The Genotype-Tissue Expression (GTEx) Project

Council of Councils

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The Challenge

How do we translate new genomic findings into clinical targets?

Open questions

Causal gene/s?
Causal mechanism?
Causal tissue/s?
Causal pathway/s?

Trait-associated DNA variant

ACGGGCAATCACGT
ACGGGCAATCACGT
ACGGGCAATCACGT
ACGGACAAACAAGT
ACGGACAAACAAGT
ACGGACAAACAAGT

Modified from Dr. Ardlie - The Broad Institute
The Opportunity
Beyond the GWAS era


Hypothesis: Disease-associated variants in noncoding regions may be affecting disease through gene regulation

Modified from Dr. Ardlie - The Broad Institute
Challenges in using eQTLs to interpret disease associations

• Measuring eQTLs in disease-relevant tissues or cell types

• Most human tissue types are hard to obtain

• Large sample sizes are required for statistical power
GTEx Goal

- Help unravel the complex interplay between genetic variation and gene expression across a wide range of non-diseased human tissues.
  - Collect over 30 tissues in rapid autopsy setting
  - WES & WGS and RNA-Seq
GTEx Pilot

1) Enroll at least 10 post mortem donors per month by the end of the pilot period

Recruitment goal met!
2) Obtain high-quality RNA, defined as a RNA Integrity Number (RIN) of > 6 for 70% of 12 or more organs

RNA quality goals met!
GTEx Scale up

• The “Atlas of Human Gene Expression”
• Comprehensive cis- and trans-eQTL results
  • 900 post-mortem donors, completely sequenced
  • Over 25,000 tissues
  • Gene expression (RNA-Seq) for >20,000 tissue samples
  • Associated clinical and histopathological information
  • Access system for data and samples
  • ELSI study of donor families
  • Beyond Gene Exp
OPO/PM Donors

Goal n=900

From each donor

BSS – Biospecimen Source Site

1. PAXgene Fixed Paraffin Embedded (PFPE)
2. One aliquot sent out RNA-Seq to 70 million reads; 76 bp paired-end Illumina HiSeq2000

High-quality RNA

CBR – Comprehensive Biospecimen Resource

NIH-supported brain bank

Flash Frozen (Entire brain)

Histopathologic review

LDACC – Laboratory, Data Analysis, and Coordinating Center

24 hrs

DNA - Stored

High-quality RNA

WES / WGS & lymphoblastoid cell line

9-11 sub-regions

CBR ➩

Flash frozen

For each tissue

Fix in PAXGene Tissue (0.2 – 0.5 gram aliquots)

1. PAXgene Fixed Paraffin Embedded (PFPE)
2. One aliquot sent out

Homogenize, extract DNA & RNA, measure RNA quality

For subset of tissues

Flash frozen

BSS ➩

NIH-supported brain bank

24 hrs

Flash Frozen (Entire brain)

Histopathologic review

DNA - Stored

WES / WGS & lymphoblastoid cell line

Donor Selection Criteria

- Any racial and ethnic group and sex
- Age 21-70
- Collection can start within 24hr of death
  - Organ/Tissue Donors (OPO) & Postmortem Donors (PM)
- Few medical exclusionary criteria:
  - HIV infection or high-risk behaviors, viral hepatitis, metastatic cancer, chemotherapy or radiation therapy for any condition within the past 2 years, whole blood transfusion in past 48 hours, or body mass index $\geq 35$ or $\leq 18.5$
  - Brain collected if not on ventilator last 24 hours
Effect of predicted protein-truncating genetic variants on the human transcriptome

Assessing allele-specific expression across multiple tissues from RNA-seq read data

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