Title
Large-scale genomics unveil polygenic architecture of human cortical surface area

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Little is known about how genetic variation contributes to neuroanatomical variability, and whether particular genomic regions comprising genes or evolutionarily conserved elements are enriched for effects that influence brain morphology. Here, we examine brain imaging and single-nucleotide polymorphisms (SNPs) data from ~2,700 individuals. We show that a substantial proportion of variation in cortical surface area is explained by additive effects of SNPs dispersed throughout the genome, with a larger heritable effect for visual and auditory sensory and insular cortices ($h^2 \sim 0.45$). Genome-wide SNPs collectively account for, on average, about half of twin heritability across cortical regions ($N = 466$ twins). We find enriched genetic effects in or near genes. We also observe that SNPs in evolutionarily more conserved regions contributed significantly to the heritability of cortical surface area, particularly, for medial and temporal cortical regions. SNPs in less conserved regions contributed more to occipital and dorsolateral prefrontal cortices.
To understand the complexity of human higher cognition, it is essential to study the properties of the cerebral cortex\(^1\)\(^-\)\(^2\).

Genetics play a critical role, as identifying the genetic underpinning of phenotypic variability provides a causal foothold. A striking feature of the human cerebral cortex is that it follows an ancient mammalian prototype but also displays an enormous expansion in cortical surface area\(^3\)\(^-\)\(^6\). This expansion did not occur homogeneously across the cortex\(^1\)\(^-\)\(^3\). The alteration of cortical organization may have significant functional consequences in human cognition. Genetic variation is thought to be a major factor in this alteration and to underlie phenotypic variability among individuals\(^1\). However, quantifying the source of genetic contribution to phenotypic differences in humans and mapping the genetic and evolutionary architecture of cortical surface area across different cortical regions are ongoing challenges.

One fundamental question is the extent to which neuro-anatomical variability among individuals is caused by genetic differences. Twin and pedigree designs have been used to estimate the 'heritability' of a phenotype by examining the resemblance of the phenotype between relatives. Heritability is the proportion of the phenotypic variance ascribable to genetic differences in a given population: the proportion of variation due to additive genetic effects (narrow-sense heritability) or the proportion of variation due to all genetic effects (broad-sense heritability)\(^7\). Twin/family studies have shown that brain phenotypes are heritable (for example, heritability up to \( \sim 0.8 \))\(^8\).

Technological advances now allow assay of individuals for millions of single-nucleotide polymorphisms (SNPs) spanning the whole genome\(^9\). Genetic similarity or relationship among a group of individuals can then be estimated through the use of dense genetic variants. By contrasting genetic similarity with phenotypic similarity, one can estimate the heritability of a phenotype in the absence of family members\(^9\),\(^10\). A recent popular method for carrying out relevant analyses involves a mixed linear model to fit a genetic relationship matrix (GRM) to measured phenotypes, carrying out relevant analyses involves a mixed linear model to fit a genetic relationship matrix (GRM) to measured phenotypes, such as the methodology built into the genome-wide complex trait analysis (GCTA) tool\(^9\),\(^11\). The resulting estimate is referred to as 'SNP' or 'chip heritability' (\( h^2 \))\(^12\),\(^13\). Using the GCTA approach, researchers have estimated that about half of the heritability of human height can be attributed to \( \sim 0.3 \) million common SNPs\(^11\). In comparison, only \( \sim 16\% \) of variability in height can be attributed to all individual SNPs discovered by genome-wide association studies\(^14\). This finding suggests that height has a polygenic architecture in which a large number of common genetic variants with small effects contribute predominantly additive to phenotypic variation.

To investigate the polygenic contribution of common SNPs to cortical structures, we apply the GCTA method to a combined sample from five cohorts. Raw imaging and genotype data from all study cohorts are processed with a standardized protocol to minimize data heterogeneity. The analysis for estimating SNP heritability is potentially sensitive to population structure (that is, population stratification and cryptic relatedness). It is therefore typical to restrict the analysis to unrelated individuals of a single genetic ancestry\(^12\). We exclude non-Europeans based on principal component analysis of the GRM. We estimate pairwise GRM using all 2,480,482 directly genotyped and imputed autosomal SNPs. We also exclude related individuals using two thresholds at an estimated GRM \( \geq 0.025 \) (more related than third or fourth cousins), or a less stringent threshold at an estimated GRM \( \geq 0.1 \). This sampling results in subsets of 2,364 or 2,698 generally unrelated individuals with European ancestry, respectively.

