Heritability of Inner Retinal Layer and Outer Retinal Layer Thickness: The Healthy Twin Study

Mingui Kong¹,²,⁵, Sungsoon Hwang³,⁵, Hyeonyoung Ko⁴, Yun-Mi Song⁴* & Don-Il Ham³*

The purpose of the study is to evaluate the heritability of inner retinal layer (IRL) and outer retinal layer (ORL) thicknesses in the healthy Korean population. This was a cross-sectional, twin and family study. We included 374 Korean adults with healthy eyes from 89 families. IRL thickness (from the internal limiting membrane to the external limiting membrane) and ORL thickness (from the external limiting membrane to the outer border of the retinal pigment epithelium layer) were measured in the nine macular subfields as defined by the Early Treatment of Diabetic Retinopathy Study using optical coherence tomography. The heritability on IRL and ORL thicknesses were investigated using a variance decomposition model. The heritability of IRL thickness was 0.87, 0.58, 0.85, 0.89, and 0.74 for the central, inner superior, inner inferior, inner temporal, inner nasal subfields, respectively; and 0.62, 0.83, 0.62, and 0.60 for the outer superior, outer inferior, outer temporal, outer nasal subfields, respectively. The heritability of ORL thickness was 0.56, 0.75, 0.66, 0.72, and 0.56 for the central, inner superior, inner inferior, inner temporal, inner nasal subfields, respectively; and 0.64, 0.63, 0.73, 0.54 for the outer superior, outer inferior, outer temporal, and outer nasal subfields, respectively. The heritability estimates of IRL thickness and ORL thickness ranged from moderate to high. The IRL thickness at the central, inner temporal, and inner inferior subfields had particularly high heritability.

The Genetic influence on diseases including myopia, age-related macular degeneration, and primary open-angle glaucoma is being aggressively investigated¹⁻⁴. Elucidating the genetic component of specific traits is also important since specific traits can be linked to and can contribute to some common diseases. Information on the genetic basis of traits will ensure more effective gene searching through linkage and association studies, and facilitate the identification of the genes involved in the aforementioned diseases. Many previous studies have reported on the heritability of representative quantitative traits such as axial length, refractive error, peripapillary retinal nerve fiber layer thickness, macular thickness, choroidal thickness, and optic nerve head morphology and have also provided information on the contribution of genetics to specific phenotypes as well as the diseases associated with those phenotypes⁵⁻¹¹.

The inner retinal layer (IRL) and outer retinal layer (ORL) are separately linked to the pathophysiology of several common diseases. For instance, the IRL is deeply involved in the pathophysiology of diabetic macular edema and retinal ischemia¹²⁻¹³, whereas the ORL undergoes degenerative changes in diabetic patients in the very early stage of diabetic retinopathy¹⁴ and predicts visual function in diabetic retinopathy and other retinal disorders¹⁵. Therefore, investigating the heritability of these ocular structures may provide genetic information and further contribute to the understanding of the genetic influence on certain diseases.

Evaluation and quantification of retinal layers have improved due to recent technological advances. Spectral-domain (SD) optical coherence tomography (OCT) presents detailed cross-sectional imaging of the retina’s ultrastructure, enabling enhanced detection, accurate measurement, and reliable analysis of retinal traits compared to the examination modalities used in the past¹⁶⁻¹⁷. Layer by layer segmentation performed automatically by the software incorporated into SD-OCT devices provides objective measures of each retinal layer compared to what was available earlier¹⁸.

¹Hangil Eye Hospital, Incheon, Republic of Korea. ²Department of Ophthalmology, Catholic Kwandong University College of Medicine, Incheon, Republic of Korea. ³Department of Ophthalmology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. ⁴Department of Family Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. ⁵These authors contributed equally: Mingui Kong and Sungsoon Hwang. *email: yunmisong@skku.edu; oculus@naver.com
Using these technological advances in the present study, we investigated the contribution of genetics to the thickness of the IRL and ORL in detail, by utilizing the data of a population-based twin and family study in South Korea.

