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Genetic influences on cortical myelination in the human brain

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Cortical myelination, which is essential for interneuronal communication and neurodevelopment, has been reported to be under genetic control. However, the degree to which genes contribute to the variability of myelination, the pattern of genetic control, and how genes influence the organization of myelination are largely unknown. To answer these questions, the present study calculated heritability estimates for myelination of the cortical regions using the high quality structural magnetic resonance imaging (MRI) scans from the Human Connectome Project pedigree cohort (n = 873, 383/490 M/F, 22-36 years of age). Then, we used transcriptional profiles to evaluate the contribution of myelination-related genes (data from the Allen Human Brain Atlas) to explain interregional variations in cortical myelination. Our results showed that all the cortical areas were modestly to moderately influenced by genetic factors (h^2 = 29%-66%, all *Ps* < 0.05 after Bonferroni correction). The genetic control of cortical myelination showed bilateral symmetry and an anterior-to-posterior gradation. A bivariate model indicated that the regions are strongly genetically correlated with their homologs in the opposite cerebral hemisphere. A cross-modal analysis did not find a correlation between cortical myelination and the expression levels of myelination-related genes. This could have been due to the small number of samples with expression data in each cortical region. Overall, our findings suggest that cortical myelination is shaped by genetic factors and may be useful to bridge the underlying genetic variants and the cognitive functioning and related neuropsychiatric disorders.

KEYWORDS

Allen Brain Institute, cerebral cortex, gene expression, genetics, heritability, Human Connectome Project, imaging, myelin map, myelination, structural MRI

1 | INTRODUCTION

The lipid myelin sheath, which forms around some neuronal axons, plays a critical role in the efficient communication within the human brain. To support information transmission, myelinated axons have a 10-fold higher signal transmission speed and need 30-fold less time for axonal repolarization than unmyelinated axons[1,2] and, thus, are essential for normal brain function.

Myelination of the brain begins early in fetal development and continues throughout life.[3] During human postnatal maturation, cortical myelin content is correlated with nonuniformities in postnatal expansion,[4] shapes functional activity[5] and allows neurodevelopment and the evolution of cognitive and behavioral functions, such as processing speed[6] and general cognitive ability.[7] Moreover, myelination abnormalities have been extensively implicated in the pathophysiology of psychiatric and neurological diseases, such as schizophrenia[8] and Alzheimer disease (AD).[9] Thus, understanding the origins of variations in myelination should provide insight into these cognitive functions and neuropsychiatric disorders. Compared with traditional histological methods, magnetic resonance imaging (MRI) facilitates the noninvasive measurement of the whole-brain myelin content in large samples, and MR-based signals have been reported to largely reflect histologically measured myelin content.[10,11] Moreover, a recent study

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estimated detailed cortical myelin maps by using the ratio of T1w/T2w image intensities to correct for MRI-related image intensity bias and to increase the contrast-to-noise ratio for myelin.[4] Therefore, this T1w/T2w technique is a reasonable measure of cortical myelin and will be used in later analysis.

Both genetic and environmental influences on myelination have been identified. On one hand, animal studies have reported hypomyelination caused by reduced *neuregulin-1* expression[12] and increased myelination induced by overexpression of the *transferrin* gene[13] in genetic mouse models. On the other hand, some studies reported functional myelin plasticity in the motor cortex after motor training in rodents[14] and reductions in myelin after maltreatment in monkeys.[15] These studies shed light on the potential origins myelination, however, the extent to which the genome and/or the environment contribute to the variations in myelination remains unknown.

Additionally, the pattern of genetic control on the myelin content across the brain has yet to be investigated. Previous studies have reported the interhemispheric symmetry patterns of both the heritability of other morphometric traits[16,17] and the gene expression in the human brain.[18] Furthermore, how genes influence the distribution of myelination across regions is not known. Because the expression levels of genes vary between brain regions,[18] some researchers have linked region-specific genetic expression to interregional variations in brain structure[19] and connectome profiles.[20] These studies have provided a valuable tool for understanding the genetic mechanisms of brain phenotypes. Thus, in the current study, we investigated the relationship between interregional profiles of myelination and those in the expression of myelination-related genes.

