

Variation in expression of thousands of genes kept under tight constraint in mice, humans

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A four-day-old mouse. Credit: Wikipedia/CC BY-SA 3.0

An international team of researchers led by Professor Thomas R. Gingeras of Cold Spring Harbor Laboratory (CSHL) and Roderic Guigo (Centre For Genomic Regulation, Barcelona) has identified some 6600 genes whose level of expression varies within a comparatively restricted range in humans and mice.

This constraint in expression, they found, is unrelated to the degree of similarity of their gene sequences. The 6600 [genes](#) represent about one-third of the total set of genes that are typically active in cells across tissues in both species, irrespective of cell type. The study, say the researchers, provides new information that will continue to assist in making the [mouse](#) an excellent model organism in which to study human diseases and biology.

"We found that evolution has placed remarkably narrow constraint on the expression levels of these 6600 genes, and we believe this reflects the importance of these particular genes for operation of all cells in all tissues in the two species," said Gingeras, who is the Head of Functional Genomics at CSHL. "What evolution is telling us is that these genes need to limit the variability of their expression irrespective of the cell type in which they are expressed—increased variation would be highly detrimental to basic cellular housekeeping. Cells need these genes to behave within a relatively narrow range in order to work properly."

The 6600 genes identified by the team have evolved in mice and people to show expression that varies over about a hundred-fold range, whether, for example, in breast tissue or lung tissue; whether in an epithelial cell or a nerve cell. This is compared to the remaining two-thirds of expressed genes, which are capable of varying their expression over a 100,000-fold range.

Gingeras and collaborators additionally found that when six very different animal species are compared, ranging from chickens to humans, there are still a set of 2500 genes they share in common whose expression is sharply constrained in the same narrow range. This shows that this regulatory mechanism is evolutionarily very old and thus important, the scientists say.

These results, published on [biorxiv.org](https://www.biorxiv.org), are part of a large body of

research reported in several scientific journals, representing the latest work of the Mouse ENCODE project. This international consortium, of which Gingeras is a principal investigator, also reports shared findings today in four papers in *Nature*. The work examines the genetic and biochemical programs involved in regulating mouse and human genomes.

At the same time, the consortium has found powerful clues to why certain processes and systems in the mouse - such as the immune system, metabolism and stress response - are so different from those in people. Building on years of mouse and gene regulation studies, they have developed a resource that can help scientists better understand how both the similarities and differences between mice and humans are written in their genomes.

The results, taken as a whole, may offer insights into gene regulation and other systems important to mammalian biology. They also provide new information to determine when and in what cell types and tissues the mouse is an appropriate model to study human biology and disease, and may help to explain some of its limitations. That, indeed, is among the implications of the work reported by Gingeras and colleagues in their new paper.

All of the newly published research results are from the mouse ENCODE project, which is an extension of the human ENCODE (ENCyclopedia Of DNA Elements) program. ENCODE is building a comprehensive catalog of functional elements in the human genome. Such elements include genes that code for proteins, non-protein-coding genes and regulatory elements that control which and when genes are turned on or off. ENCODE and mouseENCODE projects are supported by the National Human Genome Research Institute (NHGRI), part of National Institutes of Health (NIH).

"The mouse has long been a mainstay of biological research models," said NHGRI Director Eric Green, M.D., Ph.D. "These results provide a wealth of information about how the mouse genome works, and a foundation on which scientists can build to further understand both mouse and human biology. The collection of mouse ENCODE data is a tremendously useful resource for the research community."

More than a dozen related studies stemming from the MouseENCODE data also appear or will appear in journals such as *Genome Research*, *Genome Biology*, *Nature Communications*, and *Blood*.

More information: "Enhanced Transcriptome Maps from Multiple Mouse tissues Reveal Evolutionary Constraint in Gene Expression for Thousands of Genes" can be obtained at bioarxiv.org:

www.biorxiv.org/content/early/2014/10/30/010884

Provided by Cold Spring Harbor Laboratory

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