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Genome-Wide Association Study of Left-Handedness

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Abstract

handedness has been extensively studied because of its relationship with language, immune disease, and some neurodevelopmental disorders. Using GWAS data from the UK Biobank, I conducted a genome-wide association meta-analysis of handedness. I found significant loci rs13017199 and the markers related to neuron development, muscle movement, and intellectual ability. Correlation analysis implicated handedness in the possible etiology of Schizophrenia. Pathways including regulation of the immune system and brain morphology were also highlighted by Tissue-enrichment analysis. Besides, the GSEM analysis presented a possible structural model for handedness that does not include SNP effects.

Keywords: handedness, GWAS, genome, Schizophrenia

1. Introduction

handedness, also known as the dominant hand, is comparatively often the stronger, more dextrous or simply more subjectively preferred. It has been extensively studied because of its relationship with language(Knecht et al. 2000), immune disease(Geschwind and Behan 1982), and some neurodevelopmental disorders(Brandler and Paracchini 2014).

Theories of the causation of handedness are plentiful, although the majority of early suggestions can be dismissed on the basis of known anatomical evidence(Hynd et al. 1990). The evidence favors a genetic basis, but existing genetic models are all limited by the fact that data on the incidence of handedness are extremely variable(Hardyck and Petrinovich 1977). For a long time, it has been thought to be a monogenic trait that can produce an asymmetrical shift of brain mechanisms. However, a single gene explaining a sufficient amount of phenotypic variance has not been identified. The results of several recent studies suggest that a multifactorial model, including both multiple genetic and environmental factors, as well as their interactions, might be better suited to explain the complex cause of handedness.

2. Related Works

There are plenty of related work on the Left-handedness GWAS dataset. Akira Wiberg (Wiberg et al. 2019) correlated brain imaging phenotypes from 9000 UK Biobank participants with handedness, and uncovered four significant loci (rs199512, rs45608532,

rs13017199, and rs3094128), three of which are in—or expression quantitative trait loci of—genes encoding proteins involved in brain development and patterning. In particular, with rs199512, they identified a common genetic influence on handedness, psychiatric phenotypes, Parkinson's disease, and the integrity of white matter tracts connecting the same language-related regions identified in the handedness–imaging analysis.

Bolun Cheng (Cheng et al. 2020) conducted linkage disequilibrium score regression (LDSC) analysis to evaluate the genetic correlations between left-handedness and multiple mental disorders. For the observed genetic correlation with schizophrenia, transcriptome-wide association study (TWAS) was performed to identify the genes associated with left-handedness and schizophrenia, including brain RNA-seq (CBR) and brain RNA-seq splicing (CBRS). They detected several common genes, such as YWHAH, MAPT and ANO10.

3. Data

The GWAS data of left-handedness were used here (Cuellar et al.) have been collected for each of the approximately 206,399 UK Biobank participants. A subset of 438,427 participants was genotyped using the Applied Biosystems UK Biobank Axiom Array (825,927 markers), 23andMe and the International Handedness Consortium.

4. Methods

The following methods are applied to the GWAS left-handness analysis:

1. Manhattan and QQ plots
2. LocusZoom plot for the most significant locus
3. LDSC results on intercept and heritability
4. Partition trait heritability by tissue annotations and enrichment
5. Test pairwise genetic correlations
6. Structural equation modeling(GSEM)

5. Results

5.1 Manhattan and QQ plots

A Manhattan plot for the left-handedness GWAS meta-analysis is shown in Figure1. Each dot represents a SNP. The red broken line highlights the genome-wide levels of significance threshold ($P \leq 5 \times 10^{-8}$); Manhattan plot shows that the most significant SNPs are located at chromosome 2 and chromosomes 15 to 17.

1 A Quantile-quantile plot of GWAS P values against a uniform distribution is also shown below. QQ plot of the distribution of observed minus log10 P-values for left handeness against expected values drawn from a uniform distribution shows a rapid separation from the uniform distribution when $P \leq 10^{-3}$, suggesting there is a significant correlation between the phenotype and genotype I are studying.