Here, we used myelin content maps based on the Human Connectome Project's (HCP) extended twin population[21] to quantify genetic and environmental contributions to individual variability in myelination. Next, we investigated the pattern of the distribution of heritability between hemispheres. Then, we examined the potential influence of the myelination-related genes on the distribution of myelination by combining transcriptional profiles of myelination-related genes with the macroscale myelination pattern. We hypothesized that: (a) cortical myelination is heritable; (b) genetic influences on myelination follow a bilaterally symmetric pattern, similar to what has been observed in other morphometric traits; (c) interregional variations in myelination may be influenced by interregional variations in the expression of myelination-related genes.

2 | MATERIALS AND METHODS

2.1 | Subjects

All of the data for the subjects in this study were from the S900 dataset released by the HCP in December 2015 (humanconnectome.org). The data from all 897 subjects with structural imaging in the HCP S900 release were taken into account in the present study. Twenty-four subjects were excluded because of missing population information about race/ethnicity (labeled "Unknown or Not Reported"). In the end, 873 subjects remained for the analysis of the heritability of myelin. The subjects included 175 twin pairs (113 monozygotic twin (MZ) pairs with 100 siblings and 7 half siblings and 62 dizygotic twin (DZ) pairs with 54 siblings and 9 half siblings), 253 siblings, 15 half siblings and 85 unpaired individuals, aged between 22 and 37 years old (aged 28.8 $\pm$ 3.7 years, range 22-36 years). The unpaired individuals did not contribute to the estimation of genetic parameters, but allowed a more accurate estimation of mean and variance effects. The correct zygosity was applied here according to latest updated version from the HCP. All the subjects participated in a series of tests to determine if they met the inclusion criteria for the HCP.[22] The details about the collection are available in the HCP reference manual (https://www.humanconnectome.org/storage/app/media/documentation/s900/HCP_S900_Release_Reference_Manual.pdf). All subjects were provided with written informed consent on forms approved by the Institutional Review Board of Washington University.

2.2 | MRI data acquisition and processing

All the HCP subjects were scanned in a customized Siemens Magnetom Connectome 3T scanner (MAGNETOM Skyra CONNECTOM, Siemens Healthcare, Erlangen, Germany) with a 32 channel head coil. Details on the scanner, image acquisition and reconstruction were provided previously.[4] The myelin content was assessed based on T1-weighted (T1w) and T2-weighted (T2w) MRI images. The T1 images were collected by using 3D magnetization-prepared rapid gradient echo (3D-MPRAGE) sequence: echo time (TE) = 2.14 milliseconds, repetition time (TR) = 2400 milliseconds, flip angle = 8°, file of view (FOV) = 224 $\times$ 224 mm^2 and resolution = 0.7 mm isotropic. The T2 images were acquired with a 3D-T2SPACE sequence: TE = 565 milliseconds, TR = 3200 milliseconds, variable flip angle, FOV = 224 $\times$ 224 mm^2 and resolution = 0.7 mm isotropic.

Structural images were preprocessed by the WU-Minn HCP consortium using the HCP pipelines in the website: https://github.com/-Washington-University/Pipelines. The myelin maps, which were calculated using the ratio of the T1-weighted to the T2-weighted MRI,[4] were obtained from the HCP dataset.[23] We applied the myelin maps, which have done the residual bias field correction in this paper. We used the myelin values for the 105 regions in each hemisphere from the Brainnetome Atlas,[24] which is registered in the surface space of FreeSurfer's *fsaverage* subject (available at http://surfer.nmr.mgh.harvard.edu/). Because the myelin maps offered by HCP were registered to "fs_LR" surface space, a surface registration was performed. The myelin maps for each individual were transformed from "fs_LR" mesh to fsaverage mesh by applying the command metric-resample in the workbench software (http://www.humanconnectome.org/software/get-connectome-workbench.html). This is the latest recommended approach to transform the data between fsaverage and fs_LR (listed in the HCP User's FAQ). Then, the average myelin content values for all areas of the Brainnetome Atlas were computed by averaging the myelin value of all the voxels in the particular area.

