Genetic Influence on Choroidal Volume

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• PURPOSE: **To evaluate the degree of genetic influence on macular choroidal volume.**
• DESIGN: **A cross-sectional twin and family study.**
• METHODS: **In total, 353 Korean adults with healthy eyes from 78 households with 2 or more family members were included in the study. Macular choroidal volume was measured using spectral-domain optical coherence tomography with enhanced depth imaging at 9 macular subfields defined by the ETDRS. Demographics and clinical characteristics were investigated, including age, sex, axial length, hypertension, diabetes, drinking habits, and smoking status. The associations of these factors with macular choroidal volume were assessed using univariate and subsequent multivariate regression analyses while accounting for family structure. The heritability estimates of macular choroidal volume in total and at each of the 9 macular subfields were calculated after adjusting the covariates.**
• RESULTS: **Patients who were younger, male, and had a shorter axial length showed associations with greater choroidal volume ($P < .001$ for all 3 independent variables). The covariates-adjusted heritability (±standard error) of the total macular choroidal volume was 0.76 ± 0.06, and the heritabilities of choroidal volume at each subfield ranged from 0.55 ± 0.09 (inner temporal subfield) to 0.77 ± 0.08 (inner superior subfield).**
• CONCLUSION: **The macular choroidal volume is highly heritable. (Am J Ophthalmol 2021;224:143–149. © 2020 Elsevier Inc. All rights reserved.)**

THE GENETIC INFLUENCE ON MAJOR OCULAR DISeases, such as myopia, age-related macular degeneration, or primary open-angle glaucoma, has been widely investigated recently, which has promoted a better understanding of the underlying pathogenesis of these diseases.[1-3] Additionally, the genetic influences on specific ocular traits, such as axial length, refractive error, or ganglion cell complex thickness, also have been investigated because they can be directly linked and contribute to some specific ocular diseases like myopia or glaucoma.[4,5] Elucidating the genetic basis of certain ocular traits could aid in identifying the genes involved in related ocular diseases through linkage analysis and association studies.

Choroidal thickness is an important phenotype that is known to be associated with major macular diseases, including age-related macular degeneration and pachychoroid spectrum diseases.[6,7] Previously, a study of Amish twins reported that the subfoveal choroidal thickness is moderately heritable with an estimated heritability of 0.40.[8] However, this study was limited because it included both healthy eyes and eyes with age-related macular degeneration and only measured subfoveal choroidal thickness, which can be easily influenced by local changes in choroidal thickness or irregularities in the choroidoscleral border. Choroidal volume may better represent the amount of choroidal tissue quantitatively,[9] but no study has yet explored the genetic influence on macular choroidal volume. Therefore, we investigated the heritability of choroidal volume in healthy Korean adults using the data from a population-based twin and family study.

METHODS

• SETTING: This was a cross-sectional study using the data derived from the Healthy Twin Study, which 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. The methodology and protocols of the Healthy Twin Study are described in detail in previous reports.[10,11] 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.

• PARTICIPANTS: Of 649 total participants in the Healthy Twin cohort study, 418 participants had undergone a macular volumetric optical coherence tomography (OCT) scan

AJO.com Supplemental Material available at AJO.com.
Accepted for publication Dec 8, 2020.
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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2020.12.008

in the Department of Ophthalmology at the Samsung Medical Center between March 1, 2012, and December 31, 2012. Of the 418 participants with available volumetric OCT data, 30 were excluded for having high myopia (refractive error higher than −6.0 diopter [D]), 2 for pathologic myopia, 4 for age-related macular degeneration, 3 for epiretinal membrane, 1 for retinal pigment epithelium atrophy, and 16 for having poor imaging quality (quality score of less than 20 dB) or artifacts that resulted in the inability to describe choroidal margin. Because heritability analysis requires a minimum of 2 members per family, we additionally excluded 9 participants who were the only members of a family. Finally, 353 participants from 78 families with an average of 4.53 members per family were included in the study. This includes 52 monozygotic (MZ) twin pairs, 6 dizygotic (DZ) twin pairs, 95 sibling pairs, 95 father-offspring pairs, and 110 mother-offspring pairs.

