PERSPECTIVES

HUMAN GENOMICS

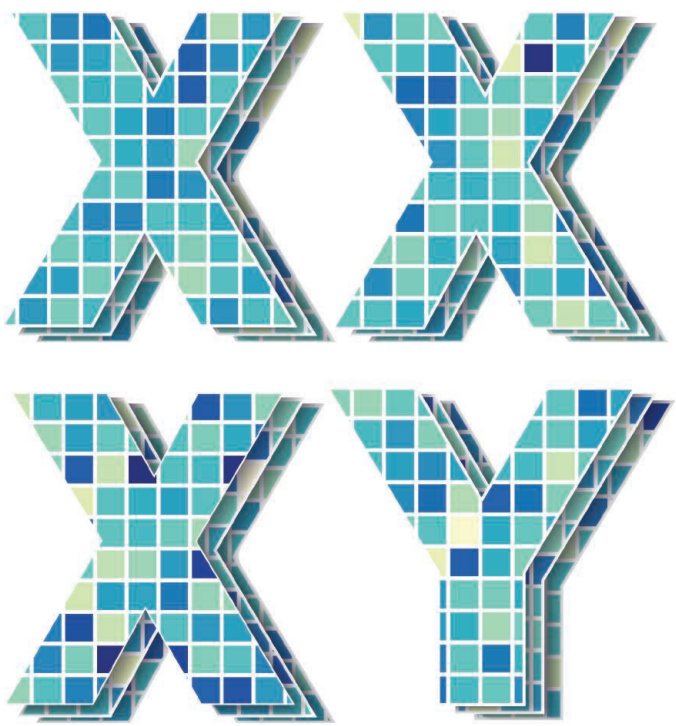
Searching for sex differences

Evolved sex differences in gene expression are pervasive, but so too is sampling bias

By **Melissa A. Wilson**

The behemoth effort, started a decade ago, known as the Genotype-Tissue Expression (GTEx) Consortium aims to discover how DNA variation affects gene expression across human tissues (*1*, *2*). As part of this consortium, on page 1331 of this issue, Oliva *et al.* (*3*) find that more than one-third of genes show sex-biased expression in at least one tissue. Four other GTEx studies, on pages 1318, 1334, 1333, and 1332 of this issue, respectively, discuss the effects of gene regulation in human tissues (*4*), identify functional rare genetic variation (*5*), study predictors of telomere length (*6*), and report cell type–specific gene regulation (*7*). What is especially notable about Oliva *et al.* is the careful analysis, which revealed that in addition to reported genetic and hormonal effects (*8*), there are cell type–specific sex differences in tissue composition. Furthermore, their work highlights that rather than being strictly dimorphic, interindividual variation results in overlapping distributions of gene expression between the sexes.

It has been hypothesized that selection shaped sex differences in immune function in response to the evolution of pregnancy and the placenta in mammals, beginning more than 90 million years ago and contributing to the observed sex differences in diseases today, including a female bias in autoimmune disease and male bias in most cancers (*9*). Sex differences in gene expression are broadly shared across mammals, but their role in shaping sex differences in disease etiology has not been thoroughly explored. Oliva *et al.* report that genes that show differences between sexes are enriched for multiple pathways, including in immune responses and cancer. Furthermore, they identify sex differences in a cluster of genes that target histone H3 lysine 27 trimethylation (H3K27me3) sites; these histone marks have also been reported to show sex-differentiated expression in the placenta (*10*). Oliva *et al.* provide a comprehensive baseline for sex differences in gene expression in unaffected tissues that can be used for future comparisons with diseased tissues. These observations may also inform about which pathways are most important in sex differences in disease etiology and aid in the development of targeted therapies.



Sex differences in gene expression vary across the genome and between individuals, as represented by these heatmaps.

(GRAPHIC) V. ALTOUNIAN/*SCIENCE* AND M. ATAROD/*SCIENCE*; (DATA) GTEX CONSORTIUM

Oliva *et al.* identified hundreds to thousands of genes (1.3 to 12.9% of the genes expressed per tissue) that show sex differences in gene expression in any given tissue but found that the effect for each individual gene is subtle (the median fold change in expression was just 1.04). This is after accounting for the cellular composition of tissues that came from males versus females. The authors hypothesize that this sex difference in cell type composition—particularly of immune-related cells, such as monocytes and neutrophils [previously reported by (*11*)]—may contribute to the underlying sex-specific dysregulation for some diseases. These sex differences in cell type composition affect estimates of gene expression and, if unaccounted for, can skew results that compare groups with unequal sex ratios. Future studies that include samples from males and females will now need to account for cell type composition in addition to sex chromosome complement and hormonal environment. This is because different sex ratios in cell type in cases versus controls may drive the gene expression signal more than the phenotype of interest.

Although the genes with the highest fold change in expression were found on the X chromosome, the X chromosome contains only 4% of genes with sex-differential expression; the remaining 96% are spread across the genome (*3*). This is important because the X chromosome is often excluded from genome-wide analyses (*12*), but in doing so, studies may be missing genes with the largest effects. Additionally, Oliva *et al.* call attention to the importance of autosomal (non–sex chromosome) gene regulation in contributing to sex differences in humans. Given this, it is also noteworthy that they show that sex-biased autosomal gene expression is not very specific for predicting the sex of the donor from which the sample was taken (84% accurate, with 56% specificity), emphasizing how labile sex-biased gene expression is across people.