Phenotype definition is critical for all genetic association studies, especially in brain imaging genetic studies, due to the high dimensionality of cortical measures (\( \sim 0.3 \) million points per subject)\(^15\). Using a data-driven, fuzzy clustering technique with magnetic resonance imaging (MRI) scans of twins, we previously parcelled cortical surface area into 12 genetic subdivisions, creating an atlas based solely on genetically informative data\(^6\),\(^16\) (Fig. 1b). Boundaries of the genetic divisions correspond largely to meaningful structural and functional regions; however, the divisions represent novel phenotypes. We use these regions, conforming to the genetic patterning of cortical surface area, to increase power for detecting effects and to minimize multiple comparisons after reducing image dimensionality to these parcels.

The aim of our large-scale whole-genome and whole-cortex analyses is to examine and dissect the polygenic genetic architecture of cortical surface area across different cortical regions.

**Figure 1** | SNP heritability. (a) Estimates of variance explained by all autosomal SNPs for each cortical region (SNP heritability) from genetic relationships \(<0.025\) (GRM <0.025). Error bars represent the s.e. of the estimates. Estimates were tested for significantly different from zero by likelihood ratio test comparing the full and reduced models. *\( P < 0.05 \), **\( P < 0.004 \) (Bonferroni correction threshold). (b) Genetic clustering map shows the anatomical location of the cortical phenotypes\(^16\). (c) SNP heritability estimates (blue bars) are overlaid on twin heritability estimates (grey bars). Shared environmental variances are small and not significant for all phenotypes. A: additive genetic variance; C: shared environmental variance; E: unique environmental variance.
**Results**

**SNP heritability.** In our five-cohort sample, we found that a substantial proportion of variation in surface area in almost all of the 12 regions is captured by all autosomal SNPs after accounting for global cortical size. A few cortical regions, such as the insula, visual and auditory sensory regions, including superior temporal and occipital cortices, have a high SNP heritability of up to ~0.45 (s.e. 0.12) (Fig. 1a; Supplementary Table 1). We reported two sets of results based on the inclusion of individuals with pairwise GRM entry scores <0.025 or <0.1 to determine the consistency of our findings. The GRM <0.1-sample offers the advantage of a larger sample size, whereas the GRM <0.025-sample is less susceptible to potential confounding from cryptic relatedness. The results from the two sets of samples are consistent (Supplementary Fig. 1a; Supplementary Table 1), supporting the reliability of our findings. To ensure the validity of the method applied to our sample, we performed a simulation study and power calculation. We also verified that our main findings were not sensitive to patient samples, nor sensitive to linkage disequilibrium (LD), that is, the correlation among SNPs, in the genome (see Supplementary Methods and Supplementary Table 2).

**Twin heritability.** We next sought to compare the SNP heritability with twin heritability estimated from 466 twins. Heritabilities of the same cortical imaging phenotypes were estimated in a classical twin model implemented in the OpenMx software suite. The results of twin heritability estimates (additive genetic variances) across different cortical regions are shown in Fig. 1c (Supplementary Table 3). The average monozygotic and dizygotic correlations across all cortical regions were 0.62 and 0.32, respectively, suggesting almost a perfect additive genetic proportion in these phenotypes.

**Partitioning of genomic variation by genic annotation.** We partitioned the variance explained by all the SNPs into genic and intergenic regions across all autosomal chromosomes. We defined genic boundaries as 20 kb upstream and downstream from the intergenic regions across all autosomal chromosomes. We defined genic boundaries as 20 kb upstream and downstream of the UTRs of each gene (Fig. 2a; Supplementary Tables 4 and 7). Furthermore, we used an LD-weighted genic annotation scheme that takes into account the LD structure to categorize SNPs that have high LD with SNPs within genic elements (Fig. 2b; Supplementary Tables 5 and 8). The results from the two methods were consistent, with evidence of enriched genetic effects in the genic regions for many cortical regions.