2.3 | Heritability estimation

For the heritability estimates, the variance components method was applied in the Sequential Oligogenic Linkage Analysis Routines (SOLAR) software package[25]. SOLAR uses maximum likelihood

variance decomposition methods derived from the strategy proposed by Amos.[26] The proportion of the variance in a phenotype is ascribed either to additive shared genetics (A) or to measurement error and other known sources of variance (E). In this model, the covariance matrix Ω for a pedigree of individuals is given by:

$$\Omega = 2\cdot\Phi\cdot\sigma_g^2 + I\cdot\sigma_e^2,$$

$\sigma_g{}^2$ is the genetic variance due to the additive genetic factors; Φ represents the kinship matrix representing the pair-wise kinship coefficients between all the individuals; $\sigma_e{}^2$ is the variance due to individual-specific environmental effects; and *I* represents the identity matrix (here environmental effects are supposed to be uncorrelated among family members[27]). The model used to fit the variability observed in the myelin content in our study is the same as previously published ones.[28,29] Narrow-sense heritability is defined as the additive genetic factors divided by the phenotypic variance $\sigma_p{}^2$ as: $h^2 = \sigma_g{}^2/\sigma_p{}^2$. The variance parameters are calculated by comparing the phenotypic covariance matrix with the covariance matrix due to kinship.[25] We also tested the significance of the heritability by comparing the likelihood of the model in which $\sigma_g{}^2$ is constrained to zero. The mean myelin values in each area of the atlas were taken as inputs in the heritability estimate in SOLAR. Before testing the significance of heritability, we adjusted the phenotype values by taking the covariates sex, age, age^2, age × sex interaction, and age^2 × sex interaction into consideration. In addition, to ensure the normality of the measurements, an inverse Gaussian transformation was applied. The outputs from SOLAR included the heritability estimate (h^2), the significance value (*p*) and the SE for each phenotype (SE).

2.4 | Genetic correlation analysis

We computed the proportions of common genetic factors that influence the homologous areas in the two hemispheres. This was performed using bivariate genetic correlation analysis methods, also applied in SOLAR. The bivariate model decomposes phenotypic associations between the myelination of bilateral areas into genetic and environmental correlation between the two traits. The phenotypic (ρ_P), genetic (ρ_G) and environmental (ρ_E) correlations between the myelination of corresponding areas in bilateral hemispheres were estimated with the following formula:

$$\rho_P = \sqrt{h_1^2}\sqrt{h_2^2}\rho_G + \sqrt{(1-h_1^2)}\sqrt{(1-h_2^2)}\rho_E$$

If the genetic correlation coefficient is significantly different from zero, then shared genetic factors are considered to influence the heritability of areas from both hemispheres.[30]

2.5 | Myelination-related gene expression

The expression levels of myelination-related genes on each cortical area were calculated using data from the Allen Brain Institute. To be more specific, transcriptional profiles were acquired from the Allen Brain Institute for Brain Science (AIBS) (an anatomically comprehensive atlas of the adult human brain transcriptome), which including 20 737 pieces of gene expression data represented by 58 692 probes. The atlas was based on postmortem tissues from six donors without a history of psychiatric or neuropathological disorders. The donors were a 24-year-old African American male (H0351.2001), a 39-year-old African American male (H0351.2002), a 57-year old Caucasian male (H0351.1009), a 31-year old Caucasian male (H0351.1012), a 49-year old Hispanic female (H0351.1015) and a 55-year old Caucasian male (H0351.1016). More details can be found in http://www.brain-map.org. Because the expression data were available for the left hemispheres of all six donors (only available for the right hemispheres of two donors), cortical samples of the left hemisphere of all six subjects were included for analysis. For each subject, the coordinates of each expression sample were transformed to Freesurfer's fsaverage from Allen Institute-provided MNI152 coordinates (https://surfer.nmr.mgh.harvard.edu/fswiki/CoordinateSystems). Then, the shortest Euclidean distance of each expression sample to cortical ribbon regions of the FreeSurfer's fsaverage image were calculated. A distance threshold of 2 mm was applied and only samples with a corresponding structural annotation from AIBS were included to avoid incorrect assignment of subcortical regions, resulting in a total of 769 selected samples.

