Identifying highly heritable brain amyloid phenotypes through mining Alzheimer's imaging and sequencing biobank data

Jingxuan Bao[1], Zixuan Wen[1], Mansu Kim[1], Xiwen Zhao[2], Brain N. Lee[1], Sang-Hyuk Jung[1], Christos Davatzikos[3], Andrew J Saykin[4], Paul M. Thompson[5], Dokyoon Kim[1], Yize Zhao[2], Li Shen[1,*], and for the ADNI

[1] Department of Biostatistics, Epidemiology and Informatics, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[2] Department of Biostatistics, Yale University School of Public Health, New Haven, CT, USA
[3] Center for Biomedical Image Computing and Analytics, Department of Radiology, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
[4] Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN, USA
[5] Imaging Genetics Center, Stevens Institute for Neuroimaging and Informatics, University of Southern California School of Medicine, Marina del Rey, CA, USA

***Please address correspondence to Li Shen PhD (Li.Shen@pennmedicine.upenn.edu)**

1. Introduction

Brain imaging genetics, an emerging and rapidly growing research field, studies the relationship between genetic variations and brain imaging quantitative traits (QTs) to gain new insights into the phenotypic characteristics and genetic mechanisms of the brain. Heritability is an important measurement to quantify the proportion of the observed variance in an imaging QT that is explained by genetic factors, and can often be used to prioritize brain QTs for subsequent imaging genetic association studies.

Most existing studies define regional imaging QTs using predefined brain parcellation schemes such as the automated anatomical labeling (AAL) atlas. However, the power to dissect genetic underpinnings under QTs defined in such an unsupervised fashion could be negatively affected by heterogeneity within the regions in the partition.

To bridge this gap, we propose a novel method to define highly heritable brain regions.

2. Method

Based on voxelwise heritability estimates, we extract brain regions containing spatially connected voxels with high heritability.

We perform an empirical study on the amyloid imaging and whole genome sequencing data from a landmark Alzheimer's disease biobank; and demonstrate the regions defined by our method have much higher estimated heritabilities than the regions defined by the AAL atlas.