**Partitioning of genomic variation by conservation annotation.** Conservation scores were derived from multiple alignments of placental mammal genomes to the human genomes. We observed that more conserved SNPs collectively have genetic influences on several cortical regions especially around the insula, superior, anterior and medial temporal lobes, including parahippocampal gyrus and entorhinal cortex (Fig. 3a; Supplementary Table 6). Less conserved SNPs collectively exhibit greater polygenic effects on occipital and dorsolateral prefrontal cortices.

**Correlation explained by genic and conserved SNPs.** We also found a highly significant correlation between the variance explained by genic SNPs and variance explained by more conserved SNPs (Fig. 3b), and between intergenic SNPs and less conserved SNPs (Supplementary Fig. 3). To rule out the possibility that genic and conservation annotation are surrogates for one another, we computed the correlation between the LD-weighted genic and conservation scores. The correlation of $r = 0.58$ indicates that substantial variation can be attributed uniquely to each (shared variance, $R^2 = 0.34$).

**Discussion**

Although identifying genetic determinants of the human brain is an active area of research, studies on the polygenic architecture of brain imaging phenotypes are limited, partially because of a lack of availability of appropriate data sets. We show that a substantial proportion of the heritable component of the cortex resides among common variants that can be interrogated via current genome-wide genotyping arrays. This suggests that with larger sample sizes, SNPs associated with cortical surface area could be discovered. A few cortical regions, such as the insula, visual and auditory sensory regions, including superior temporal and occipital cortices, have a high SNP heritability of up to ~0.45 (s.e. 0.12). Recent evidence suggests that non-heritable genetic variation might be widespread in the brain and has potential contribution to complex functional diversification. Our results show that heritable genetic variation has substantial impact on cortical area variation. Thus, these findings imply that genetic underpinnings of brain phenotypes likely involve the combined effects of many common variants of small effects, as well as non-heritable genetic variation. SNP heritability estimates quantify the overall contribution of the additive effects of all SNPs, which provides a lower bound of the narrow-sense heritability of the trait estimated in pedigree studies, since pedigree information captures the effects of all genetic variants on phenotypic similarity. We observe broad agreement between SNP and twin heritability across cortical regions. Similar to the height study, we captured about half of twin heritability on average with the SNP heritability across cortical regions. However, some regions, such as the motor–premotor cortex and prefrontal areas, have high twin heritability but low SNP heritability. This finding suggests that non-additive genetic effects could play a role in these phenotypes, because the additive genetic effects estimated from the twin model potentially include non-additive effects such as epistatic interactions and inherited epigenetic variation. Alternatively, ungenotyped causal variants affecting these regions might have lower allele frequencies than do common SNPs, and/or are not tagged by the genotyped SNPs. Furthermore, the difference could also be due purely to sampling variation—including differences in age, gender and ancestry—or random errors (for example, both twin and SNP heritability estimates have average s.e. of ~0.11). Taken together, the observed information provides clues, and lower and upper bounds of genetic effects, in the search for trait-associated variants. Obtaining evidence for the polygenic architecture of complex traits provides a rationale for further dissecting the contribution of particular genomic regions to phenotypic expression. Specifically, we focus on the genetic effects of genic and regulatory element regions of the genome. SNPs in these functional genomic regions have been shown to be enriched for associations across diverse phenotypes. We therefore partitioned the variance explained by all the SNPs into genic and intergenic regions across all autosomal chromosomes. We defined genic boundaries as 20 kb upstream and downstream from the UTRs of each gene (Fig. 2a; Supplementary Table 4). Furthermore, we used an LD-weighted genic annotation scheme that takes into account the LD structure to categorize SNPs that have high LD with SNPs within genic elements (Fig. 2b; Supplementary Table 5). The results from the two methods were consistent, with evidence of enriched genetic effects in the genic regions for many cortical regions.
The 1000-fold difference in cortical surface area between humans and mice may contribute to our complex behaviours. The cerebral cortex subserves an array of higher-order brain functions that are uniquely specialized in humans, and changes in these functions and their networks may make us prone to neurobiological disorders such as schizophrenia, autism or Alzheimer’s disease. Therefore, it is of particular interest to explore the contribution of genetic variants that are presumably more human specific in their evolutionary lineage than other variants. Conservation scores were derived from multiple alignments of placental mammal genomes to the human genomes. We observed that more conserved SNPs collectively have genetic influences on several cortical regions especially around the insula, superior, anterior and medial temporal lobes, including parahippocampus gyrus and entorhinal cortex (Fig. 3a; Supplementary Table 6). Several of these regions belong to the allocortex, which has fewer cortical laminae than the neocortex and is regarded as evolutionarily more primitive. On the other hand, less conserved SNPs collectively exhibit greater polygenic effects on occipital and dorsolateral prefrontal cortices, the regions that subserve visual perception and executive function respectively. Visual specialization is one hallmark of primate brain evolution. Primates have relatively enlarged visual areas and are visually orientated mammals. The dorsolateral prefrontal cortex is located in the expanded prefrontal cortex of primates, and is a vital region of distributed brain networks linked to many complex cognitive functions in humans.