• **CHOROIDAL VOLUME ASSESSMENT:** Macular volumetric OCT scans were obtained using a spectral domain-OCT (Spectralis OCT; Heidelberg Engineering, Heidelberg, Germany) with enhanced depth imaging. All OCT scans were operated by a single well-trained technician. A macular map was generated in a 30×30-degree square centered on the fovea, including 31 horizontal B-scans with a total of 25 frames averaged for 1 B-scan image. Individual keratometric values and refractions were entered into the software program to estimate optical magnification.

To assess choroidal volume, we used a built-in retinal thickness map analysis software, which is designed to display the volume and average thickness of the retinal layer for each of the 9 subfields defined by the ETDRS (central, 4 inner quadrants, and 4 outer quadrants).[12] Segmentation lines in all 31 horizontal scans of each subject were manually changed, the internal limiting membrane layer was moved to the outer part of the retinal pigment epithelial level, and the Bruch membrane segmentation line was moved to the outer border of the choroid.[9] We obtained choroidal volume and average choroidal thickness in each subfield displayed in the software and calculated the average macular choroidal thickness by dividing the sum of choroidal volume in 9 subfields by the total macular area. The measurement process and calculation of average macular choroidal thickness are described in Supplementary Figures S1 and S2 in detail. Segmentation was performed by 2 retinal specialists (S.H. and M.K.) who were blinded to each other's measurements. The mean values of the 2 measurements were used for the analyses in this study. Intraclass correlation coefficient (2-way random effects/absolute agreement) of total choroidal volume was assessed to evaluate intergrader reproducibility.[13]

• **MEASUREMENT OF OTHER OCULAR FACTORS:** All study participants underwent a comprehensive ophthalmic evaluation, including best-corrected visual acuity measured by the Snellen chart, intraocular pressure by an applanation tonometer, nondilated refraction by an autorefractor (Topcon AT; Topcon Corp, Tokyo, Japan), and axial length by corneal touch A-scan ultrasonography (Model 820; Allergan-Humphrey, San Leandro, California, USA). Dilated color fundus photographs were also taken using a fundus camera TRC 50 (Topcon, Paramus, New Jersey, USA) or Nonmyd 7 (Kowa, Tokyo, Japan) to identify any retinal pathology. Two retinal specialists (S.H. and M.K.) evaluated the clinical records, ocular measurements, and color fundus photographs to determine the presence of ocular surgery history, amblyopia, and retinal/choroidal pathologies that could affect choroidal volume and distribution.

• **MEASUREMENT OF SYSTEMIC FACTORS:** All study subjects underwent a routine blood pressure measurement and lab blood test. A trained research nurse measured blood pressure (BP) twice using a standard mercury sphygmomanometer, and the average value of the 2 measurements was used for analyses. Fresh serum was collected after a minimum 12-hour overnight fast, and the concentrations of glucose, hemoglobin A_{1c}, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides were measured using enzymatic or homogeneous assay kits with the ADVIA 1650 analyzer (Siemens, Munich, Germany). Hypertension was defined as having high systolic BP (≥140 mm Hg), high diastolic BP (≥90 mm Hg), or current use of a BP-lowering agent. Diabetes was defined as having a fasting glucose level of ≥126 mg/dL, hemoglobin A_{1c} level of ≥6.5%, or use of a glucose-lowering agent. Weight (kg) and height (m) were measured in light clothing using standardized scales and stadiometers, and body mass index was calculated by dividing the weight (in kilograms) by the height (in meters) squared. Data on medical history, drinking habits, and smoking status were collected using a self-administered questionnaire.

• **STATISTICAL ANALYSIS:** All analyses were conducted using the data obtained from the right eye of every participant. The demographic and clinical characteristics of the participants were analyzed. Univariate and subsequent multivariate linear regression analyses were performed to determine the associations of the overall choroidal volume with other ocular and systemic factors that could possibly affect choroidal volume. Parameters presenting an association ($P < .10$) in the univariate analysis were included in the subsequent multiple linear regression analyses. In all regression models, family structure was taken into account. The Bonferroni method for multiple testing was considered for interpretation of statistical results; P values $<.004$ (.05 divided by 14, as there were 14 independent variables) were considered to be statistically significant in the final regression model. Intraclass correlation coefficients (ICCs) of choroidal volumes were calculated within specific familial relationship types, including MZ twins, sibling pairs, and parent-offspring pairs. DZ twins were pooled with siblings because the shared genes within DZ twin pairs is similar