5.2 LocusZoom plot

The LocusZoom plot showing the window near the most significant locus: rs13017199. Minus log10 P-values are shown along the left y-axis, and the right y-axis corresponds

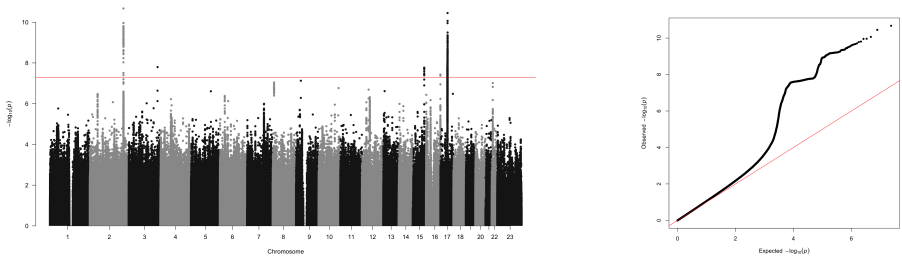

Figure 1. Manhattan and QQ plots

to the recombination rate, plotted as a blue line. The x-axis indicates the chromosomal position. The variants are colored according to their correlation (r2) with the lead variant (see legend). For the markers I observed MAP2 and UNC80. MAP2 are neuron-specific proteins, which implicate a role in neuron development(Goedert 1991). While the UNC80 is a Protein Coding gene, where the mutation may causes muscle weakness, intellectual disability, dyskinesia, and dysmorphism(Perez et al. 2016).

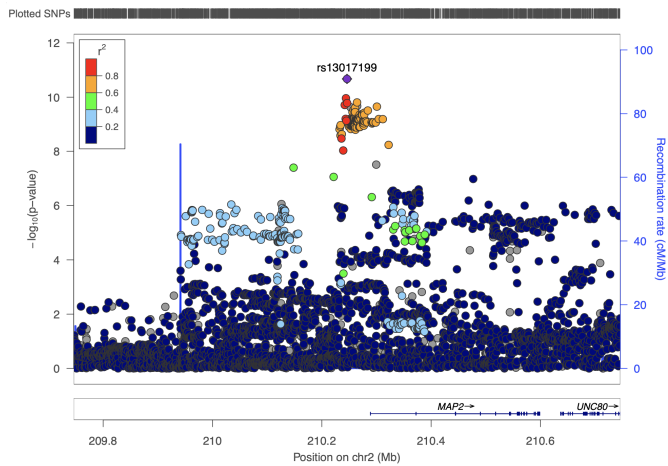

Figure 2. LocusZoom plot

5.3 LDSC Intercept and Heritability

After reformatting our Summary Statistics, the LDSC is conducted to analyze the intercept and heritability. Table 1 shows basic metadata about the summary statistics. Since the mean chi-square is below 1.02, the data are suitable for LD Score regression.

The following table 2 is the heritabilities of left-handedness from single-trait LD Score regression estimated on the observed scale(compared with Insomnia GWAS data). Note that Lambda GC is $median(chi^2)/0.4549$. Mean chi^2 is the mean chi-square statistic. Intercept is the LD Score regression intercept. Ratio measures the proportion

Table 1. Metadata of the summary statistics

Lambda GC	1.1113
Mean Chi^2	1.1261
Intercept	1.0063 (0.0065)
Ratio	0.0503 (0.0518)

of the inflation in the mean chi^2 that the LD Score regression intercept ascribes to causes other than polygenic heritability. Since the intercept is close to 1 and the ratio is close to zero, our results are in the reasonable range.

Table 2. Heritability of left-handeness

Total Observed scale h2	0.0308 (0.003)
Lambda GC	1.1144
Mean Chi^2	1.128
Intercept	1.0036 (0.0074)
Ratio	0.028 (0.0575)

5.4 Pairwise genetic correlations

Table 3 shows the pairwise genetic correlations between left-handedness and Insomnia, cannabis dependence, schizophrenia, and daytime napping. In the columns, rg is the genetic correlation, se is the standard error of rg, p is the p-value for rg; $h2_{obs}$ and $h2_{obsse}$ are observed scale h2 for trait 2 and standard error, $h2_{int}$ and $h2_{intse}$ are single-trait LD Score regression intercept for trait 2 and standard error, $gcov_{int}$ and $gcov_{intse}$ are cross-trait LD Score regression intercept and standard error. A significant genetic correlation was only observed between handedness to Schizophrenia and handedness to Insomnia. Of these two traits, Schizophrenia has the highest significance as well as the largest correlation.

