability of macular thickness, we fitted a variance decomposition model to partition the total phenotypic variation of macular thickness measures into additive genetic ( $\delta a^2$ ), shared environmental component within a family ( $\delta c^2$ ), and individual specific unique environmental components ( $\delta e^2$ ).<sup>26</sup> The key assumption of this model is that the effects of shared environmental factors are common to the members of a family and that the three factors ( $\delta a^2$ ,  $\delta c^2$ , and  $\delta e^2$ ) have independent and additive effects on the trait variance. Thus, the total residual variances are the sum of the additive and individual specific variance components ( $\delta p^2 = \delta a^2 + \delta c^2 + \delta e^2$ ). Heritability ( $b^2$ ) in the narrow sense was calculated as the ratio of the additive component and the total variance ( $\delta a^2/\delta p^2$ ), which represents the proportion of residual variance attributed to additive genetic factors. Age, sex, and axial length were adjusted for the heritability estimation. The Sequential Oligogenic Linkage Analysis Routines program (SOLAR, ver. 2.0; Southwest Foundation for Biomedical Research, San Antonio, TX)<sup>27</sup> was used for quantitative genetic analyses.

## RESULTS

Table 1 displays the demographic characteristics and macular thicknesses of the study participants at each subfield. Average macular thickness was lowest at the fovea and highest at the inner superior subfield. Overall, macular thickness was higher at the inner subfields compared with the outer subfields.

Table 2 shows the estimated heritability of macular thickness at each subfield and the intraclass correlations of macular thickness within monozygotic twin pairs, parent-child pairs, and sibling pairs. The intraclass correlations of macular thickness within the monozygotic twin pairs were more than twice those of parent-child pairs and sibling pairs at most subfields, with the exceptions of the outer nasal and outer temporal areas. Age, sex, and axial length accounted for 2–20% of the variations in macular thickness.

Heritability of macular thickness at each subfield after adjusting for age, sex, and axial length were 0.76, 0.73, 0.70, 0.56, 0.67, 0.70, 0.73, 0.29, and 0.36 at the fovea, inner superior area, inner inferior area, inner nasal area, inner temporal area, outer superior area, outer inferior area, outer nasal area, and outer temporal area, respectively.

## DISCUSSION

In this study of Korean twins and family members, genetic factors were found to play a significant role in determining macular thickness in a normal Korean population.

Familial aggregation of risk factors of a disease is an important clue for elucidating causes of the disease<sup>28</sup>; studies involv-

TABLE 1. Demographic Characteristics and Regional Macular Thicknesses of Study Participants

Factor	Monozygotic Twins	Siblings*	Parents	Overall
Persons, <i>n</i>	234	356	167	757
Male, %	35.9	39.9	41.3	39.0
Age, y, mean $\pm$ SD	39.1 $\pm$ 7.9	37.6 $\pm$ 10.1	59.4 $\pm$ 7.8	42.9 $\pm$ 12.6
Macular thickness, $\mu$ m, mean $\pm$ SD				
Fovea	189.4 $\pm$ 18.6	189.3 $\pm$ 19.1	183.7 $\pm$ 22.0	188.1 $\pm$ 19.7
Inner superior	272.2 $\pm$ 13.0	271.8 $\pm$ 14.5	262.7 $\pm$ 16.6	269.9 $\pm$ 15.1
Inner inferior	269.6 $\pm$ 13.3	268.4 $\pm$ 15.1	260.3 $\pm$ 16.3	267.0 $\pm$ 15.3
Inner nasal	266.5 $\pm$ 15.0	264.3 $\pm$ 17.6	256.0 $\pm$ 16.1	263.1 $\pm$ 16.9
Inner temporal	263.7 $\pm$ 14.1	263.7 $\pm$ 17.0	257.1 $\pm$ 18.9	262.3 $\pm$ 16.8
Outer superior	237.3 $\pm$ 13.1	236.4 $\pm$ 14.0	229.9 $\pm$ 16.1	235.2 $\pm$ 14.5
Outer inferior	227.9 $\pm$ 13.1	225.9 $\pm$ 14.2	221.4 $\pm$ 16.3	225.5 $\pm$ 14.5
Outer nasal	243.6 $\pm$ 22.9	240.1 $\pm$ 25.1	234.2 $\pm$ 22.9	239.9 $\pm$ 24.2
Outer temporal	232.7 $\pm$ 23.1	231.9 $\pm$ 24.6	229.3 $\pm$ 23.6	231.6 $\pm$ 23.9

\* Dizygotic twins were included.

