**Project (1)**

The Religious Orders Study (ROS) is a longitudinal clinical-pathologic cohort study of aging and Alzheimer's disease (AD) run from Rush University that enrolled individuals from religious communities for longitudinal clinical analysis and brain donation. The Religious Orders Study (ROS) is a longitudinal clinical-pathologic cohort study of aging and Alzheimer's disease (AD) run from Rush University that enrolled individuals from religious communities for longitudinal clinical analysis and brain donation. Mostafavi lab has performed qQTL analysis on these samples and we will integrate it with AD GWAS loci, PPI networks and transcriptional profiles as follows:

GWAS studies have identified large number of genetic loci influence complex traits but the molecular mechanism by which this happens is not well understood. One of the ways genetic variants can influence end phenotype is by modulating gene expression (eQTLs). Looking for overlaps between complex trait-associated variants and eQTL variants has been successfully used as evidence of a common causal molecular mechanism [Giambartolomei et al]. We propose to intergrade the AD GWAS hits (Rosenthal et al.) with ROSMAP Frontal Cortex eQTLS identified in Mostafavi lab.

After identifying colocolized GWAS and eQTLS’s signals we will focus on protein-protein interactions of these prioritized genes and build networks using human PPI databases (GeneMANIA, String). This will enable us to look at the functional enrichment of networks around genes with genetic evidence and point out novel targets which are protein interactors of genetically identified genes. In order to assign causality to these genes identified we will use Bayesian network methodology (**conditional probability methodology- Describe here)** to assign causality between the genes identified based on PPI and AD traits.

**Project (2)**

Transcriptionally profiled post mortem tissue is from whole brain that is composed of multiple cell types. We propose to develop a methodology to assess the cell-type composition of whole tissue by de-convolution the gene expression signatures or 8 brain specific cell types across the ROSMAP dataset. This type of methodology has been used before to de-convolute expression signals from mixture of cell types (Gong et al). We will use cell specific markers from the brain identified in Zhang et al. We will then correlate estimated cell type numbers with end phenotypes to de-convolute the difference between genes expression changes associated with end phenotypes from genes whose expression is changing due to cellular composition.

This approach will also allow us to between eQTLs estimated from whole tissue expression data and specific cell types.

**References:**

Rosenthal. SL. Kamboh MI. Curr Genet Med Rep (2014) 2:85–101

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Gong T, Szustakowski JD. Bioinformatics. 2013