**Project Description**

**Genomic mapping of neuroimaging endophenotypes of psychiatric disorders**

1. Specific Aims and Significance

It has been recently shown that a substantial proportion (50%) of autism risk is captured by common genetic variants of small effect (Gaugler et al. 2014). This result suggests that in many cases it is likely not one or a few genes or mutations that determine the presence of an autistic phenotype, but a genomic, highly diluted, massively polygenic accumulation of frequent variants. We have recently shown that neuroanatomical variability in the IM- AGEN cohort is also captured by frequent variants (Toro et al 2014). We could then map the genetic correlation between autism risk and neuroimaging, which would in turn help identify brain structures whose genetic bases are strongly overlapping with those of autism. Such genomic mapping of neuroimaging phenotypes could also enable us to obtain relevant biological information for psychiatric disorder with massively polygenic architectures.

We have the following three specific aims for our proposed research.

1. We propose to estimate genetic correlations between risk to psychiatric disorders and neuroimaging by combining cohorts of genotyped patients, for example, the Autism Genome Project in the case of autism, and cohorts of MRI scanned, genotyped controls, such as IMAGEN.
2. We plan to combine the ENIGMA cohort with the IMAGEN cohort in our analysis, which would potentially produce a total sample size of about 20,000 subjects to ensure statistical power to reliably detect small to moderate genetic correlations.
3. We propose new statistical methodology for genomic mapping of neuroimaging en- dophenotypes of psychiatric disorders. We extend the genome-wide complex trait analysis (GCTA) of Yang et al. (2011), which focuses on linear association between phenotype and genome. Our new method permits nonlinear association, and also in- corporates nonlinear interactions of genes, by utilizing least squares kernel machine and specially designed kernel for genomic features.

[Anything to add here about the significance of this work?]

2. Material and Methods

2.1. IMAGEN and ENIGMA consortium

The data for this project already exist in the IMAGEN (Schumann et al., 2010) and ENIGMA (Thompson et al, 2014) consortia. Both R. Toro and JB Poline are members of these consortia and have access to the data. The project described here has been submitted and approved by both IMAGEN and ENIGMA. These consortia provide access to both the primary data (IMAGEN) and the subjects genetic relation matrix (ENIGMA). With potential access to over 20,000 subjects, these data provide us enough power to detect small effects of heritability and genetic correlations.

2.2. Genome-wide complex trait analysis

Lexin

2.3. Least squares kernel machine and Wright-Fisher kernel

Lexin

2.4. Previous work and preliminary results

We have recently shown, using the MRI and genetic data collected by IMAGEN, that an important part of the diversity of neuroanatomical phenotypes is captured by thousands of common SNPs, each of small-effect (Toro et al 2014). The strong heritability of phenotypes such as intracranial volume ( 50%) or brain volume ( 45%) allowed us to obtain statistically significant estimations of the variance captured by SNPs. However, the standard errors were large ( 20%). Power estimations show that a cohort of 4,000 subjects would be required to decrease standard error to 10%, and 8,000 subjects would be required to further decrease standard error to 5% The extra statistical power would not only allow us to have better estimations of the amount of neuroanatomical variance captured by SNPs, but also to detect more subtle effects than those we could detect with 1,765 subjects. We propose here to lead an effort to replicate and extend our previous results. Through the ENIGMA consortium we could potentially have access to a cohort of 20,000 subjects. Thanks to the expertise that we have acquired with the analysis of the IMAGEN cohort, we have now the knowledge and the infrastructure to perform the mega-analysis of genomic mapping of complex traits. We would also benefit from the work already done in the context of the participation of IMAGEN to the ENIGMA 1 project (ICV, BV, Hipp) and the ENIGMA 2 project (subcortical structures).

[Lexin will add more stat method previous work here]

3. Research Team

Lexin Li is a new faculty in the departement of Biostats at Berkeley. He has experience in both imaging and genetic data.

JB Poline is a researcher at the Brain Imaging Center at Berkeley. He has been the lead of the biostatistics and bioinformatics subproject of the IMAGEN consortium and has collaborated with ENIGMA on several projects.

Roberto Toro is a tenured researcher at Pasteur in a human genetic laboratory specialized in autism research. R. Toro has a wide experience on imaging and imaging genetics. The three individuals gather the necessary experience and expertise for the success of this project.

4. Work Plan

* First kick off meeting at the Pasteur Institute, Paris. Objectives of the meeting:
  + set up the collaboration tools (github account, common repositories, etc)
  + Develop a simulation dataset to validate estimation procedure (R. Toro, JB Poline, L. Li)
  + Bring participants up to date: genetic correlation current estimation procedures,
* During month 1-8, we will accomplish the following tasks.
  + Develop a simple simulation tool for validation
  + Obtain first genetic kindship matrix from IMAGEN and ENIGMA
  + Develop standard and regularized genetic correlation estimation procedures
* During month 9-12:
  + test the regularized estimation procedures on both simulated and actual kinship matrices. Compare results with standard GCTA approach. Publish the results.

5. References

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