Title: Voxelwise Genome-Wide Association Study (vGWAS)

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Aim of Investigation: The structure of the human brain is highly heritable, and influenced by many common genetic variants, but many of these are currently unknown. Recent advances in neuroimaging and genetics have allowed collection of both highly detailed structural brain scans and genome-wide genotype information. This wealth of information presents a new opportunity to find the genes influencing brain structure.
Methods: Here we explored the relation between 545,871 single nucleotide polymorphisms in each of 252,407 voxels of the entire brain across 719 elderly subjects including subjects with Alzheimer's disease, Mild Cognitive Impairment, and healthy elderly controls scanned and genotyped as part of the Alzheimer's Disease Neuroimaging Initiative. We used tensor-based morphometry to measure individual differences in brain structure at the voxel level relative to a study-specific template based on healthy elderly subjects. Following this, (1) we conducted a genome-wide association analysis at each voxel; (2) we selected only the most associated SNP; (3) the effective number of statistical tests was calculated through fitting parameters of the Beta distribution; (4) the *P*-value for association was corrected across all SNPs via an inverse Beta transformation; and (5) the "corrected" *P*-value maps were assessed for how they controlled the false discovery rate to correct for multiple spatial comparisons.
Results: Our novel method was able to address the multiple comparisons, across the image and the genome, and computational burden associated with the unprecedented amount of data. We identified several genes worthy of further exploration , including *XKR4*, *PIP4K2A*, *CSMD2*, *CADPS2*, and *PIP3-E*. These genes have high relevance to brain and cytoskeletal structure; some have been previously associated with psychiatric disease. Additionally, the minimum number of subjects needed to replicate the findings was calculated through a resampling approach.
Conclusions: In summary, here we presented a novel method to discover genetic variations associated with brain structure. The resulting method can integrate a large amount of biological information, and still allows sufficient power to detect significant variants.

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