We first selected a set of 137 myelin-related genes compiled by a recent literature[31] (listed in Table S1). These genes have various myelin-related functions, including structural, developmental, compositional and maintenance functions. To obtain specific gene sets in myelination, we also constructed following four different gene sets for myelination with the online tool Harmonize[32] (http://amp.pharm.mssm.edu/Harmonizome/): myelination, central nervous system myelination, regulation of myelination and positive regulation of myelination, from the Gene Ontology dataset. The list of myelination-related genes in each gene sets is shown in Table S2. Take the first gene set (137 genes from literature), for example, for each sample from each subject, the expression profiles of each genes within the gene set were extracted and calculated as the average of the normalized expression levels (provided by the AIBS, described in http://help.brain-map.org/display/humanbrain/Documentation) of probes corresponding to the particular gene. Next, for each gene (137 genes) in each area (105 in the left hemisphere in the Brainnetome Atlas) of each subject (six donors), subjects were controlled as a confound for all samples, then the gene expression profiles of all samples within a particular area across the six donors were averaged to create one value, resulting in a data matrix of 137 × 105. This was followed by taking the mean average across the genes in the same area, resulting in 105 values representing the expression level of genes within the myelination gene set for each of the 105 brain areas. The procedures were carried out five times, each with one gene set. Finally the expression level in 105 brain areas was generated for each given gene set.

2.6 | Statistical analysis

To test whether the organization of the genetic effect follows a bilaterally symmetric pattern, a series of tests were carried out. First, we calculated the correlation of the heritability between the left and right hemispheres; second, we screened to see if any area had significantly different heritability estimates between the hemispheres using a method published previously.[28] The confidence interval (CI) for the heritability estimates in each area was computed under the

asymptotic normality assumption of the maximum likelihood estimator using the following formula: asymptotic CI at 100(1 − α)% is (h^2 − Z[α/2] × σ, h^2 + Z[α/2] × σ).[33] For 95%, Z(α/2) = 1.96. The two estimates were significantly different at 100 (1 − α)%, if:

$$\text{diff} = \left|h^2_{\text{right}} - h^2_{\text{left}}\right| \geq Z(\alpha/2) \times \left(\sigma_{h^2_{\text{right}}} + \sigma_{h^2_{\text{left}}}\right)$$

Third, bivariate genetic correlation analyses were performed to test whether common genetic factors influence the heritability between homologous areas in the two hemispheres.

To investigate the relationship between the interregional variations in the microscale gene expression and the macroscale cortical myelination, we performed the Pearson's correlation analyses between the two traits. Namely, the association between the transcriptional profiles of the selected gene set (105 values, one for a brain area) and the myelination value in these areas (105 values, one for a brain area) was calculated. The correlation was carried out five times, each with one gene set. To correct for multiple comparisons, the statistical significance level of these analyses of variance (ANOVAs) was set as $P < 0.01$ (0.05/5[Gene Sets], i.e., Bonferroni correction for family-wise error).