**Results**

Among the study participants, 143 (38.2%) were male and 231 (61.8%) were female. The ages of the participants ranged from 18 to 82 years, with an average age of 44.23 ± 13.08 (mean ± standard deviation) years. The average axial length was 23.66 ± 13.08 mm (central subfield) to 263.70 ± 21.52 mm (inner nasal subfield). And the mean thickness of the ORL ranged from 175.60 ± 21.52 μm (central subfield) to 263.70 ± 21.52 μm (inner nasal subfield). And the mean thickness of the ORL ranged from 175.60 ± 21.52 μm (central subfield) to 263.70 ± 21.52 μm (inner nasal subfield).

### Table 1. Age- and sex-specific distribution of inner retinal layer thickness. Data are presented as mean ± standard deviation.

| Inner Retina | Center          | Inner Superior | Inner Inferior | Inner Temporal | Inner Nasal | Outer Superior | Outer Inferior | Outer Temporal | Outer Nasal |
|--------------|-----------------|----------------|---------------|----------------|-------------|----------------|---------------|----------------|------------|
| All (n=374)  | 175.60 ± 19.41  | 260.77 ± 15.84 | 243.75 ± 15.43 | 263.70 ± 15.48 | 222.72 ± 13.42 | 212.13 ± 13.83 | 208.75 ± 12.93 | 239.60 ± 15.89 |
| Women (n=231)|                 |                |               |                |             |                |               |                |            |
| <35          | 171.27 ± 18.56  | 263.33 ± 12.51 | 259.52 ± 14.58 | 245.37 ± 13.59 | 261.90 ± 14.20 | 224.28 ± 13.94 | 215.88 ± 12.68 | 209.50 ± 11.65 | 242.12 ± 16.88 |
| 35–44        | 173.05 ± 16.00  | 261.81 ± 25.66 | 260.43 ± 12.66 | 245.19 ± 10.80 | 263.41 ± 12.38 | 226.37 ± 11.69 | 215.54 ± 13.93 | 207.67 ± 11.43 | 244.89 ± 14.18 |
| 45–54        | 166.77 ± 15.59  | 259.82 ± 14.13 | 256.13 ± 13.86 | 243.07 ± 13.36 | 259.82 ± 14.38 | 222.13 ± 11.28 | 212.83 ± 11.82 | 208.48 ± 13.46 | 237.72 ± 13.96 |
| 55–64        | 173.76 ± 18.52  | 251.86 ± 14.08 | 249.03 ± 14.35 | 237.68 ± 12.75 | 252.81 ± 13.25 | 217.43 ± 13.06 | 204.68 ± 13.79 | 201.62 ± 13.75 | 230.41 ± 12.71 |
| 65 ≤         | 164.09 ± 27.56  | 247.00 ± 21.37 | 250.45 ± 18.52 | 253.64 ± 16.44 | 251.73 ± 21.52 | 213.45 ± 12.25 | 199.36 ± 14.12 | 198.55 ± 12.24 | 230.82 ± 16.32 |

**Men (n=143)**

| Inner Retina | Center          | Inner Superior | Inner Inferior | Inner Temporal | Inner Nasal | Outer Superior | Outer Inferior | Outer Temporal | Outer Nasal |
|--------------|-----------------|----------------|---------------|----------------|-------------|----------------|---------------|----------------|------------|
| <35          | 181.81 ± 15.22  | 273.93 ± 7.66  | 270.81 ± 9.70  | 257.17 ± 9.29  | 274.57 ± 8.67 | 250.57 ± 9.64  | 218.00 ± 8.25  | 217.98 ± 7.00  | 217.98 ± 10.99 |
| 35–44        | 184.75 ± 20.82  | 267.25 ± 13.76 | 268.89 ± 14.45 | 254.54 ± 12.47 | 269.36 ± 15.05 | 217.61 ± 13.59 | 211.07 ± 14.11 | 208.61 ± 12.42 | 239.57 ± 15.68 |
| 45–54        | 183.89 ± 21.88  | 271.67 ± 13.21 | 271.42 ± 14.20 | 257.83 ± 12.36 | 273.50 ± 12.44 | 224.39 ± 15.41 | 213.03 ± 14.72 | 214.39 ± 13.96 | 242.11 ± 14.82 |
| 55–64        | 179.43 ± 17.59  | 265.30 ± 13.68 | 260.70 ± 14.35 | 249.96 ± 13.91 | 264.83 ± 14.52 | 218.91 ± 10.54 | 205.35 ± 11.58 | 206.96 ± 9.59  | 233.30 ± 14.37 |
| 65 ≤         | 192.93 ± 24.10  | 252.50 ± 26.67 | 250.29 ± 25.53 | 241.29 ± 24.79 | 256.50 ± 25.41 | 212.07 ± 17.74 | 200.71 ± 18.05 | 199.57 ± 15.61 | 224.00 ± 23.99 |

