UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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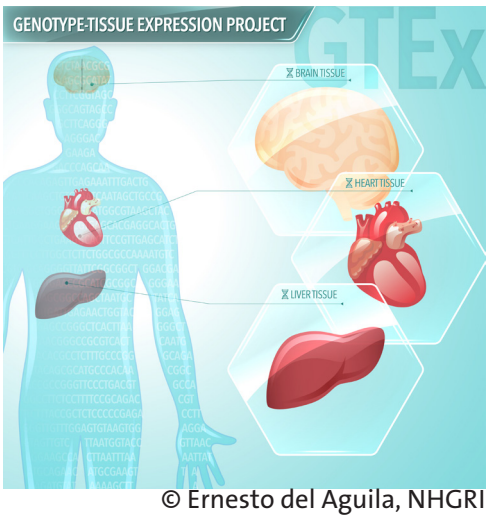
A LARGE INTERNATIONAL PROJECT REVEALS NEW INSIGHTS INTO HOW DNA DIFFERENCES INFLUENCE GENE ACTIVITY AND DISEASE SUSCEPTIBILITY



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Researchers co-led by Professor Emmanouil Dermitzakis, geneticist at the University of Geneva (UNIGE) Faculty of Medicine and at the Swiss Institute of Bioinformatics (SIB), have created a new and much-anticipated data resource to help them find out how differences in an individual's genetic make-up can affect gene activity and contribute to disease. Funded by the US National Institutes of Health (NIH), this project of international scale will enable them to examine many different types of human tissues and cells at the same time, and promises to open new avenues to the understanding of human biology. The scientists reported initial findings from a two-year pilot study in several studies appearing on May 8, 2015, in *Science* and other journals. They provide new insights into how genomic variants – inherited spelling changes in the DNA code – can control how, when and how much genes are turned on and off in different tissues and can predispose people to diseases, such as cancer, heart disease and diabetes.

The Genotype-Tissue Expression (GTEx) project was designed to sample as many tissues as possible from a large number of individuals in order to understand the causal effects of genes and variants, and which tissues contribute to predisposition to disease. "The number of tissues examined in GTEx provides an unprecedented depth of genetic variation. It gives us unique insights into how people differ in gene expression in tissues and organs from both genomic and environmental causes." said Emmanouil Dermitzakis, Ph.D., professor of genetics at the UNIGE Faculty of Medicine, Switzerland, group leader at the Swiss Institute of Bioinformatics, and a co-corresponding author on the main Science paper.

NIH launched the GTEx project in 2010 to create a reference database and tissue bank for scientists to study how genomic variants may affect gene activity and disease susceptibility. Investigators are collecting more than 30 tissue types from autopsy or organ donations and tissue transplant programs, and analyze both DNA and RNA from samples. The project will eventually include tissue samples from about 900 deceased donors.

In the main Science paper, researchers analyzed the gene activity readouts of more than 1,600 tissue samples collected from 175 individuals and 43 tissues types. Investigators focused much of the analysis on samples from the nine most available tissue types: adipose, tibial artery and nerve, heart, lung, skeletal muscle, skin, thyroid and blood.

The genetic blueprint of every cell is the same, but what makes a kidney cell different from a liver cell is which genes are turned on and off and how active they are. GTEx investigators used a methodology --"expression quantitative trait locus" (eQTL) analysis -- to gauge how

variants affect gene activity. An eQTL is an association between a variant at a specific genomic location and the level of activity of a gene in a particular tissue. One of the goals of GTEx is to identify eQTLs for all genes and assess whether or not their effects are shared among multiple tissues.

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Investigators discovered a set of variants with common activity among the different tissue types. In fact, about half of eQTLs for protein-coding genes were active in all nine tissues. “We didn’t know how specific this regulation would be in specific tissues,” said co-corresponding author Kristin Ardlie, Ph.D., who directs the GTEx Laboratory, Data Analysis and Coordination Center (LDACC) at the Broad Institute of MIT and Harvard in Cambridge, Massachusetts. “The analysis showed a fair number of variants are common across tissues, and at the same time, there are subsets that are tissue-specific.”

Even when active in multiple tissues, the same variant can often have a different effect in different tissues. GTEx researchers found, for example, that a variant that affects the activity of two genes associated with blood pressure had a stronger impact on gene expression relevant to blood pressure in the tibial artery – even though there was greater gene activity in other tissues.

The researchers identified approximately 10,300 eQTL genes for the tissues they examined when applying new multi-tissue methods to leverage analysis across all tissues. “Comparing tissue-specific eQTLs with genetic disease associations might help provide insights into which tissues are the most relevant to a disease”, noted Prof. Dermitzakis. In addition, they also found a great deal of eQTL sharing among tissues, which can help explain how genetic variants affect the different tissues they are active in.

The GTEx resource is being developed in part to meet a growing scientific need. Scientists have used genome-wide association studies (GWAS) to study the roles that genomic variants play in disease. By comparing thousands of genomic variants in people with a disease to thousands without, they can associate genomic variants and regions in the genome with diseases. But these associations don’t necessarily explain what specific genomic variants do and how they might affect the biology and development of disease.

“GTEx will be a great resource for understanding biological function, and will have many practical applications in areas such as drug development,” said Jeff Struewing, M.D., from the NIH. “Scientists studying asthma or kidney cancer, for example, will be interested in understanding how variants work in the lung, kidney or other organs.”

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