

National Advisory Council for Human Genome Research (NACHGR)

February 10, 2020

Concept Clearance for FOAs

Developmental Genotype-Tissue Expression (dGTEx)

Purpose

The National Human Genome Research Institute (NHGRI) proposes a new initiative, Developmental Genotype-Tissue Expression (dGTEx), to catalog and analyze transcriptional profiles from a wide variety of tissues from neonates, children, and adolescents in a post-mortem setting. NHGRI proposes two RFAs for cooperative agreements, one managed by NHGRI to provide support for a Laboratory, Data Analysis, and Coordinating Center (LDACC), and the other managed by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) to support Tissue Procurement Centers to enroll donors and provide tissue samples to the LDACC. The proposed LDACC will work with Tissue Procurement Centers to receive tissue samples from ~120 donors, perform gene expression analysis and deposit data in relevant controlled access databases. This is an expansion on the recently completed [Genotype-Tissue Expression \(GTEx\) project](#), in which dGTEx will help explore and understand the typical patterns of gene expression during development.

The goals of the dGTEx initiative are to establish a resource database and associated tissue bank to study gene expression patterns in multiple reference (predominantly normal) tissues during neonatal and pediatric development and associate these expression patterns with genomic sequence variation. GTEx measured gene expression in whole tissues and this will be continued in dGTEx; in addition, single cell analysis will also be incorporated to study RNA expression in populations of single cells. This will provide information to understand how distinct cell types influence each other during development of complex organs and tissues.

Background

The premise of GTEx (FY10-FY16) was to correlate gene expression and genetic variation within the same individual across multiple tissues and examine individual variation within a tissue across an adult population. GTEx provided a comprehensive survey of gene expression in adult human tissues. Studying gene expression in the neonatal and pediatric periods would fill key gaps in our understanding of the role of gene expression in normal human development, providing insight into disease processes that have their origins before maturation is complete and potentially into how developmental gene expression patterns affect important clinical factors such as drug response in early and later childhood. It can also provide a baseline for comparing gene expression and regulation patterns in normal development with expression studies in disease cohorts.

NHGRI and NICHD hosted a joint workshop in April 2018 entitled "[Genomic Medicine for Reproductive, Prenatal, and Neonatal Health](#)." The following issues were considered – current technologies ready for implementation; ethical, legal, and social implications; and challenges to

implementing genomic medicine in reproductive, prenatal, and neonatal health. The creation of a genotype-tissue expression project for neonates and children was one recommendation that emanated from the workshop.

In preparation for dGTEx, a Bioethics Consultation Service was requested to explore the ethical issues of posthumous genomic research in neonatal and pediatric settings. Recommendations to consider prior to and during the project included: 1) engaging the families and healthcare staff to identify how to approach tissue procurement in a manner that would be acceptable to grieving parents; 2) considering eligibility criteria for participation; 3) asking questions that are absolutely necessary at the time of consent, and 4) following up with general study results and maintaining communication.

In collaboration with NICHD, we inquired about the feasibility of organ donation research from neonatal and pediatric experts in the field and attended two Steering Committee Meetings – Collaborative Pediatric Critical Care Research Network and Neonatal Research Network. Experts reported that families are amenable towards organ donation research and emphasized the importance of working with organ procurement organizations.

Proposed Scope and Objectives

The major objectives of the project are to: 1) create an atlas of tissue gene expression in the developing human by performing RNA-Seq on whole tissues and in single cell or homogeneous cell populations collected from neonatal and pediatric donors in a post-mortem setting; 2) analyze regulatory variation and its effect on gene expression; and 3) create and make available a biobank of neonatal and pediatric tissues and associated data for further characterization.

To achieve these objectives, dGTEx will collect ~120 donors or more, sampling 20-30 tissues per donor, including brain, similar to what was collected in GTEx. Genome sequencing will be performed on each donor, RNA sequencing on ~1,500 tissue samples (10-15 per donor), and single cell sequencing on a subset of tissues. In addition to genome and RNA sequencing, dGTEx will also consider other types of analyses to study regions that are related to transcriptional activity such as chromatin accessibility, histone modification, and DNA methylation.

The LDACC will perform 2 major functions, as a molecular laboratory and a data analysis and coordinating center. As a molecular laboratory, the LDACC will purify DNA and RNA nucleic acids from tissue aliquots; perform next-generation sequencing, whole genome and transcriptome; and operate a cell culture facility. Responsibilities as a data analysis and coordinating center include ensuring close coordination among the Tissue Procurement Centers, monitoring study progress and laboratory performance, preparing statistical and other reports, performing basic analysis of data from expression analyses, and submitting datasets to be deposited in to the GTEx portal and any other repositories.

The Tissue Procurement Centers will consist of components supporting the procurement of tissues which include identifying and enrolling donors, acquiring multiple tissue samples from each donor, and using appropriate methods to collect, handle, and store samples. Additional

responsibilities include providing expert pathological review of each specimen, collecting clinical and other types of data, and conducting ethical, legal, and social implication (ELSI) research.

Procuring tissues from recently deceased children is an essential component in the implementation of this initiative. ELSI research at the procurement sites could assess the attitudes and impact of tissue donation for research on all stakeholders, how reporting aggregate results is perceived by donor families, or possible other issues.

The availability of a biobank of tissues will allow for additional assays to be performed later as desired. We anticipate depositing data in the [AnVIL](#) (Analysis, Visualization, and Informatics Lab-space) to increase the opportunity for researchers to access the data for further analyses. Data may also be made available through other databases such as [dbGaP](#) and [GTEx portal](#). The value to the scientific community of generating these data can be seen from the success of GTEx publications. To date, over 2,000 publications have been issued consisting of consortium and non-consortium papers.

Relationship to Ongoing Activities

dGTEx would build upon the successful GTEx model by including neonatal and pediatric donors, analyzing gene expression and genetic variation within pediatric subgroups and between adults (based on prior GTEx data) and children. The Human BioMolecular Atlas Program (HuBMAP) facilitates research in single cell analysis within tissues to explore the relationship between cellular organization and function in adults while dGTEx will focus on single cell analysis during human development. The Human Cell Atlas also aims to create a reference map of all human cells through single cell genomics. dGTEx would augment and complement the single cell domain by analyzing single cells from different developmental time points and understanding gene expression for single cell populations within a tissue.

dGTEx is significant to NHGRI's Strategic Planning goals as it provides an opportunity to build upon functional genomics by establishing role(s) of genes and regulatory elements in developmental pathways, networks, and phenotypes. Genomic variations exert their effects on human health and disease throughout the lifespan. Genomic data resources, GTEx and ENCODE ([Encyclopedia of DNA Elements](#)), lack data from early developmental stages, and thus are missing critical information about important human phenotypes that are expressed early in life.

Mechanism of Support

Two RFAs for cooperative agreements will be published: the Laboratory, Data Analysis, and Coordinating Center (U24) managed by NHGRI; and the Tissue Procurement centers (U24) by NICHD. Anticipated duration of the program is 5 years, starting in FY2021. Solicitations for Statistical analysis and Integration of dGTEx data will be published in the out years.

Funds Anticipated

NHGRI and NICHD will each commit ~\$14M over 5 years for a total of ~\$28M, with one award for the LDACC anticipated. Co-funding will be sought from other Institutes and Centers.