4. Conclusion

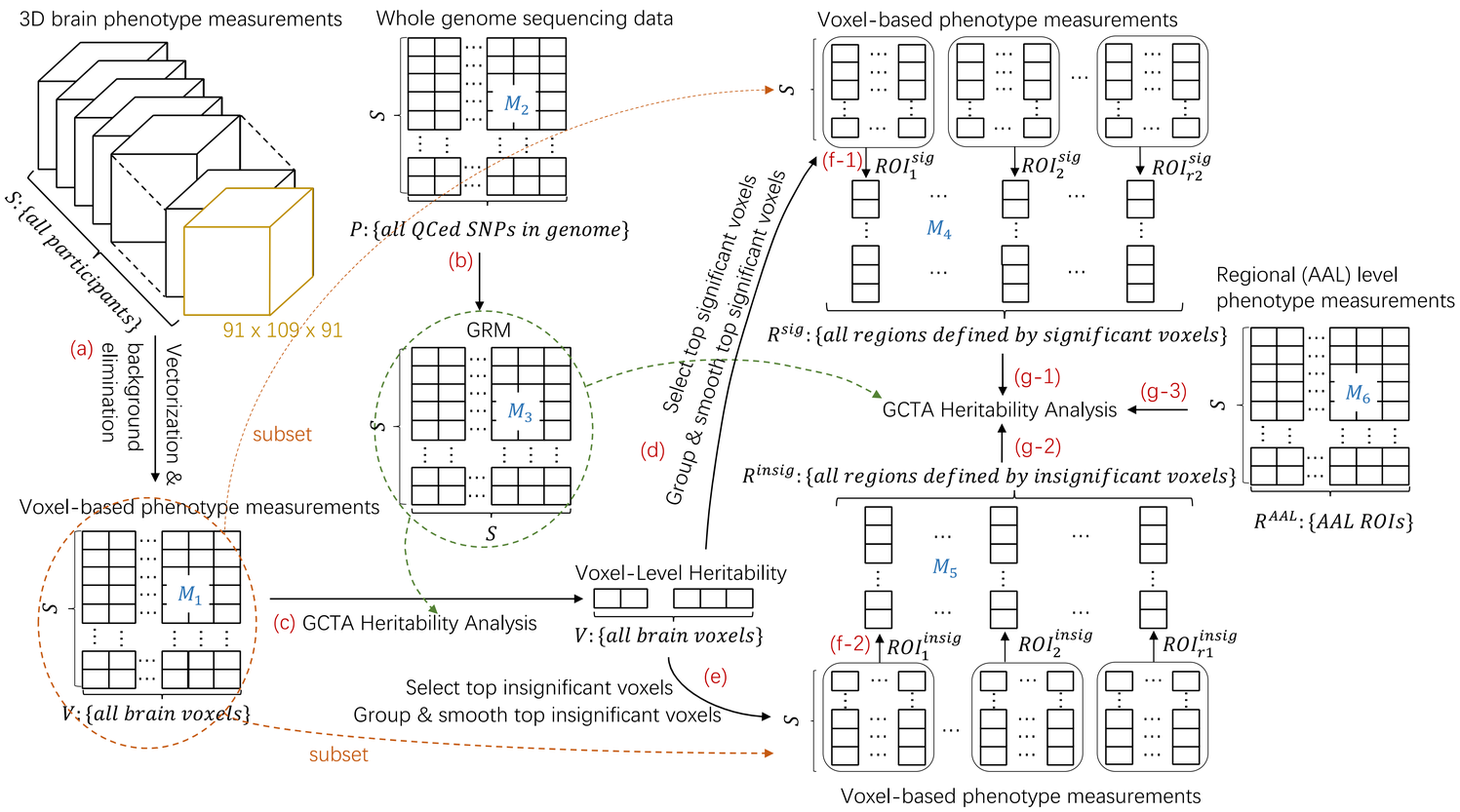
Our proposed method refines the imaging endophenotype constructions in light of their genetic dissection, and yields more powerful imaging QTs for subsequent detection of genetic risk factors along with better interpretability.

5. Acknowledgements

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI).

This work was supported in part by the National Institutes of Health [RF1 AG068191, U01 AG068057, R01 LM013463, R01 AG071470, R01 AG058854, P30 AG010133, S10 OD023495].

2. Method (Cont.)



3. Results

(a) Proposed self-defined regions (extracted from top GCTA significant voxels)

Regions	ROI_{total}	$ROI_{>90\%}$	$ROI_{>80\%}$	$ROI_{>50\%}$	$ROI_{<20\%}$	$ROI_{<10\%}$
Top 10% voxels	83	83(100%)	83(100%)	83(100%)	0(0%)	0(0%)
Top 20% voxels	119	117(98.3%)	119(100%)	119(100%)	0(0%)	0(0%)
Top 30% voxels	132	126(95.5%)	132(100%)	132(100%)	0(0%)	0(0%)
Top 100% voxels	118	99(83.9%)	114(96.6%)	118(100%)	0(0%)	0(0%)

(b) AAL atlas

Regions	ROI_{total}	$ROI_{>90\%}$	$ROI_{>80\%}$	$ROI_{>50\%}$	$ROI_{<20\%}$	$ROI_{<10\%}$
AAL atlas	116	14(12.1%)	21(18.1%)	64(55.2%)	22(19.0%)	16(13.8%)

(c) Regions extracted from top GCTA insignificant voxels

Regions	ROI_{total}	$ROI_{>90\%}$	$ROI_{>80\%}$	$ROI_{>50\%}$	$ROI_{<20\%}$	$ROI_{<10\%}$
Top 10% voxels	120	2(1.7%)	2(1.7%)	2(1.7%)	117(97.5%)	117(97.5%)
Top 20% voxels	116	10(8.6%)	10(8.6%)	10(8.6%)	105(90.5%)	90(77.6%)
Top 30% voxels	95	24(25.3%)	24(25.3%)	26(27.4%)	55(57.9%)	47(49.5%)