TABLE 2. Interclass Correlations\* and Heritability Estimates\* for Regional Macular Thickness

Macular Subfields	Intraclass Correlation Coefficients (95% CI)			Heritability‡ (SE) (n = 757 persons)	Variation Explained by Covariates*
	Monozygotic Twins Pairs (n = 117 pairs)	Parent–Child Pairs (n = 685 pairs)	Sibling† Pairs (n = 523 pairs)		
Fovea	0.72 (0.63–0.80)	0.26 (0.19–0.33)	0.30 (0.22–0.38)	0.76 (0.03)	0.12
Inner superior	0.68 (0.57–0.77)	0.31 (0.24–0.37)	0.36 (0.28–0.43)	0.73 (0.03)	0.19
Inner inferior	0.69 (0.58–0.77)	0.26 (0.19–0.33)	0.35 (0.27–0.42)	0.70 (0.04)	0.17
Inner nasal	0.56 (0.42–0.67)	0.22 (0.15–0.29)	0.22 (0.14–0.30)	0.56 (0.05)	0.15
Inner temporal	0.63 (0.50–0.72)	0.24 (0.17–0.31)	0.29 (0.21–0.36)	0.67 (0.05)	0.15
Outer superior	0.71 (0.61–0.79)	0.32 (0.25–0.38)	0.35 (0.27–0.42)	0.70 (0.07)	0.08
Outer inferior	0.80 (0.73–0.86)	0.32 (0.25–0.38)	0.39 (0.31, 0.46)	0.73 (0.07)	0.05
Outer nasal	0.29 (0.11–0.45)	0.14 (0.07–0.22)	0.07 (–0.02–0.15)	0.29 (0.10)	0.03
Outer temporal	0.37 (0.20–0.52)	0.15 (0.08–0.22)	0.13 (0.05–0.22)	0.36 (0.06)	0.02

CI, confidence interval.

\* Age, sex, and axial length were considered.

† Dizygotic twins were included.

‡ Heritability at all subfields was significant ( $P < 0.01$ ).

ing twins can provide strong evidence of genetic effects by helping to distinguish genetic influences from environmental influences. The hitherto reported heritability of macular thickness has been obtained from twin studies in Western populations.<sup>14,15</sup> Our study is the first East Asian study to investigate the genetic effects on macular thickness in twins and their family members. Although direct comparison of the heritability of macular thickness at all subfields is not possible due to the difference in observed subfields between studies, consistently high heritability of macular thickness at the foveal region (i.e., 85% in an Australian study,<sup>14</sup> 90% in a British study,<sup>15</sup> and 76% in the present Korean study) supports the presence of specific genetic factors that control macular thickness. In addition, given the high degree of heritability of macular thickness observed in normal persons, retinal pathology related to macular thickness is likely to be controlled by genetic factors.

The estimated heritability from a twin-only study may be inflated if dominant genetic effects exist. Therefore, a study using both twins and extended families provides a more accurate estimation of heritability because the extended family study can take into consideration various family relationships with different genetic correlations. As such, the heritability of macular thickness in this Korean sample was slightly lower than that in the previous British and Australian twin studies.

Macular thickness varied across subfields in the present study. It was thickest at the superior and inferior quadrants of the inner zone. Variation in macular thickness has been consistently described in previous studies and presumably occurs due to the superior and inferior arcuate bundling of nerve fibers.<sup>11,29</sup> In the outer zone, we observed that macular thickness was thickest in the nasal quadrant, which is consistent with the anatomic relationships of converging nerve fibers at the optic disc.