**Discussion**

Heritability is a proportion of individual genetic variance that accounts for total phenotypic variance, and twin studies or family studies can offer information about heritability by separating the genetic and environmental components in phenotypic variances. The Healthy Twin Study generates data that can provide precise estimates of the genetic contribution to a wide range of traits and has already reported on the heritability of axial length, refractive error, high order aberration, intraocular pressure, disc morphology, and macular thickness. In the Healthy Twin Study, axial length, anterior chamber depth, and spherical equivalent of refractive error showed high heritability of 0.86, 0.83, and 0.78, respectively, whereas corneal high order aberration and direction of retinal vessels showed weak inheritance ranging from 0.03 to 0.22. In addition to these results, information generated from the present study elucidates and clarifies the heritability of IRL and ORL thickness.

Some previous studies have already demonstrated the heritability of total macular thickness. Chamberlain et al. studied the retinal thicknesses of 109 Australian twin pairs in nine macular subfields as defined by the ETDRS, and presented the heritability of macular thickness in the central subfield, inner ring subfields, and outer ring subfields to be 0.85, 0.81, and 0.81, respectively. Another such study was the British twin study of 155 female twin pairs, which presented the heritability of only the central macular thickness to be 0.90. The Healthy Twin Study also presented detailed information on the heritability of macular thickness in nine subfields as defined by the ETDRS, and the age-, sex-, and axial length-adjusted heritability of macular thickness in each subfield...
mostly ranged from 0.56 to 0.76, except for the outer nasal and outer temporal subfields. These previous studies elucidated the moderate to high heritability of macular thickness in different ethnicities.

In addition to reports on the heritability of macular thickness, the present study is the first to demonstrate the heritability of the thickness of the IRL and ORL. We separated the retina into the IRL and ORL since they are separately involved in various pathologic ocular conditions. In reference to diabetic retinopathy, retinal ischemia and consequent macular edema mainly involve the IRL, whereas the ORL is highly associated with and could pre-

| Outer Retina | Center | Inner Retina | Superior | Inferior | Temporal | Nasal | Outer Retina | Superior | Inferior | Temporal | Nasal |
|--------------|--------|--------------|----------|----------|----------|-------|--------------|----------|----------|----------|-------|
| All (n = 374) | 92.61 ± 0.71 | 83.13 ± 0.49 | 81.73 ± 0.40 | 83.81 ± 0.48 | 84.43 ± 0.47 | 80.03 ± 0.46 | 77.76 ± 0.48 | 78.94 ± 0.44 | 79.30 ± 0.43 |
| Men (n = 231) | 93.90 ± 0.87 | 83.17 ± 0.30 | 82.52 ± 0.62 | 84.30 ± 0.24 | 85.13 ± 0.00 | 78.92 ± 2.58 | 78.02 ± 2.13 | 78.90 ± 2.57 | 79.43 ± 2.47 |
| Women (n = 143) | 93.57 ± 0.76 | 83.05 ± 0.27 | 81.32 ± 0.23 | 83.98 ± 0.27 | 84.25 ± 0.23 | 79.68 ± 2.35 | 77.59 ± 2.28 | 78.92 ± 2.51 | 78.79 ± 2.28 |

Table 2. Age- and sex-specific distribution of outer retinal layer thickness. Data are presented as mean ± standard deviation.

Table 3. Intra-familial relationship and heritability (h²) for inner retinal layer thickness. A, additive genetic effects; C, shared environment effects; E, unique environment effects; SE, standard error. *Estimated by the intra-class correlation coefficient (95% CI) after adjusting for age, sex, axial length, diabetes, hypertension, and smoking. †Adjusted for age, sex, axial length, diabetes, hypertension, and smoking.
Table 4. Intra-familial relationship and heritability ($h^2$) for outer retinal layer thickness. A, additive genetic effects; C, shared environment effects; E, unique environment effects; SE, standard error. *Estimated by the intra-class correlation coefficient (95% CI) after adjusting for age, sex, axial length, diabetes, hypertension, and smoking. **Adjusted for age, sex, axial length, diabetes, hypertension, and smoking.

