Toward Precision Medicine, May 1, 2016

Dr. Ben Logsdon, Senior Scientist, Sage Bionetworks/ ADRC Affiliate Member. *Toward Precision Medicine - Transcriptomic Network Prioritization of Alzheimer's Disease Drivers*

Dr. Logsdon introduced the AMP-AD, an initiative of the Accelerating Medicines Partnership (AMP) powered by the NIH, 6 biopharmaceutical companies, academic institutions, and nonprofit organizations. The program aims to transform the current model for developing new diagnostics and treatments for chronic diseases. Instead of identifying etiology of disease, the goal of AMP-AD is to accelerate the discovery of therapeutic targets for AD.

Logsdon, a senior scientist at SAGE Bionetworks, leads the network working group of AMP-AD. His team analyzes mountains of genome-wide gene expression data from multiple cohorts of patients with AD and without. They conduct large gene co-expression studies to identify the signals and pathways reproducibly associated with AD pathology and known AD biology, in context of transcriptomics.

The data comes from the Ross Map Study (molecular characterizations of tissue, genotyping); Mt. Sinai (4 brain regions, RNA sequencing, Whole Exome Sequencing); Florida Systems Biology at Mayo Clinic; Emory (Next generation proteomics on tissue samples, including data from ACT and Baltimore Study of Aging); Duke (Metabolic characterization of blood for lipids and cholesterol); Harvard's Bruce Yankner (repressor element 1-silencing transcription factor (REST).

Specifically, Logsdon's team looks at the levels of RNA expression across patients from these studies. They are trying to uncover the biology driving changes in genetic expression across patients. They want to know if they can use similarities in terms of these expression patterns across the genome; rather than looking at single genes, they are looking across whole genome. With a map of genes with similar patterns of gene expression, they can start to group genes into these functional units that correspond to biological processes.

They are working to produce a gene-gene correlation matrix across samples, which reveals block patterns of genes activated in similar ways across patients, plausibly acting

in concert. Logsdon's team wants to understand whether these blocks are signatures of neurons or astrocytes, or signatures of dysregulation of proteostasis or RNA splicing.

Currently, they are at work on building a resource for the AD research community through the AMP-AD Knowledge Portal, the distribution site for data, analysis results, analytical methodology and research tools. The portal will provide a set of new hypotheses that can be more thoroughly interrogated. The AMP-AD Knowledge Portal data is available to investigators and is updated periodically based on rapid data release timelines: **https://www.synapse.org/#!Synapse:syn2580853/wiki/409840**

Logsdon emphasized that this resource aims to move the field toward the goal of finding treatments, which hasn't happened yet. Specifically, it will help researchers understand the influence of a specific gene variant on the pattern of expression of downstream genes or other genes in relevant pathways. This information could be useful in situations in which a genetic risk variant, such as TREM2, proves impossible to impact with a drug; researchers could search this database for gene targets near TREM2 that might be more druggable.

So far, their preliminary findings show that all AD modules are enriched for genetic expression in microglia and endothelial cell populations, which is consistent with evidence.

In the discussion, Tom Byrd and Dirk Keene raised the general concern about drawing conclusions about AD biology from postmortem brain samples. Instead of showing drivers of disease, they suggested, the tissue analysis may simply reflect microglial response to the long-over disease process. Logsdon responded that they are focusing on transcriptomic data, which should provide information about the patient's genes regardless of how the disease impacted the expression of genes over time.

For more information about AMP-AD, please visit:
https://www.nia.nih.gov/alzheimers/amp-ad

To read about Ben Logsdon, read his profile:
https://depts.washington.edu/mbwc/about/profile/ben-logsdon

Access the AMP-AD Knowledge Portal:
https://www.synapse.org/#!Synapse:syn2580853/wiki/409840