# ARTICLE IN REVIEW:

## The atlas of genetic regulatory effects across human tissues

**SUMMARY:** The Genotype-Tissue Expression (GTEx) project launched in 2010 with the goal of improving knowledge of genetic effects in complex diseases and traits across human tissues. Powerful tools, such as RNA sequencing, whole-genome sequencing, and genome-wide association studies were used to map variations in gene expression and regulatory mechanisms across diseased, complex, and normal human tissues – resulting in the version 8 (v8) catalog of GTEx data. This expansive library provides insight into genetic cell-type interactions and the effect of cell types within shared tissues on physiology and pathophysiology. The results indicate shared biology within the same tissue based on cell-type composition, transcriptome variation, and genetic regulatory effects. These similarities are likely due to genetic regulatory effects in shared cell types. Well-powered analyses also enable better understanding of multiple independent regulatory effects on the same gene (allelic heterogeneity) which can result in complex traits. From this information comes a powerful tool in identifying causal disease genes and estimating the dosage-risk relationship. Mechanistic insights into the cellular cause of allelic heterogeneity also provides higher resolution and finer dissection of genetic association data. With careful interpretation, the GTEx v8 data provides powerful information on the genetic variation and mechanisms of complex traits across human tissues. While the data are far from complete, additional studies and catalog development will provide diverse and pertinent information for scientific discoveries for years to come.

### Diverse catalog of tissues and cells:

The v8 release from the GTEx consortium encompasses genetic data from 49 human tissues or cell lines. Included in the data set are 15,201 tissue samples from 838 donors. LifeNet Health provided tissues from research-consented donors in support of this effort.

### Insight across population and sexes:

Donors were 66.4% males and 33.5% females of European American (85.3%), African American (12.3%), Asian American (1.4%), and Hispanic or Latino (1.9%) ancestry. Such diversity provides a broad perspective on the genetic variation underlying the differences in human traits and diseases across sex and ethnicity.

### Genetic impact on complex traits:

By comparing quantitative trait data across several tissue types, a meta analysis was able to identify several causal regulatory traits. In further comparisons with genome wide association studies (GWAS), the presence of similar cell types within differing tissues seemed to be a determining factor rather than the cellular regulatory networks. At an even further level, fine mapping of quantitative trait data pointed to possible causal disease genes which may be useful in estimating dosage-risk relationships.

## Tissues analyzed in the GTEx catalog
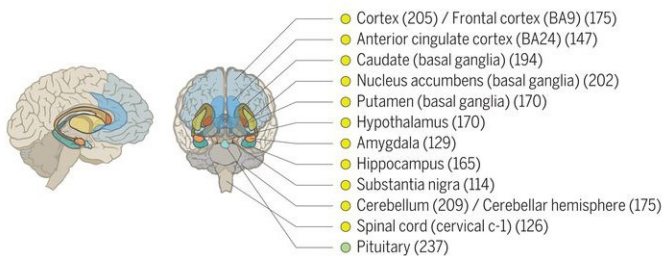


Sample and data types in the GTEx v8 study. (A) Illustration of the 54 tissue types examined (including 11 distinct brain regions and two cell lines), with sample numbers from genotyped donors in parentheses and color coding indicated in the adjacent circles. Tissues with 70 or more samples were included in QTL analyses.

Figure 1A reproduced with permission. Copyright 2020 American Association for the Advancement of Science
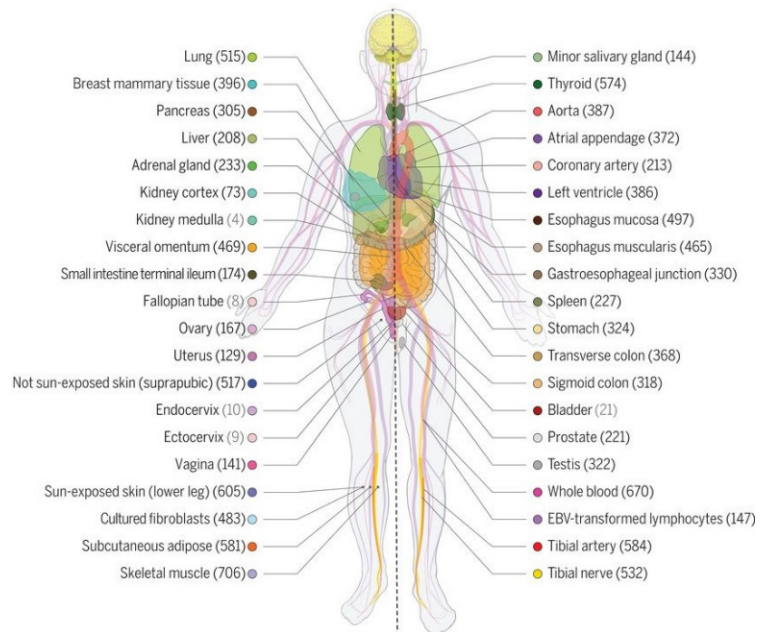
## Reference:

1. GTEx Consortium. The GTEx Consortium atlas of genetic regulatory effects across human tissues. Science. 2020 Sep 11;369(6509):1318-1330. doi: 10.1126/science.aaz1776. *Full author list at the end of article

**LifeNet Health®**
**LifeSciences**