3 | RESULTS

After quantitative heritability analyses of myelination in each area from the Brainnetome Atlas, we found that additive genetics accounted for an average of 0.50 ± 0.08 (range 0.29-0.66) of the myelination, suggesting that brain has moderately heritable myelination. All areas had heritability estimates that remained significant after a strict Bonferroni correction for multiple comparisons ($P < 0.05/210$ number of areas considered $\approx 2.38 \times 10^{-4}$). These heritability estimates and their associated *P*-values are presented in Figure 1 and summarized in Table S3. We also estimated the heritability myelination for every brain area using an ACE model (C: common environment). Because the household information is not directly available in HCP data, two individuals were assumed to share the same household if they reported to HCP the same two parents. No areas had common environment estimates that remained significant after the Bonferroni correction for multiple comparisons (all *P*s > 2.38×10^{-4}). These estimates for genetic and common environmental effects and their associated *P* values are shown in Table S4.

Areas in the left hemisphere have a heritability that is similar to those in the right hemisphere (for left hemisphere, 0.501 ± 0.079, range 0.32-0.66; for right hemisphere, 0.499 ± 0.081, range 0.29-0.66). Next, we tested the correlation between hemispheres of the heritability for 105 areas on each side. The heritability estimates across hemispheres were significantly positively correlated (Pearson correlation: $r = 0.79$, $P = 1.4 \times 10^{-23}$). Then, we tested whether any area showed a significant difference in genetic control in the two hemispheres. No area reached significance using the abovementioned criterion for a CI of ±σ(95%) (ie, $\text{diff} = \left|h^2_{\text{right}} - h^2_{\text{left}}\right| > 1.96 \times (\sigma^2_{h^2_{\text{right}}} + \sigma^2_{h^2_{\text{left}}})$). Next, to investigate whether the corresponding areas of myelination in the different hemispheres were controlled by identical genes, we also performed a genetic correlation analysis based on a bivariate model and observed that the corresponding areas of myelination in the left and right hemispheres have a high genetic relationship (0.91 ± 0.073, all *P*s < 0.05, genetic correlation values are given in Table S5). Together, these findings strongly suggest global symmetry between the hemispheres in the regional heritability of myelination.

Finally, we calculated the correlation between the expression levels of the myelination-related genes and macroscale cortical myelination. Only the expression of gene set "Regulation Of Myelination" was significantly correlated with the myelination level ($r = -0.31$, $P = 1.93 \times 10^{-3}$). Other gene sets did not survive Bonferroni corrections (for the first gene set from literature, $P = 0.72$; for the gene set "Positive Regulation Of Myelination," $P = 0.015$; for the gene set "Central Nervous System Myelination," $P = 0.65$; for the gene set "Myelination," $P = 0.50$).

4 | DISCUSSION

In this study, we used myelin content maps for 873 subjects from the HCP dataset to estimate the heritability of cortical myelination and showed modest to moderate heritability estimates ranging from 29% (superior frontal gyrus region) to 66% (lateral occipital cortex region). The genetic control of the myelination exhibited a bilaterally

