MISSISSIPPI CENTER FOR CLINICAL AND TRANSLATIONAL RESEARCH

MCCTR Support of Transcriptomics in Jackson Heart Study Participants

The MCCTR is supporting RNA extraction from cryopreserved peripheral blood mononuclear cells of 1,055 Jackson Heart Study (JHS) participants, using baseline samples (2000-2004). The extracted RNA will be sequenced with funding from R01 HL129132 (PI Alex Reiner), and gene-specific transcripts will be quantified.

- Value of the data to be produced: DNA variants that are associated with the transcription levels of specific genes (expression quantitative trait loci or eQTLs) can directly affect the quantitative expression of the encoded proteins. Massively parallel sequencing of messenger RNA from the available JHS samples will enable the detection of genetic variants that regulate the transcription of potentially any gene that is expressed in mononuclear cells. Individuals of African ancestry harbor a rich pool of genetic variation, including many genetic variants that are absent from other populations. Although eQTL datasets for European ancestry populations have been available for several years, the current effort, supported by the MCCTR, will produce the largest eQTL dataset to date for an African ancestry population.

  Transcriptome-wide association studies (TWAS) use eQTL data to predict the transcription levels of the related genes in individuals with only genotype data available. The predicted transcription levels can then be tested for their association with important biologic traits and outcomes such as cholesterol levels, type 2 diabetes, or coronary artery disease. TWAS approaches have a lower burden of multiple testing correction compared to single variant GWAS, and they improve mechanistic interpretation by linking imputed mRNA transcript levels, instead of single variants, to trait variation. eQTLs from circulating leukocytes often generalize to other tissues, and in other cases their association with disease may be mediated through leukocyte biology (e.g. through effects on the vascular endothelium). TWAS has successfully identified genes missed by single variant analysis for cancer, schizophrenia, cardiovascular disease, and other conditions [1-4]. Along with TWAS, there are many other well-developed methods to utilize a novel eQTL dataset in African Americans (gene set enrichment analyses, colocalization, etc.). The availability of this powerful eQTL dataset will enable discovery of novel disease mechanisms across a wide variety of conditions in the JHS and other large cohorts of African Americans who have undergone genotyping or whole genome sequencing, including clinical cohorts developed using electronic medical records.

- Benefit to JHS, UMMC, and MCCTR investigators: (1) JHS investigators can be expected to be primary authors or coauthors of a large number of papers based on these data. (2) The availability of this eQTL dataset will enable future applications for funding based on JHS data or potentially involving African Americans from the UMMC clinical population. For example, one could propose genotyping studies of African American patients who have undergone specific imaging studies, to identify imputed transcripts that associate with clinically important structural findings. Other possibilities include TWAS of mothers who have had pre-eclampsia vs. those who have not, or TWAS to identify transcripts that predict degree of success of bariatric surgery or response to exercise. Importantly, through established mechanisms, any UMMC or JHS investigator can potentially access and use these JHS transcriptomic data by developing a JHS-approved ancillary study or manuscript proposal (see https://www.jacksonheartstudy.org/ for instructions on submitting a proposal).

- Assistance for prospective UMMC and MCCTR investigators: Technical approaches for TWAS and other RNA expression-based analyses are well-developed but require expertise in statistical genetics as well as programming skills. UMMC investigators with such skills include Jeanette Simino, Yan Gao, Hao Mei, and Solomon Musani. Investigators who are associated with Dr. Reiner's R01 could also help with protocol development and analysis, including Dr. James Wilson (Beth Israel Deaconess Medical Center), Dr. Alex Reiner (University of Washington, Seattle), Dr. Leslie Lange (University of Colorado, Denver), and Dr. Laura Raffield (University of North Carolina).

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