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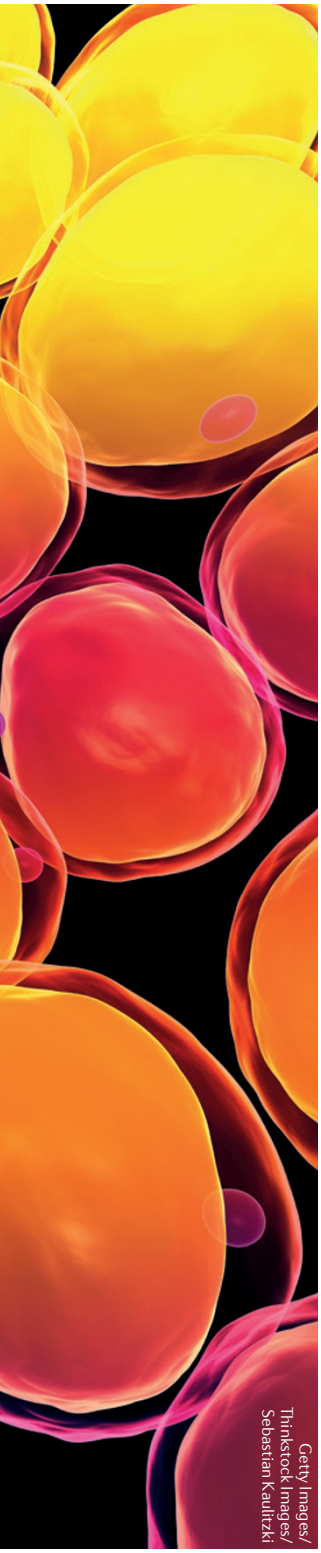

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HUMAN GENETICS

GTEx pilot quantifies eQTL variation across tissues and individuals

The comprehensive characterization of regulatory variants across a broad range of human tissues and cell types is critical for the functional interpretation of genome-wide association study (GWAS)-associated loci and insights into mechanisms of disease. Although studies mapping expression quantitative trait loci (eQTLs) in humans contribute to these efforts, they have mostly been limited to cell lines, blood and a few accessible tissue types, including skin and fat. The Genotype–Tissue Expression (GTEx) Consortium now reports several initial studies in this US National Institutes of Health Common Fund project that have mapped eQTLs and their effects across a wide range of human tissue types, providing a first view into the extent of variation across tissues and individuals, as well as an eQTL catalogue and tissue bank that provide a much-needed genomics resource.

The GTEx pilot phase includes samples from 175 next-of-kin consented adult post-mortem donors. High-throughput RNA sequencing (RNA-seq) data are available for samples from 43 tissues, with an average of 28 tissue samples collected per individual from 54 body sites. These initial publications focused primarily on RNA-seq data from 9 tissues (adipose, tibial artery, heart, lung, muscle, tibial nerve, skin, thyroid and whole blood), for which there were ≥80 samples available, providing sufficient power for *cis*-eQTL detection. The number of genes with at least one significant *cis*-eQTL varied widely by tissue, from 919 in heart to 2,244 in thyroid tissue. To allay some concerns over the use of post-mortem samples, they sought replication of these SNP–gene pairs in two separate data sets. The authors found a large extent of eQTL sharing across multiple tissues: >50% of all detected eQTLs were shared across these 9 tissues. In addition, most of the shared eQTLs show a consistent direction of effect across tissue types. The authors also demonstrate that the use of multi-tissue analyses increases the power to detect eQTLs, using Bayesian models to combine information across tissues. They define groups of co-expressed genes, or modules, within tissues, as well as regulatory variants (module QTLs, or modQTLs) influencing the switching of some genes between modules across different tissues or individuals.

Melé *et al.* used the GTEx data set to characterize patterns of transcriptome variation across individuals and tissues. They found that tissues show characteristic transcriptional signatures, with a sharp contrast between solid and non-solid tissues. Within tissues, transcription was attributable to a small number of genes (a few hundred genes accounted for ~50% of transcription in most tissues), while there was a limited extent of tissue specificity overall, with <200 genes expressed exclusively in a particular tissue. This may suggest wide-scale tissue heterogeneity or a low level of basal transcription shared across cell types.

Rivas *et al.* catalogued predicted protein-truncating variants (PTVs) and their effect on the human transcriptome in a combined data set including GTEx and RNA-seq data from lymphoblastoid cell lines from 462 healthy individuals from the Geuvadis project.

Baran *et al.* took a genome-wide approach to characterize imprinting of genes using allele-specific expression data from GTEx as well as several other studies, identifying 42 genes in 27 loci showing patterns of imprinted gene expression. They find widespread tissue specificity of imprinting, as well as suggestive evidence for interindividual variation.

An important use of the GTEx data set will be to prioritize candidate genes within GWAS-associated loci. The availability of this eQTL catalogue from multiple human tissues will also: allow for evaluation of the tissue specificity of associated loci; highlight tissues of relevance for a given disorder; and suggest potential mechanisms. The GTEx project continues to scale up to collect 20,000 tissues including >50 tissue types from 900 post-mortem donors.

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ORIGINAL RESEARCH PAPERS The GTEx Consortium. The Genotype–Tissue Expression (GTEx) pilot analysis: multitissue gene regulation in humans. *Science* **348**, 648–660 (2015) | Melé, M. *et al.* The human transcriptome across tissues and individuals. *Science* **348**, 660–665 (2015) | Rivas, M. A. *et al.* Effect of predicted protein-truncating genetic variants on the human transcriptome. *Science* **348**, 666–669 (2015) | Baran, Y. *et al.* The landscape of genomic imprinting across diverse adult human tissues. *Genome Res.* **25**, 814–824 (2015) | Pierson, E. *et al.* Sharing and specificity of co-expression networks across 35 human tissues. *PLoS Comput. Biol.* **11**, e1004220 (2015)

FURTHER READING Albert, F. W. & Kruglyak, L. The role of regulatory variation in complex traits and disease. *Nat. Rev. Genet.* **16**, 197–212 (2015) | The GTEx Consortium. The Genotype–Tissue Expression (GTEx) project. *Nat. Genet.* **45**, 580–585 (2013)

WEB SITES

GTEx Portal: http://www.gtexportal.org/