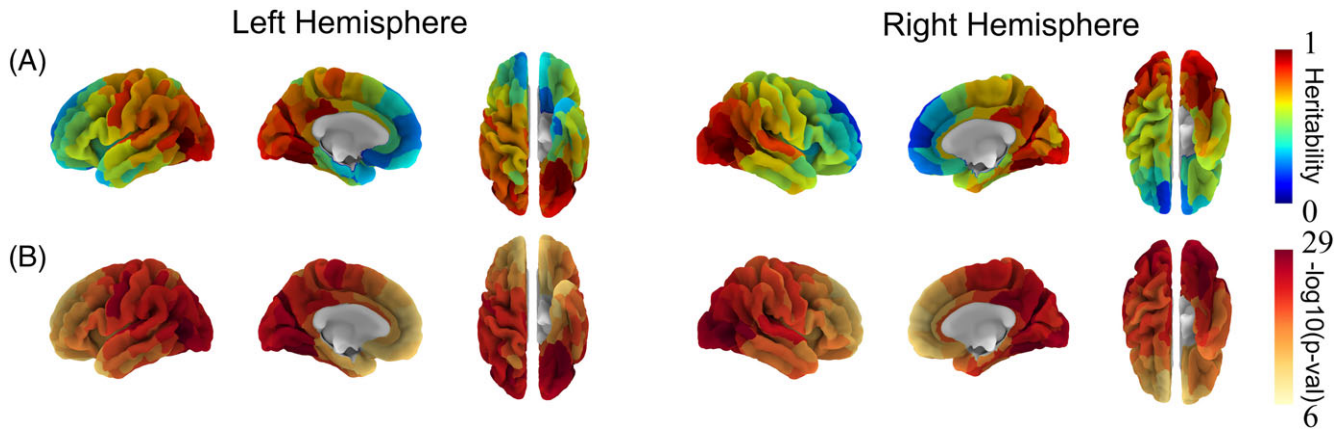

FIGURE 1 (A) Heritability and (B) associated -log10 (*P*-values) for all the areas from the Brainnetome Atlas

symmetric and anterior-to-posterior (A-P) graded pattern. These results can help us investigate the genetic basis of myelination and aid in understanding the genetic effect on cognitive function and neuropsychiatric disorders related to normal and abnormal myelination.

To our knowledge, this is the first study to estimate the additive genetic effects on cortical myelination. Numerous lines of evidence implicate myelin in critical processes of brain development and brain functioning. For instance, myelin content is correlated with cortical expansion[34] during human postnatal maturation. Specifically, lightly myelinated cortical areas tend to expand more than heavily myelinated areas after birth.[4] Moreover, studies have reported the role of myelination in cognitive ability[7] as well as myelin abnormalities in schizophrenia,[35] bipolar disorder[36] and AD.[9] Therefore, it is particularly interesting to explore genetic contributions to myelination. Since we found that myelination of all the areas was significantly heritable even after a strict Bonferroni correction, myelination measurements can be seen as promising targets for studying the genetic mechanisms of brain functioning, behavior and brain disorders. In addition, our myelination measurements were modestly to moderately heritable (0.29-0.66), indicating contributions from both genetic and environmental factors. This is in line with animal studies, which found that hypomyelination was related to reduced *neuregulin-1* expression in mice[12] and that reduced myelin could be identified in adolescent rhesus monkeys that had experienced maternal infant maltreatment.[15] These findings strongly imply that cortical myelination does not have a single or simple cause and suggests that both genetic and environmental factors are potential targets for the early detection and treatment of related brain disorders.

The results showed a bilaterally symmetric pattern of genetic influence across the brain, with similar levels and high correlations of heritability in the two hemispheres (r = 0.79, $P = 1.40 \times 10^{-23}$). This is in line with previous findings of heritability for other brain phenotypes, such as surface area[16] and gray matter volumes.[17] The comparable heritability estimates do not necessarily mean the same genes involved, thus, to investigate whether the myelination of corresponding structures across hemispheres were influenced by the same genetic factors, we performed bivariate analyses and confirmed high and significant genetic correlations between homologs in the two hemispheres (0.91 $\pm$ 0.073, all *Ps* < 0.05, range 0.64-1.00). This is in agreement with previous studies that showed that the brain phenotype in one hemisphere is likely to be under the control of the same genes in the opposite hemisphere.[16,37,38] In addition, between-hemispheric global symmetry in regional gene expression has been reported from a transcriptional study.[18] Therefore, the symmetric distribution of the heritability of myelination could be explained by a common genetic factor that accounts for myelination in corresponding regions bilaterally and by mirror images of genetic expression in the two hemispheres.