This study was not without limitations. First, because the zygosity of twin pairs was determined by a zygosity questionnaire in 33% of the twin pairs, misclassification bias may have affected our estimates. However, given that the zygosity questionnaire was found to be 94.3% accurate, it is unlikely that residual misclassification effects biased our findings. Although we estimated heritability with adjustments for age and sex, there could be additional unmeasured covariates other than genetic factors that may influence macular thickness. Second, although inaccurate retinal boundary detection may happen in the OCT scan (Stratus), a study on this issue found no significant difference in retinal thickness between manual and automated measurements in normal eyes.<sup>30</sup> Given that the participants of our study were all with normal eye condition,

significant bias from inaccurate retinal boundary detection seems less likely. Third, there could be an argument about OCT scan protocol. The fast macular thickness map protocol we used is the most widely used of protocols in clinical practice and many studies because of its less time-consuming characteristics, notwithstanding that it often provides low resolution. Previous studies reported that both fast macular thickness map and radial line protocols provide similar and low segmentation errors and their automated results were close to those of manual measurements except for patients with exudative age-related macular degeneration.<sup>31,32</sup> Given that our study enrolled only healthy subjects, measurement of macular thickness using the fast macular thickness map protocol does not seem to cause significant bias.

In conclusion, the present Korean twin and family study reconfirmed the high heritability of macular thickness as previously described in Western samples. This finding suggests that genetic factors have significant effects on macular thickness.

## References

- Bolz M, Ritter M, Polak K, et al. The role of Stratus OCT in anti-VEGF therapy. Qualitative and quantitative assessment of neovascular AMD. *Ophthalmology*. 2008;115:650–655.
- Ach T, Hoeh AE, Schaal KB, Scheuerle AF, Dithmar S. Predictive factors for changes in macular edema in intravitreal bevacizumab therapy of retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol*. 2010;248:155–159.
- Aiello LP, Edwards AR, Beck RW, et al. Factors associated with improvement and worsening of visual acuity 2 years after focal/grid photocoagulation for diabetic macular edema. *Ophthalmology*. 2010;117:946–953.
- Sony P, Sihota R, Tewari HK, Venkatesh P, Singh R. Quantification of the retinal nerve fibre layer thickness in normal Indian eyes with optical coherence tomography. *Indian J Ophthalmol*. 2004;52:303–309.
- Alamouti B, Funk J. Retinal thickness decreases with age: an OCT study. *Br J Ophthalmol*. 2003;87:899–901.
- Yamada H, Yamakawa Y, Chiba M, Wakakura M. Evaluation of the effect of aging on retinal nerve fiber thickness of normal Japanese measured by optical coherence tomography. *Nippon Ganka Gakkai Zasshi*. 2006;110:165–170.
- Asefzadeh B, Cavallerano AA, Fisch BM. Racial differences in macular thickness in healthy eyes. *Optom Vis Sci*. 2007;84:941–945.
- Samarawickrama C, Wang JJ, Huynh SC, et al. Ethnic differences in optic nerve head and retinal nerve fibre layer thickness parameters in children. *Br J Ophthalmol*. 2010;94:871–876.