Intra-familial relationship

|                     | Monozygotic twin | Father-offspring | Mother-offspring | Pooled dizygotic and Sibling | A    | C    | E    | SE    |
|---------------------|------------------|-----------------|-----------------|------------------------------|------|------|------|-------|
| Center              | 0.67 (0.48–0.79) | 0.02 (−0.19–0.22) | 0.21 (0.02–0.37) | 0.16 (−0.05–0.35) | 0.56 | 0.44 | 0.05 | 0.16  |
| Superior            | 0.80 (0.68–0.88) | 0.09 (−0.11–0.29) | 0.29 (0.12–0.45) | 0.35 (0.15–0.52) | 0.75 | 0.25 | 0.02 | 0.19  |
| Inferior            | 0.67 (0.49–0.79) | 0.17 (−0.04–0.36) | 0.26 (0.08–0.43) | 0.15 (−0.06–0.35) | 0.66 | 0.34 | 0.06 | 0.20  |
| Temporal            | 0.79 (0.66–0.87) | 0.12 (−0.08–0.32) | 0.25 (0.07–0.42) | 0.28 (0.07–0.46) | 0.72 | 0.28 | 0.02 | 0.17  |
| Nasal               | 0.68 (0.51–0.80) | 0.08 (−0.13–0.28) | 0.24 (0.06–0.41) | 0.26 (0.05–0.44) | 0.56 | 0.44 | 0.07 | 0.21  |

Outer

|                     | Monozygotic twin | Father-offspring | Mother-offspring | Pooled dizygotic and Sibling | A    | C    | E    | SE    |
|---------------------|------------------|-----------------|-----------------|------------------------------|------|------|------|-------|
| Superior            | 0.71 (0.54–0.82) | 0.07 (−0.14–0.27) | 0.33 (0.16–0.48) | 0.19 (−0.02–0.38) | 0.64 | 0.34 | 0.01 | 0.20  |
| Inferior            | 0.63 (0.44–0.77) | 0.09 (−0.12–0.29) | 0.26 (0.08–0.42) | 0.20 (−0.01–0.39) | 0.63 | 0.33 | 0.01 | 0.15  |
| Temporal            | 0.80 (0.67–0.88) | 0.05 (−0.16–0.25) | 0.30 (0.13–0.46) | 0.14 (−0.07–0.34) | 0.73 | 0.25 | 0.02 | 0.15  |
| Nasal               | 0.62 (0.43–0.76) | 0.07 (−0.13–0.27) | 0.30 (0.16–0.43) | 0.30 (0.11–0.47) | 0.54 | 0.42 | 0.05 | 0.24  |

Methods

Participants. This was a cross-sectional study performed with recorded data of the participants of the Healthy Twin Study. The Healthy Twin study is a nationwide prospective cohort study that recruited Korean adult twins and their extended family members to investigate the genetic and environmental determinants of a wide range of traits. A more detailed description of the methodology and protocols of the Healthy Twin Study is available in previous reports.26,27

Among a total of 649 participants of the Healthy Twin cohort study, 418 participants had taken macular volumetric OCT scan in the Department of Ophthalmology at the Samsung Medical Center between March 16, 2012 and December 15, 2012. Among 418 participants with available OCT data, 44 participants were excluded for the following reasons: 30 had high myopia, 2 had pathologic myopia, 4 had age-related macular degeneration, 3 had epiretinal membrane, 1 had RPE atrophy, and 4 had poor quality of image (quality score of less than 20 dB) or image with artifact which resulted in aberrant segmentation. Finally, 374 subjects from 89 families with average 4.20 members were included in the study.

The study was approved by the institutional review board of Samsung Medical Center (IRB file number 2005-08-113) and it adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants after explanation of the nature and possible consequences of the study.
Analysis of clinical records and ocular measurements. Comprehensive ophthalmic examinations were conducted in the Department of Ophthalmology at the Samsung Medical Center in Seoul, South Korea. Medical and ocular histories of the participants were taken and they underwent, visual acuity (VA) assessment, intraocular pressure measurement, non-cycloplegic refraction with an autorefractor (Topcon AT; Topcon Corp., Tokyo, Japan), and axial length measurement with A-scan ultrasonography (Model 820; Allergan-Humphrey, San Leandro, CA). After pupil dilation, color fundus photography was performed using a fundus camera (TRC 50, Topcon, Paramus, New Jersey, USA; or Nonmyd 7, Kowa, Tokyo, Japan). Two retinal specialists (S.H. and M.K.) evaluated the clinical records, ocular measurements, and color fundus photographs. Eyes with a previous history of ocular surgery or ocular conditions that may affect retinal thickness, such as severe cataract, glaucoma, epiretinal membrane, diabetic retinopathy, retinal vein occlusion, age-related macular degeneration, and pathologic myopia were excluded from the study.