We also found a highly significant correlation between the variance explained by genetic SNPs and variance explained by more conserved SNPs (Fig. 3b), and between intergenic SNPs and less conserved SNPs (Supplementary Fig. 3). These findings suggest the existence of a possible pattern in which phenotypic variation in more conserved cortical regions is influenced to a greater degree by more conserved and genetic SNPs, and more human-specific cortical regions are influenced to a greater degree by less conserved and intergenic SNPs. Our result is preliminary, but this trend may be biologically plausible and is noteworthy for further investigation.

We show that a substantial proportion of the heritable component of the cortex resides among common variants that can be interrogated via current genome-wide genotyping arrays. By leveraging genetic and conservation annotations we were able to reveal that particular genomic regions are enriched for variants that influence variation in cortical surface area. Each cortical region appears to have elements of region-specific genetic architecture, which might relate to functional specialization of the cortical regions. Elucidating the sources of these genetic effects will allow investigators to prioritize resources for future investigations. Cortical surface area is similar to other complex traits in terms of polygenicity distributed among common variants and genetic effects enriched in genomic regions. Yet, the human brain is a uniquely complex phenotype, in that its genomic properties appear as complex as its functional capacity. In this light, it should be acknowledged that beyond polymorphisms and structural variants in the genome, epigenomics, alternative splicing and somatic mosaicism may contribute to phenotypic diversity in normal brain development. A variety of data types together will help to advance our understanding of the human cortex as an adaptive and plastic entity that is shaped both by genetics and by its interaction with the environment.

### Methods

**Participants.** A total of 3,696 subjects with available and sufficient quality MRI scans from 5 cohorts were analysed. We removed non-European descents and related individuals. The combined sample of five cohorts is made of 605 subjects from the Thematically Organized Psychosis study (mean age: 35 years, range = 17–70 years); 842 Health Study of Nord-Trøndelag (HUNT) subjects (mean age: 58 years, range = 50–66 years); 325 Norwegian Cognitive NeuroGenetics subjects (mean age: 52 years, range = 19–79 years); and 726 Alzheimer’s Disease Neuroimaging Initiative subjects (mean age: 75 years, range = 55–92 years) and 1,188 Pediatric Imaging Neurocognition and Genetics subjects (mean age: 12 years, range = 3–21 years) (see Supplementary Methods for more details).

The samples for the twin analysis were part of the Vietnam Era Twin Study of Aging (VETSA) study. There were 466 participants at age 51–60 years, of which 99 pairs were dizygotic twins and 134 pairs monozygotic twins. The sample is representative of US middle-aged men in their lifestyle and health characteristics.

Each study was approved by the local Institutional Review Board: South East Norway (Thematically Organized Psychosis and Norwegian Cognitive NeuroGenetics) and Mid Norway (HUNT) Regional Ethical Committee (HUNT), and UC San Diego (Paediatric Imaging Neurocognition and Genetics and VETSA).