In addition, we showed strong A-P graded patterns of heritability of myelination, with higher heritability for posterior areas and lower values for anterior structures. Several decades ago, based on observations in rhesus macaques, Cheverud et al[39] postulated that the morphology of earlier developing brain structures is more genetically predetermined. Since myelination progresses from posterior to anterior,[40] our findings are consistent with these studies that indicated that myelination variations in posterior regions, which develop earlier, are more genetically influenced, and that those in anterior areas, which develop earlier,[40] are influenced to a lesser extent. Rodent studies have also shown that a number of specific genes that influence key processes in cortical myelination, such as Igf1[41] and Cnp1,[42] are differentially expressed along the A-P axis in the developing cerebral cortex.[43] Our finding of an A-P gradient genetic pattern of myelination echoes these studies in animal models.

As hypothesized, interregional variations in myelination can be explained, in part, by interregional variations of the expression of myelination-related genes in the "Regulation of Myelination" pathway. This observation extends the existing literature on the regional variability of myelination across the brain[4] and the regional nonuniformity in cortical development before birth.[44] Many genes in this pathway have been noted to be of particular importance in myelination. For example, the *myelin regulatory factor* (*MYRF*) gene encodes a transcription factor that is required for central nervous system myelination and may regulate oligodendrocyte differentiation. It is thought to act by increasing the expression of genes that effect myelin production but may also directly promote myelin gene expression (provided by the National Center for Biotechnology Information Reference Sequence Database, November 2014). The *noncompact myelin associated protein* (*NCMAP*) gene encodes myelin-associated protein involved in structural constituent of myelin sheath and myelin formation (Inferred from Biological aspect of Ancestor). However, the small number of samples in the current study (a mean of 7.23 $\pm$ 5.02 [range 0-26] samples for each area) may limit the representation of the mRNA expression levels in each brain region, especially when individual variability in mRNA expression is taken into account. Besides, we did not find significant correlation in other gene sets. Therefore, future replication studies are needed to validate this association. More direct biological evidence is also required to elucidate the relationship between the expression of these genes and the cortical myelination.

It should be noted that the heritability estimation of myelin was based on the ratio of the MRI T1w and T2w images, which was only a relative measure of myelin. Previous studies have indicated the T1w/T2w ratio is sensitive to myelin content,[4,45] and has been applied to successfully map the myeloarchitectonic properties of many cortical regions.[4] A strong correlation between MRI intensities and histologically measured myelin content has also been reported.[11] Although T1w/T2w largely reflects myelin, more direct biological evidence, that is, histological results, are required to validate the genetic contribution to cortical myelination.

Another thing to mention is that the T1w/T2w ratio is a unitless quantity. Various physical scanners or pulse sequences may affect the myelin map values and in turn constrain the application in comparison of myelin maps across subjects. For the HCP dataset used here, all T1w and T2w images were acquired on the same scanner with the same sequence to ensure consistency across subjects.[21] Besides, the T1w/T2w ratio has been successfully applied to the study of myelin across subjects, such as cortical demyelination in multiple sclerosis,[46] the lifelong effect of age on cortical myelination[47] and the association with cognitive performance.[47] In addition, we calculated the heritability based on the adjusted myelin value, in which the myelin map values of a region was divided by the average value of the whole

brain. The new heritability was highly correlated with the original ones across the cortical regions (Pearson $r = 0.74$, $P = 8.1 \times 10^{-20}$, Figure S1). With all these aspects in mind, the T1w/T2w ratio in the current study could be a valuable neuroscientific tool for studying cortical myelin content across subjects. However, our findings of the heritability of cortical myelin are preliminary, more studies to validate these findings are required.

In summary, to our knowledge, this is the first study to investigate genetic influences on cortical myelination. It provides strong support for the hypotheses that myelination is heritable and that the genetic control of cortical myelination shows bilateral symmetry and an anterior-posterior gradient. Our establishment of the heritability of myelination provides at least some of the necessary evidence required before myelination can be considered as an endophenotype for cognitive functions and brain disorders. Furthermore, given the modest to moderate heritability, it should be pointed out that, in addition to genetic polymorphisms and expressions, environmental factors contribute to the diversity of myelination and should be considered in future genomic investigations into the diverse and complex traits of the human brain.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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