Optical coherence tomography. Macular volumetric OCT scans were obtained with the Heidelberg’s Spectralis HRA+OCT (version 1.7.0.0; Heidelberg Engineering, Heidelberg, Germany). The raster scan image was composed of 31 b-scans, each consisting of 768 A-scans, 9.0 mm in length, and spaced 240 μm apart, covering a 30-degree × 25-degree macular area. Segmentation of the retinal layers of every single horizontal scan was performed automatically using the new software for the Heidelberg’s Spectralis OCT, which provides thickness maps divided into nine subfields as defined by the Early Treatment Diabetic Retinopathy Study (ETDRS)32. IRL thickness was defined as the distance between the internal limiting membrane and the external limiting membrane, and ORL thickness was defined as the distance between the external limiting membrane and the outer border of the retinal pigment epithelium layer. With the data from the segmentation process, we calculated the numeric averages of the thicknesses of the IRL and ORL layers for each of the nine subfields (central subfield, four inner quadrant subfields, and four outer quadrants subfields). The numerical values of the IRL and ORL thicknesses recorded were used in the analyses.

Statistical analyses. All analyses were carried out using the data of the right eye of every participant. Intra-class correlation coefficients (ICCs) of the IRL and ORL thickness in each subfield were calculated within specific familial relationship types including monozygotic (MZ) twins, sibling pairs, and parent-offspring pairs. Dizygotic (DZ) twins were pooled with siblings because the genetic sharing within DZ twin pairs is similar to the genetic sharing between siblings, and the number of DZ twin pairs was too small to be separated39. While estimating ICCs, age, sex, axial length, presence of diabetes, and hypertension, and smoking history were adjusted as they may influence macular thickness33–37.

By employing variance-component methods38, we estimated the heritability of IRL and ORL thickness. We applied a variance decomposition model to partition the total phenotypic variation (p2) of IRL and ORL thickness measures into additive genetic component (a2), shared environmental components within a family (c2), and individual-specific unique environmental components (e2). Shared environmental components within a family (c2) refer to environmental factors that are shared by family members and render members of the same family more alike such as diet, socioeconomic status, and residential area. Individual-specific unique environmental components (e2) are environmental factors that are not shared with other family members and create differences between members of the same family such as relationships with friends, sports participation, even including measurement errors39. 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 (a2, c2, and e2) 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 (p2 = a2 + c2 + e2). We have fitted all plausible models such as ACE, AE, CE, or E, then compared their Akaike’s Information Criterion (AIC), and selected the model best fitted the data for each subfield based on the smallest AIC value among them. Heritability (h2) in the narrow sense was calculated as the ratio of the additive genetic component and the total variance (a2/p2), which represents the proportion of genetic contribution to the traits. We adjusted for age, sex, axial length, the presence of diabetes and hypertension, and smoking history in the estimation of heritability.

Descriptive statistics and ICC calculation were performed using SAS software version 9.4 (SAS Institute, Cary, NC). The Sequential Oligogenic Linkage Analysis Routines (SOLAR) ver. 2.0 program (Southwest Foundation for Biomedical Research, San Antonio, TX, USA)35 was used for quantitative genetic analyses.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Received: 5 December 2019; Accepted: 4 February 2020;
Published: 26 February 2020

References

1. Hornbeak, D. M. & Young, T. L. Myopia genetics: a review of current research and emerging trends. Curr. Opin. Ophthalmol. 20, 356–362 (2009).
2. Hageman, G. S. et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc. Natl Acad. Sci. USA 102, 7227–7232 (2005).
3. Klein, R. J. et al. Complement factor H polymorphism in age-related macular degeneration. Sci. 308, 385–389 (2005).
4. Springelkamp, H. et al. New insights into the genetics of primary open-angle glaucoma based on meta-analyses of intraocular pressure and optic disc characteristics. Hum. Mol. Genet. 26, 438–453 (2017).
5. Kim, M. H. et al. Heritability of myopia and ocular biometrics in Koreans: the healthy twin study. Invest. Ophthalmol. Vis. Sci. 54, 3644–3649 (2013).
6. Lim, D. H. et al. The Heritability of Corneal and Ocular Higher-Order Aberrations in Koreans: The Healthy Twin Study. *Invest. Ophthalmol. Vis. Sci.* 56, 3919–3928 (2015).