**Genotype quality control and imputation.** All studies were genotyped using different commercial arrays. Standard genome-wide association quality control measures were applied to each study individually using the Plink toolset. Samples missing >5% of SNPs, with a minor allele frequency of <1%, or failing a test of Hardy–Weinberg equilibrium (P < 1 × 10^{-7}) were excluded. Individual samples showing an over- or underabundance of heterozygosity (≥5 s.d. from the mean) were labelled as poor quality and also excluded from subsequent analyses. Furthermore, to ensure that all individuals were unrelated, functions available in
the software package GCTA\textsuperscript{45} were used to estimate kinship values from SNP genotypes for all pairs of individuals in the combined cohort. Population stratification and ancestry were assessed against a reference sample consisting of individuals from the HapMap III\textsuperscript{46} and 1000 Genomes\textsuperscript{47} via principal component stratification and ancestry were assessed against a reference sample consisting of 2,364 individuals for the subsequent analyses. In this combined cohort of individuals with an estimated relatedness of 0.1, 241 individuals were removed, leaving a total of 2,698 European ancestry with minimal relatedness between subjects (GRM\textsuperscript{2}).

SNP heritability. We used a mixed linear model to fit a covariance structure of GRM to a vector of measured phenotypes via the GCTA tool\textsuperscript{9,11} to estimate the proportion of phenotypic variance captured by all autosomal SNPs. The analyses included common SNPs (for example, minor allele frequency > 0.01). We included the top 10 eigenvectors of the principal component analysis of an allele-sharing matrix or GRM as covariates to capture any remaining population structure in our European data set.

As described further in the Supplementary Methods, the mixed linear model analysis in quantitative genetics partitions the phenotypic variance–covariance matrix between two (or more) specified matrices. One typical form is:

$$\text{Var}(Y) = \sigma^2_g G + \sigma^2_c I$$

where $G$ is a matrix of kinship or genetic correlation coefficients and $I$ is the $n \times n$ identity matrix, which assumes independence of environmental effects (that is, no shared environment) and measurement error across individuals. Estimates $\sigma^2_g$ and $\sigma^2_c$ are typically obtained via restricted maximum likelihood. Narrow-sense heritability, $h^2$, the proportion of phenotypic variance explained by additive genetic effects, is estimated by

$$h^2 = \frac{\sigma^2_g}{\sigma^2_g + \sigma^2_c}$$

The resulting estimate is referred to as 'SNP' or 'chip heritability' ($h^2$), since it is based on the SNPs used to construct the GRM\textsuperscript{12,13}.

Partitioning of genomic variation by genic annotation. We partitioned the variance explained by all of the SNPs into genic and intergenic regions of the whole genome. We obtained 24,526 gene boundaries from the UCSC Genome Browser hg19 assembly. We defined genic boundaries as ±20 kb upstream and downstream from the 3' and 5' UTRs of each gene, where genic and intergenic coverages are roughly equal (~50%). This definition was used previously\textsuperscript{17}. We estimated the proportion of variance explained by genic and intergenic regions. The results are shown in Fig. 2a and Supplementary Table 4 for the GRM<0.025-sample and Supplementary Fig. 2a and Supplementary Table 7 for the GRM<0.1-sample. We further used an LD-
weighted genic annotation scheme that takes into account the LD structure to select SNPs that are related to exon, intron, 3’ UTR, 5’ UTR and 1 kb upstream and downstream of genes (six genic categories) (see Supplementary Methods).

**Partitioning of genomic variation by conservation annotation.** We partitioned the variance explained by all of the SNPs into low- and high-conserved regions of the whole genome based on conservation annotation. We obtained a conservation annotation database from the UCSC Genome Browser hg19 assembly. The conservation scores were derived from alignments of placental mammals to human genome. PhastCons is a hidden Markov model-based method that estimates the probability that each nucleotide belongs to a conserved element, based on the multiple alignments.

We assigned weights to conservation scores based on the LD information. We applied the pairwise LD matrix to the vector of phastCons scores. We expect that SNPs with the LD-weighted conservation annotation show more consistent and less noisy association signals. After the LD weighting, 48,523 of the ~2.4 million SNPs had no scores and were eliminated from the subsequent analysis. We selected the median as a threshold to partition the genome evenly into low- and high-conserved SNPs (~50%). We estimated the proportion of variance explained by low- and high-conserved genomic regions. The results are shown in Fig. 3a and Supplementary Table 6 for the GRM<0.025-sample, and Supplementary Fig. A and Supplementary Table 9 for the GRM<0.1-sample.

**References**


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Author contributions

Additional information
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Pediatric Imaging, Neurocognition and Genetics Study (PING)
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