to those between siblings, and the number of DZ twin pairs was too small to be separated.[10] The heritabilities of choroidal volumes were calculated using variance-component methods.[14] There are 2 types of heritability: broad-sense heritability and narrow-sense heritability. Broad-sense heritability is the proportion of variation in a trait explained by all genetic factors, including additive, dominant genetic effects, and epistasis (genetic interactions). On the other hand, narrow-sense heritability is the proportion of variation in a trait due to additive genetic effects only. In the present study, we estimated the narrow-sense heritability of choroidal volume through the following method. The total phenotypic variation (p^2) of choroidal volumes was separated into additive genetic components (a^2), shared environmental components within a family (c^2), and individual-specific unique environmental components (e^2). The analysis assumed that the effects of shared environmental factors (c^2) are common among family members and that the 3 factors (a^2, c^2, and e^2) have independent and additive effects on the variance of the trait. Thus, the total phenotypic variance equals the sum of the additive and individual-specific variance components ($p^2 = a^2 + c^2 + e^2$). We fitted all plausible models, including ACE, AE, CE, or E; compared their Akaike's information criterion (AIC); and selected the best-fitting model based on the smallest AIC value. The narrow-sense heritability (h^2) was calculated as the proportion of the additive genetic components to the total variance (a^2/p^2), 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 status in the linear mixed model for estimation of ICC and heritability, as these traits may influence choroidal volume. Descriptive statistics, regression analysis, and ICC calculations were performed using R version 3.6.2 (GenABEL, kinship2, hglm package). The Sequential Oligogenic Linkage Analysis Routines (SOLAR) Eclipse, version 8.4.2 (Southwest Foundation for Biomedical Research, San Antonio, Texas, USA), was used for heritability analyses.[15]

RESULTS

TABLE 1 PRESENTS THE DETAILED DEMOGRAPHIC AND CLINical characteristics of the study participants. There were 137 male and 216 female participants with an average age of 48.4 ± 13.8 years ranging from 18 to 80 years. In total, 74 subjects (21.0%) were hypertensive, 20 (5.7%) were diabetic, and 13 (3.7%) were current smokers. Twelve eyes had history of cataract extraction, and none of the patients had prior glaucoma surgery or vitrectomy/buckling.

Table 2 shows choroidal volume distribution and the average choroidal thickness calculated over the total macular area and at each subfield. The macular choroidal volume was 7.50 ± 2.25 mm^3 (range: 2.47-14.87), and the calculated average choroidal thickness of the overall macular area was 265.4 ± 79.5 μm (range: 87-526). The intergrader reproducibility of macular choroidal volume was high, with an intraclass correlation coefficient of 0.988 and a coefficient of reproducibility of 0.71 mm^3.

TABLE 1. The Demographics and Clinical Characteristics of the Study Participants

Characteristics	Value
Age, y	48.4 ± 13.8 (18-80)
Sex, male, n (%)	137 (38.8)
Axial length, mm	23.67 ± 1.03 (20.86-26.78)
IOP, mm Hg	14.5 ± 3.2 (8.8-46.4)
Hypertension	74 (21.0)
Diabetes	20 (5.7)
Systolic BP, mm Hg	112.8 ± 15.7 (80-172)
Diastolic BP, mm Hg	71.8 ± 9.7 (50-99)
Hemoglobin A_{1c}, %	5.4 ± 0.6 (4.5-11.2)
HDL-C, mg/dL	53.6 ± 11.9 (29-105)
LDL-C, mg/dL	112.3 ± 30.1 (42-217)
TG, mg/dL	121.5 ± 65.4 (36-539)
Body mass index	23.7 ± 3.1 (16.25-34.29)
Alcohol consumption	
None	109 (30.9)
Once a week or less	174 (49.3)
More than once a week	70 (19.8)
Smoking status	
Current	13 (3.7)
Past	97 (27.5)
Never	243 (68.8)

BP = blood pressure, HDL-C = high-density lipoprotein cholesterol, IOP = intraocular pressure, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride.

Continuous variables are described as mean ± standard deviation (range), and categorical parameters are described as total numbers (percentage).

The results of univariate and multivariate regression analyses for total macular choroidal volume while adjusting for family structure are depicted in Table 3. Patients who were older, female, and had a longer axial length showed associations with a smaller choroidal volume in the multivariate regression analysis with beta values of −0.073, −0.771, and −0.625, respectively.