9. Kelty PJ, Payne JF, Trivedi RH, Kelty J, Bowie EM, Burger BM. Macular thickness assessment in healthy eyes based on ethnicity using Stratus OCT optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2008;49:2668–2672.
10. Huynh SC, Wang XY, Rochtchina E, Mitchell P. Distribution of macular thickness by optical coherence tomography: findings from a population-based study of 6-year-old children. *Invest Ophthalmol Vis Sci.* 2006;47:2351–2357.
11. Massin P, Erginay A, Haouchine B, Mehidi AB, Paques M, Gaudric A. Retinal thickness in healthy and diabetic subjects measured using optical coherence tomography mapping software. *Eur J Ophthalmol.* 2002;12:102–108.
12. Zou H, Zhang X, Xu X, Yu S. Quantitative in vivo retinal thickness measurement in Chinese healthy subjects with retinal thickness analyzer. *Invest Ophthalmol Vis Sci.* 2006;47:341–347.
13. Luo R, Ge J, Liu X, Wang M, Ling Y, Zheng X. A quantitative measurement of retinal nerve fiber layer thickness by optical coherence tomography in normal Chinese people. *Yan Ke Xue Bao.* 1998;14:207–209.
14. Chamberlain MD, Guymer RH, Dirani M, Hopper JL, Baird PN. Heritability of macular thickness determined by optical coherence tomography. *Invest Ophthalmol Vis Sci.* 2006;47:336–340.
15. Liew SH, Gilbert CE, Spector TD, Marshall J, Hammond CJ. The role of heredity in determining central retinal thickness. *Br J Ophthalmol.* 2007;91:1143–1147.
16. Sung J, Cho SI, Lee K, et al. Healthy Twin: a twin-family study of Korea—protocols and current status. *Twin Res Hum Genet.* 2006;9:844–848.
17. Song YM, Lee D, Lee MK, et al. Validity of the zygosity questionnaire and characteristics of zygosity-misdiagnosed twin pairs in the Healthy Twin Study of Korea. *Twin Res Hum Genet.* 2010;13:223–230.
18. Hee MR, Izatt JA, Swanson EA, et al. Optical coherence tomography of the human retina. *Arch Ophthalmol.* 1995;113:325–332.
19. Kim TW, Park KH, Kim DM. An unexpectedly low Stratus optical coherence tomography false-positive rate in the non-nasal quadrants of Asian eyes: indirect evidence of differing retinal nerve fiber layer thickness profiles according to ethnicity. *Br J Ophthalmol.* 2008;92:735–739.
20. Schuman JS, Pedut-Kloizman T, Hertzmark E, et al. Reproducibility of nerve fiber layer thickness measurements using optical coherence tomography. *Ophthalmology.* 1996;103:1889–1898.
21. Paunescu LA, Schuman JS, Price LL, et al. Reproducibility of nerve fiber thickness, macular thickness, and optic nerve head measurements using Stratus OCT. *Invest Ophthalmol Vis Sci.* 2004;45:1716–1724.
22. Pons ME, Garcia-Valenzuela E. Redefining the limit of the outer retina in optical coherence tomography scans. *Ophthalmology.* 2005;112:1079–1085.
23. Luo HD, Gazzard G, Fong A, et al. Myopia, axial length, and OCT characteristics of the macula in Singaporean children. *Invest Ophthalmol Vis Sci.* 2006;47:2773–2781.
24. Wong AC, Chan CW, Hui SP. Relationship of gender, body mass index, and axial length with central retinal thickness using optical coherence tomography. *Eye.* 2005;19:292–297.
25. Duan XR, Liang YB, Friedman DS, et al. Normal macular thickness measurements using optical coherence tomography in healthy eyes of adult Chinese persons: the Handan Eye Study. *Ophthalmology.* 2010;117:1585–1594.
26. Hopper JL, Visscher PM. Variance component analysis. In: Elston RC, Olson JM, Palmer L, eds. *Biostatistical genetics and genetic epidemiology.* Milton, Queensland (Australia): John Wiley & Sons Ltd.; 2002:779–780.
27. Almasy L, Blangero J. Multipoint quantitative-trait linkage analysis in general pedigrees. *Am J Hum Genet.* 1998;62:1198–1211.
28. Hopper JL, Carlin JB. Familial aggregation of a disease consequent upon correlation between relatives in a risk factor measured on a continuous scale. *Am J Epidemiol.* 1992;136:1138–1147.
29. Hee MR, Puliafito CA, Duker JS, et al. Topography of diabetic macular edema with optical coherence tomography. *Ophthalmology.* 1998;105:360–370.
30. Leung CK, Chan WM, Chong KK, et al. Alignment artifacts in optical coherence tomography analyzed images. *Ophthalmology.* 2007;114:263–270.
31. Taban M, Sharma S, Williams DR, Waheed N, Kaiser PK. Comparing retinal thickness measurements using automated fast macular thickness map versus six-radial line scans with manual measurements. *Ophthalmology.* 2009;116:964–970.
32. Eriksson U, Alm A. Repeatability in and interchangeability between the macular and the fast macular thickness map protocols: a study on normal eyes with Stratus optical coherence tomography. *Acta Ophthalmol.* 2009;87:725–730.