Table 3. Pairwise genetic correlations

trait 2	rg	se	z	p	$h2_obs$	$h2_{obsse}$	$h2_{int}$	$h2_{intse}$	$gcov_{int}$	$gcov_{intse}$
Insomnia	0.0788	0.0396	1.9894	0.0467 *	0.0014	6.2197e-05	1.013	0.0086	0.0025	0.005
Cannabis Dependence	0.0496	0.0634	0.7825	0.4339	0.0197	0.0017	1.0	0.0075	-0.001	0.0051
Schizophrenia	0.1428	0.0364	3.9265	8.6180e-05 **	0.0065	0.0002	1.053	0.0131	-0.0039	0.0064
$Daytime_{Napping}$	0.0781	0.0434	1.7997	0.0719	0.0839	0.0034	1.0355	0.0116	0.0042	0.0061
$Leisure_{Computer Use}$	0.0223	0.0363	0.6146	0.5388	0.0015	5.7283e-05	1.0411	0.0094	0.0024	0.0052

5.5 Enrichment plot

Partition trait heritability by tissue annotations is run by LDSC, and the enrichment results are interpreted with the following plot 3. Where the most significant trait is the CD4+ T helper 17 cells, which play important roles in the pathogenesis of

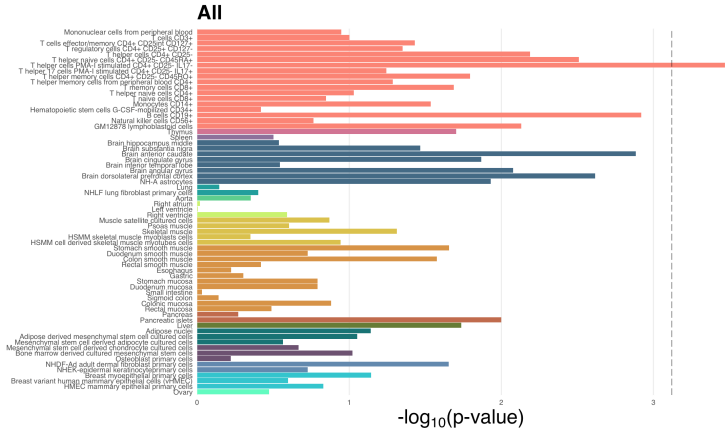

Figure 3. Enrichment plot

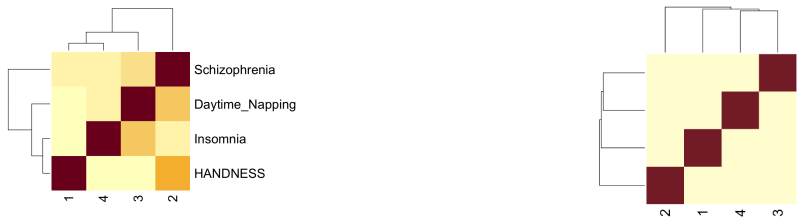

Figure 4. Genetic Correlation Matrix and Model Implied Matrix

autoimmune diseases and in the host response to infection and cancer. Besides, all the red regions are relatively highly significant, suggesting a relationship between left-handedness and the immune system.

5.6 Structural equation modeling

Genomic Structural Equation Modelling (Genomic SEM) is a flexible statistical framework method for modeling the joint genetic architecture of constellations of genetically correlated traits and incorporating genetic covariance structure into multivariate GWAS discovery. I applied Genomic SEM to left-handedness and Insomnia, schizophrenia, and daytime napping GWAS summary statistics for the individual phenotypes of interest. I first run multivariable LD-Score regression to obtain the genetic covariance (S) matrix and corresponding sampling covariance matrix (V). Figure 4 shows the two matrixes. The I run a common factor model using the p-factor LDSC output with DWLS estimation. The results are manually inserted into a path diagram to produce the following Figure 5.

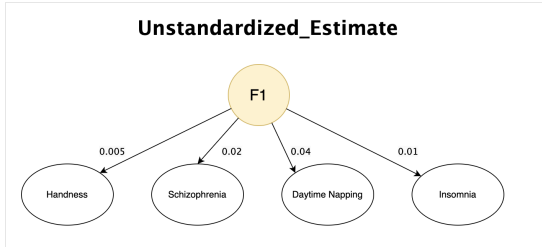

Figure 5

6. Conclusion

Using data from the UK Biobank, 23andMe and the International Handedness Consortium, I conducted a genome-wide association meta-analysis of handedness. I found rs13017199 and other significant loci on chromosomes 2,3,15,16,17 that are highly related to handedness. Some markers suggest that handedness may be related to neuron development, muscle movement, and intellectual ability. Correlation analysis implicated handedness in the possible etiology of Schizophrenia. Pathways including regulation of the immune system and brain morphology were also highlighted by Tissue-enrichment analysis. Besides, the GSEM analysis presented a possible structural model for handedness that does not include SNP effects. Overall, the study provides a novel clue for understanding the genetic correlation between left-handedness and other GWAS summary statistics, substantiating the concerns that handedness is partly heritable and affected by multiple chromosomes.

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Appendix 1. Codes

https://github.com/KaiyanM/BMI826