Table 4 shows the heritability of choroidal volume in total and at each macular area with the ICCs of various intrafamilial relationship types after adjusting for covariates, including age, sex, axial length, diabetes, hypertension, and smoking status. The ICC was highest in MZ twin pairs in all macular subfields from 0.69 (outer inferior subfield) to 0.87 (inner superior subfield). The covariates-adjusted heritability of the total macular choroidal volume was 0.76, and the heritabilities of choroidal volume at each subfield ranged from 0.55 (inner temporal subfield) to 0.77 (inner superior subfield).

TABLE 2. Choroidal Volumes and Average Choroidal Thickness in Each Macular Subfield of the Study Participants

	Choroidal Volume, mm^3	Average Choroidal Thickness, μm
Overall macula	7.50 ± 2.25 (2.47-14.87)	265.4 ± 79.5 (87-526)
Subfields		
Central	0.23 ± 0.08 (0.05-0.43)	295.9 ± 97.2 (68-551)
Inner superior	0.46 ± 0.15 (0.03-0.88)	291.0 ± 92.9 (16-558)
Inner inferior	0.45 ± 0.15 (0.14-0.87)	284.6 ± 94.4 (87-552)
Inner temporal	0.44 ± 0.15 (0.05-1.01)	283.2 ± 92.4 (29-641)
Inner nasal	0.44 ± 0.15 (0.05-0.83)	279.3 ± 96.0 (32-530)
Outer superior	1.49 ± 0.43 (0.54-2.78)	280.4 ± 81.0 (102-524)
Outer inferior	1.41 ± 0.47 (0.41-3.21)	265.1 ± 88.0 (77-605)
Outer temporal	1.40 ± 0.43 (0.47-2.93)	263.4 ± 80.9 (89-533)
Outer nasal	1.20 ± 0.44 (0.34-2.55)	225.8 ± 82.3 (65-481)

Variables are described as mean ± standard deviation (range).

TABLE 3. Regression Analyses of Systemic and Ocular Factors Associated With Macular Choroidal Volume Accounting for Family Structure

	Univariate		Multivariate[a]	
Covariates	Beta	*P* Value	Beta	*P* Value
Age	−0.070 ± 0.008	<.001	−0.073 ± 0.009	<.001
Sex	−0.532 ± 0.244	.030	−0.771 ± 0.234	<.001
Axial length	−0.225 ± 0.117	.056	−0.625 ± 0.107	<.001
IOP	0.049 ± 0.036	.18	—	—
Hypertension	−1.442 ± 0.273	<.001	−0.565 ± 0.274	.040
Diabetes	−1.029 ± 0.497	.040	−0.003 ± 0.439	.99
HDL-C	0.005 ± 0.010	.60	—	—
LDL-C	−0.004 ± 0.004	.34	—	—
TG	−0.001 ± 0.002	.62	—	—
Body mass index	−0.079 ± 0.038	.041	−0.010 ± 0.036	.78
Alcohol consumption				
Never	(reference)	—	—	—
Equal to or less than 1/week	0.930 ± 0.266	<.001	0.272 ± 0.247	.27
More than 1/week	1.156 ± 0.330	<.001	0.631 ± 0.310	.043
Smoking habit				
Never	(reference)	—	—	—
Past	0.276 ± 0.264	.30	—	—
Current	0.493 ± 0.634	.44	—	—

BP = blood pressure, HDL-C = high-density lipoprotein cholesterol, IOP = intraocular pressure, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride.

[a]Adjusted for variables with a *P* value <.10 in the univariate analysis.

DISCUSSION

TWIN AND FAMILY STUDIES OFFER HERITABILITY ESTIMATES by separating the genetic and environmental components in phenotypic variances. The Healthy Twin Study generated quality data that can provide precise estimates of the genetic contribution, and it revealed the heritability of various ocular parameters.[16-19] In the Healthy Twin Study cohort, axial length, anterior chamber depth, and spherical equivalent showed high heritabilities of 0.86, 0.83, and 0.78, respectively,[16] whereas corneal high-order aberration showed a weak inheritance of 0.03-0.22.[17]

In addition to previous findings, the present study further elucidated the heritability of macular choroidal volume. Total macular choroidal volume showed high heritability of 0.76 after adjusting covariates such as age and sex. Choroidal volumes in different subfields had different

TABLE 4. Intraclass Correlation Coefficients for Each Intrafamilial Relationship and Heritability (h^2) of Choroidal Volume in the Overall Macular Area and in Each Macular Subfield