7. Chamberlain, M. D., Guymier, R. H., Dirani, M., Hopper, J. L. & Baird, P. N. Heritability of macular thickness determined by optical coherence tomography. *Invest. Ophthalmol. Vis. Sci.* 47, 336–340 (2006).

8. Sardell, R. J. et al. Heritability of Choroidal Thickness in the Amish. *Ophthalmol. 123*, 2537–2544 (2016).

9. van Kootwijk, L. M. et al. Genetic contributions to glaucoma: heritability of intraocular pressure, retinal nerve fiber layer thickness, and optic disc morphology. *Invest. Ophthalmol. Vis. Sci.* 48, 3669–3676 (2007).

10. Han, J. C. et al. Heritability of the morphology of optic nerve head and surrounding structures: The Healthy Twin Study. *PLoS One* 12, e0187498 (2017).

11. Kwun, Y. et al. Genetic influences on macular thickness in Koreans: the healthy twin study. *Invest. Ophthalmol. Vis. Sci.* 52, 9523–9526 (2011).

12. Gundogan, F. C. et al. Early Neurodegeneration of the Inner Retinal Layers in Type 1 Diabetes Mellitus. *Ophthalmologica* 235, 125–132 (2016).

13. van Dijk, H. W. et al. Selective loss of inner retinal layer thickness in type 1 diabetic patients with minimal diabetic retinopathy. *Invest. Ophthalmol. Vis. Sci.* 50, 3404–3409 (2009).

14. Tavares Ferreira, J. et al. Retinal Neurodegeneration in Diabetic Patients Without Diabetic Retinopathy. *Invest. Ophthalmol. Vis. Sci.* 57, 6455–6460 (2016).

15. Elway, L. S., Zaki, M. A. & Raslan, O. A. Outer Retinal Layer Thickness as Good Visual Predictor in Patients with Diabetic Macular Edema. *Retina* 38, 805–811 (2018).

16. Chen, T. C. et al. Spectral domain optical coherence tomography: ultra-high speed, ultra-high resolution opthalmic imaging. *Arch. Ophthalmol. 123*, 1715–1720 (2005).

17. Spaide, R. F., Koizumi, H. & Pozzoni, M. C. Enhanced depth imaging spectral-domain optical coherence tomography. *Am. J. Ophthalmol.* 146, 496–500 (2008).

18. Garvin, M. K. et al. Automated 3-D intraretinal layer segmentation of macular spectral-domain optical coherence tomography images. *IEEE Trans. Med. Imaging* 28, 1436–1447 (2009).

19. Sung, J. et al. Healthy Twin: a twin-family study of Korea—protocols and current status. *Twin Res. Hum. Genet.* 9, 844–848 (2006).

20. Sung, J. et al. Do we need more twin studies? The Healthy Twin Study. *Int. J. Epidemiol.* 35, 488–490 (2006).

21. Liew, S. H., Gilbert, C. E., Spector, T. D., Marshall, J. & Hammond, C. J. The role of heredity in determining central retinal thickness. *Br. J. Ophthalmol.* 91, 1143–1147 (2007).

22. Pilotto, E. et al. En Face Optical Coherence Tomography to Detect and Measure Geographic Atrophy. *Invest. Ophthalmol. Vis. Sci.* 56, 8120–8124 (2015).

23. Lim, J. I. et al. A pilot study of Fourier-domain optical coherence tomography of retinal dystrophy patients. *Am. J. Ophthalmol.* 146, 417–426 (2008).

24. Choi, S. S. et al. In vivo imaging of the photoreceptor mosaic in retinal dystrophies and correlations with visual function. *Invest. Ophthalmol. Vis. Sci.* 47, 2080–2092 (2006).

25. Costa, R. A. et al. Optical coherence tomography 3: Automatic delineation of the outer neural retinal boundary and its influence on retinal thickness measurements. *Invest. Ophthalmol. Vis. Sci.* 45, 2399–2406 (2004).