The GTEx Consortium has generated an invaluable resource through the generous involvement of patients and their families. However, like many consortia, sampling biases hinder investigation of interindividual variation. Details about the sampling are, with much appreciation, made transparent by the consortium on the GTEx Portal (*13*).

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Just over two-thirds (67.1%) of the samples are from males. This means that studies are unevenly statistically powered to detect sex differences. It also means that studies that use the GTEx data as a reference set for comparison with disease state, for example, should take into account the relative proportion of samples from males and females (in both sets) because the relative sex effects on gene expression may not be the same in both.

Also, more than half of the samples come from people 50 years and older. This means that the samples are skewed toward understanding gene expression in tissues that have had many different exposures, potentially contributing to the observed interindividual variation, and does not reflect expression of tissues across the life span. Considering variation across the life span is especially critical for understanding how puberty and menopause, for example, affect gene regulation between the sexes.

Last, representation of global human genetic variation is low, with nearly 85% of samples collected from white people of European descent. There is a dearth of information about genetic variation and gene expression outside of a narrow range of recent genetic ancestries (*14*). This is critical for human health because inferences about genetic risk from one group of people with recent shared ancestry often do not generalize to others (*15*).

Given these limitations of the samples, it is even more surprising—and should be motivating to human geneticists—how much interindividual variation is observed in gene expression among the people included in the GTEx Consortium. This should be a call to projects to expand the representation of human variation in future studies. ■

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SEISMOLOGY

Quiet Anthropocene, quiet Earth

Seismic noise levels that correlate with human activities fell when pandemic lockdown measures were imposed

By **Marine A. Denolle**[1] *and* **Tarje Nissen-Meyer**[2]

Our planet vibrates incessantly, sometimes with notable but more often with imperceptible intensity. Conventional seismology attempts to decipher vibrational sources and path effects by studying seismograms—records of vibrations measured with seismometers. In doing so, scientists seek either to understand the tectonic processes that lead to strong ground motions and earthquake failure (*1*) or to probe otherwise inaccessible planetary interiors (*2*). Progress in these areas of research typically has relied on the rare and geographically irregular occurrence of large earthquakes. However, anthropogenic (human) activities at Earth's surface also generate seismic waves that instruments can detect over great distances. On page 1338 of this issue, Lecocq *et al.* (*3*) report on a quieting of anthropogenic vibrations since the start of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic.

Seismology has benefited from a surge in seismic data volume, computational power, and corresponding methodological development. These advances have enabled seismologists to branch away from traditional source and subsurface characterization of the energy from earthquakes and human-made blasts. The expansion of seismic networks has allowed the observation of previously unseen natural processes as diverse as wildlife activity (*4*), bed load transport in rivers, glacier sliding (*5*), and surface-mass wasting (*6*). In particular, scientists use continuous, ambient seismic vibrations to probe volcanic activities (*7*) and groundwater resources (*8*), to track storms (*9*), and to decipher ice sheet processes (*10*).

Human cultural noise carries seismic signatures mostly at frequencies above 1 Hz, whether the source is transient (entertainment; individual cars, trains, or planes), harmonic (wind turbines, machinery), or diffuse (railroads, highways) (*11*, *12*) (see the figure). Overall, anthropogenic seismic noise levels have increased over the past few decades, and there is a clear positive correlation between this increase and gross domestic product (*13*). But when the SARS-CoV-2 pandemic began to ravage the planet, humans—and Earth—went quiet.

Through a global analysis of seismic noise levels, Lecocq *et al.* found that most sites experienced a drastic reduction in noise levels in the 4- to 14-Hz frequency band. This reduction was much greater than those observed during the annual noise-level cycles of national or religious holidays. Daily CO_2 emissions fell only 11 to 25% (*14*), whereas anthropogenic vibrations dropped by 75% in most countries that imposed lockdown measures. Among countries with the greatest noise reductions were China, Italy, and France—all densely populated places with strong government responses (that is, with high virus-containment indices) (*15*).

Lecocq *et al.* also detected a correlation between seismic data and new types of time series, such as urban audible sound from acoustics data and cell phone mobility data. The authors observed the greatest correlations between seismic noise levels and two common types of pandemic mitigation: surface transportation and nonessential business activities. Lecocq *et al.* did not detect a strong correlation between lockdown and seismic noise reduction at other frequency bands, which might be explained by certain uninterrupted human activities such as power generation (*14*).

For all its hardships, the lockdown has unlocked a door to scientific inquiry into environmental noise and global collaboration. At a fundamental level, low noise benefits traditional seismology, hence the recent noise decrease might open new windows of opportunity; study areas hindered by urban noise might now be targets for detecting microseismicity or for improved subsurface imaging. The crucial next step, as ever in seismology, is to determine the causative nature of these signals beyond their correlation—thus turning anthropogenic noise into informative signals that allow scientists to address new questions. For example: Is there feedback between anthropogenic vibrations and Earth processes? And will seismic monitoring of anthropogenic and environmental activities become complementary, economically valuable alternatives to conventional techniques? To achieve these advances, seismologists must develop new ways of processing data

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