	Intraclass Correlation Coefficients (95% CI)[a]				Variance Component[a]				Heritability[a]		
	Monozygotic Twin Pair	Father-Offspring Pair	Mother-Offspring Pair	Dizygotic Twin Pair and Sibling	Best-Fitting Model	A	C	E	$h^2 \pm$ SE	*P* Value	Variance Explained by Covariate
Number of subjects	104 (52 pairs)	190 (95 pairs)	220 (110 pairs)	177 (98 pairs)							
Overall choroidal volume	0.83 (0.70, 0.91)	0.23 (0.05, 0.43)	0.11 (0.00, 0.29)	0.21 (0.07, 0.38)	AE	0.76	0.00	0.24	0.76 ± 0.06	<.001	0.243
Subfield choroidal volume											
Central	0.79 (0.63, 0.88)	0.29 (0.11, 0.48)	0.04 (0.00, 0.21)	0.15 (0.01, 0.31)	AE	0.67	0.00	0.33	0.67 ± 0.07	<.001	0.181
Inner											
Superior	0.87 (0.77, 0.93)	0.11 (0.00, 0.31)	0.02 (0.00, 0.19)	0.13 (0.01, 0.28)	AE	0.77	0.00	0.23	0.77 ± 0.08	<.001	0.079
Inferior	0.70 (0.52, 0.83)	0.27 (0.09, 0.46)	0.09 (0.00, 0.26)	0.18 (0.04, 0.35)	AE	0.61	0.00	0.39	0.61 ± 0.08	<.001	0.235
Temporal	0.72 (0.54, 0.84)	0.15 (0.00, 0.35)	0.02 (0.00, 0.15)	0.12 (0.00, 0.27)	AE	0.55	0.00	0.45	0.55 ± 0.09	<.001	0.190
Nasal	0.71 (0.53, 0.83)	0.34 (0.16, 0.53)	0.09 (0.00, 0.26)	0.21 (0.07, 0.38)	AE	0.57	0.00	0.43	0.57 ± 0.08	<.001	0.198
Outer											
Superior	0.78 (0.63, 0.88)	0.25 (0.07, 0.45)	0.12 (0.00, 0.29)	0.18 (0.03, 0.35)	AE	0.72	0.00	0.28	0.72 ± 0.06	<.001	0.200
Inferior	0.69 (0.50, 0.82)	0.19 (0.00, 0.38)	0.10 (0.00, 0.28)	0.25 (0.10, 0.42)	AE	0.61	0.00	0.39	0.61 ± 0.08	<.001	0.253
Temporal	0.78 (0.63, 0.88)	0.19 (0.01, 0.38)	0.11 (0.00, 0.29)	0.13 (0.00, 0.29)	AE	0.67	0.00	0.33	0.67 ± 0.07	<.001	0.299
Nasal	0.79 (0.64, 0.88)	0.34 (0.16, 0.53)	0.17 (0.01, 0.35)	0.26 (0.11, 0.42)	AE	0.72	0.00	0.28	0.72 ± 0.06	<.001	0.213

A = additive genetic components, C = shared environmental components within a family, E = individual-specific unique environmental components, h^2 = heritability estimates.

[a]Adjusted for age, sex, axial length, the presence of diabetes and hypertension, and smoking status (none/past/current).

estimates of heritability ranging from 0.55 to 0.77. Various levels of heritability within the same choroidal tissue might be attributable to the following 2 reasons. First, measurement error could have contributed to the variability of heritability. Second, choroidal thickness itself can be easily influenced by local changes in sclera or location of certain choroidal vessels, and this variation could have caused the random error and resulted in the different estimates of heritability. Choroidal volume in each subfield can easily be influenced by this random error, but the total choroidal volume covers a much larger area and is less likely to be influenced. This explains the reason for total macular choroidal volume having relatively higher heritability compared with choroidal volume in each subfield.