26. Li, S. T., Wang, X. N., Du, X. H. & Wu, Q. Comparison of spectral-domain optical coherence tomography for intra-retinal layers thickness measurements between healthy and diabetic eyes among Chinese adults. *PLoS One* 12, e0177515 (2017).

27. Wang, X. N., Li, S. T., Li, W., Hua, Y. J. & Wu, Q. The thickness and volume of the choroid, outer retinal layers and retinal pigment epithelium layer changes in patients with diabetic retinopathy. *Int. J. Ophthalmol.* 11, 1957–1962 (2018).

28. Wong, R. L., Lee, J. W., Yau, G. S. & Wong, I. Y. Relationship between Outer Retinal Layers Thickness and Visual Acuity in Diabetic Macular Edema. *Biomed. Res. Int.* 2015, 981471 (2015).

29. Won, J. Y., Kim, M. & Park, Y. H. Postoperative changes in the retinal thickness and volume after vitrectomy for epiretinal membrane and internal limiting membrane peeling. *Med. 96*, e6709 (2017).

30. Cicinelli, M. V., Marchese, A., Bandello, F. & Coppola, M. Inner Retinal Layer and Outer Retinal Layer Findings after Macular Hole Surgery Assessed by means of Optical Coherence Tomography. *J. Ophthalmol.* 2019, 3821479 (2019).

31. Lee, G. I., Park, K. A., Son, G., Kong, D. S. & Oh, S. Y. Optical coherence tomography analysis of inner and outer retinal layers in eyes with chiasmal compression caused by suprasellar tumours. *Acta Ophthalmol.* (2019).

32. Frank, R. N., Schulz, L., Abe, K. & Iezzi, R. Temporal variation in diabetic macular edema measured by optical coherence tomography. *Ophthalmol. 111*, 211–217 (2004).

33. Alasal, T. et al. Analysis of normal retinal nerve fiber layer thickness by age, sex, and race using spectral domain optical coherence tomography. *J. Glaucoma* 22, 532–541 (2013).

34. Alamouti, B. & Funk, J. Retinal thickness decreases with age: an OCT study. *Br. J. Ophthalmol.* 87, 899–901 (2003).

35. Luo, H. D. et al. Myopia, axial length, and OCT characteristics of the macula in Singaporean children. *Invest. Ophthalmol. Vis. Sci.* 47, 2773–2781 (2006).

36. Kong, M., Kwun, Y., Sung, J., Ham, D. I. & Song, Y. M. Association Between Systemic Hypertension and Macular Thickness Measured by Optical Coherence Tomography. *Invest. Ophthalmol. Vis. Sci.* 56, 2144–2150 (2015).

37. El-Shazly, A. A. E., Farweez, Y. A. T., Elewa, L. S., Elzankalony, Y. A. & Farweez, B. A. T. Effect of Active and Passive Smoking on retinal nerve fiber layer thickness, and optic disc morphology. *Invest. Ophthalmol. Vis. Sci.* 48, 3669–3676 (2007).

38. Keller, M. C. et al. Modeling extended twin family data I: description of the Cascade model. *Twin Res. Hum. Genet.* 12, 8–18 (2009).

39. Carlstedt, R., A. Handbook of integrative clinical psychology, psychiatry, and behavioral medicine: perspectives, practices, and research. Chapter 5 title: Behavioral Genetics by Vinkhuyzen AE, van der Sluis S, Posthuma D pp 81–82 (2010).

### Author contributions

Don-II Ham and Yun-Mi Song designed the study. Mingui Kong, Sungsoon Hwang, and Hyeonyoung Ko analyzed the clinical data. Mingui Kong and Sungsoon Hwang wrote the final paper. Don-II Ham and Yun-Mi Song reviewed the design, the results, and the final paper. Mingui Kong and Sungsoon Hwang contributed equally to the manuscript as first authors. Don-II Ham and Yun-mi Song contributed equally to the manuscript as corresponding authors. All authors read and approved the final manuscript.

### Competing interests

The authors declare no competing interests.

### Additional information

Correspondence and requests for materials should be addressed to Y.-M.S. or D.-I.H.

Reprints and permissions information is available at [www.nature.com/reprints](http://www.nature.com/reprints).