There are many external determinants that largely influence choroidal thickness, including age, sex, and axial length; this influence was confirmed by our regression analyses.[20] In the genetic aspect, 2 genetic loci have been identified as associated with choroidal thickness. Hosoda and associates performed a genome-wide association study in a healthy Japanese cohort and identified that rs800292 in complement factor H (CFH) and rs3793217 in vasoactive intestinal peptide receptor 2 (VIPR2) are significantly associated with choroidal thickness.[21] These genes may affect choroidal thickness through some underlying mechanisms. For example, CFH is known to bind to adrenomedullin, which has a vasodilatory effect and could contribute to choroidal vasodilation.[22] Additionally, vasoactive intestinal peptide, a VIPR2 agonist, also has vasodilatory effects in various vascular tissue as well as roles in controlling corticosteroid secretion, which might be associated with the mineralocorticoid pathway.[23,24] Polymorphisms in these genes might affect the vasodilatory effect on choroid and thus influence choroidal thickness. However, further studies are required to fully elucidate the genetic background of choroidal volume.

Sardell and associates reported that subfoveal choroidal thickness has a heritability of 0.40 (95% CI 0.14-0.51), suggesting that choroidal thickness is moderately heritable.[8] In contrast, the heritability of macular choroidal volume in our study was much greater than that of the previous report. The lower heritability in the previous study may be attributed to the following reasons. First, Sardell and associates included not only healthy eyes but also eyes with various degrees of age-related macular degeneration. Inclusion of ocular diseases that might alter choroidal thickness could increase the random error level, resulting in underestimated heritability. Because age-related macular degeneration is associated with thinner choroidal thickness, the inclusion of eyes with degeneration likely influenced the heritability estimates of subfoveal choroidal thickness. Moreover, Sardel and associates only measured the subfoveal choroidal thickness, which is more likely to be affected by focal variation in choroidal contour when compared with choroidal volume, thus resulting in greater random error and subsequently underestimated heritability. The high heritability of choroidal volume in our study indicates that the genetic influence on choroid is significant and would be much greater than previously expected by ophthalmologists.

The present study has several strengths. First, a large number of participants with healthy eyes were included. The large cohort provided a high statistical power, and the inclusion of healthy eyes enabled the accurate calculation of the estimated heritability of choroidal volume by avoiding misleading outliers. Second, the Healthy Twin Study was an extended family study including twins and their first-degree relatives. This allowed us to calculate narrow-sense heritability estimates and to avoid the possibility of obtaining inflated heritability estimates that occur when dominant genetic effects exist in a classic twin model including only MZ and DZ twins.

This study also had some limitations. First, we only included Korean participants. Choroidal volume could vary between ethnic groups, and this should be taken into account when generalizing these results to other ethnicities. Second, the medical history questionnaire items in our study did not include questions regarding previous steroid use, so we were not able to provide data regarding the history of steroid use. Third, our study included a relatively small number of DZ twins compared to MZ twins. Considering the DZ-MZ ratio in the general population of South Korea,[25,26] the present study had skewed participation, favoring MZ twins. The inclusion of more DZ twin pairs would have enhanced our findings. Nevertheless, we included a sufficient number of extended family members to compensate for the small DZ number, and this also has led us to estimate narrow-sense heritability. Therefore, we believe that the results of our study are still valid and reliable. Fourth, heritability, the main outcome of the study, only provides information on the combined additive effects of all genes. Therefore, further research is warranted to investigate the specific genes that determine choroidal thickness. Lastly, the study only investigated choroidal volume using normal healthy eyes and thus cannot provide information of the genetic influence on pachychoroid ("abnormally" thick choroid) and structural changes, such as inner choroidal attenuation or pachyvessels found in pachychoroid diseases. Our findings cannot be generalized to pachychoroid disease. Future research investigating the heritability of pachychoroid and structural parameters such as choriocapillaris attenuation, pachyvessel, and choroidal vascularity index[27] would provide more insight into the genetics of pachychoroid.

In conclusion, this study provided valuable information on the heritability of choroidal volume. The heritability of macular choroidal volume was very high. We hope our results help future genetic research on the choroid.

FUNDING/SUPPORT: THIS STUDY WAS SUPPORTED BY A GRANT FROM THE KOREA HEALTH TECHNOLOGY R&D PROJECT through the Korea Health Industry Development Institute, South Korea (no. HI14C0064) and a basic science research program through the National Research Foundation of Korea (NRF), South Korea funded by the Ministry of Education, Science, and Technology (no. 2012-0004255). The funding organizations had no role in the design or conduct of this research. S. Hwang and M. Kang are co-first authors of this study. Financial Disclosures: The authors indicate no financial support or conflicts of interest. All authors attest that they meet the current ICMJE criteria for authorship.

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