Single cell analysis captures a genomic phenomenon that fuels the complexity and diversity of living things

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A Ludwig Cancer Research study has uncovered a phenomenon that alters prevailing views of how the genome is expressed to make and sustain the life of mammals. Published in the journal *Science*, the paper helps explain why genetically identical animals are sometimes so different in their biology and appearance, and why some inherited disorders caused by a shared set of aberrant genes can be of such variable severity in different people.

"We have captured a fundamental randomness at the level of gene expression that has never before been described—one that persists throughout development and into adulthood," says Ludwig scientist Rickard Sandberg at the Karolinska Institutet in Sweden. The discovery was made possible by a powerful new technique developed by Sandberg's lab for analyzing the global expression of genes in single cells.

With the exception of a subset of genes found on sex chromosomes, every mammal inherits one copy of every gene from each of its parents. Each of those copies is known as an allele, and alleles often differ measurably from their genomic siblings—a fact that accounts for a good deal of human and animal diversity. It has, however, long been unclear whether each allele in any given cell or organism is expressed equally, or whether one allele is favored over the other. The current study finds that only one allele is expressed in between 12 and 24 percent of all such

pairs encoded by the mouse genome. Further, the selection of expressed alleles varies randomly from cell to cell, and switches frequently between the two options throughout their lives.

Biologists typically assume that most alleles, with a few exceptions, are equally expressed on all chromosomes except those that determine sex. They have long known, however, that "imprinted" genes—which may be modified to selectively express only one of the two alleles—are an exception. But such genes only account for 1 percent of the total. "We find that for those genes that are not imprinted, roughly one in five alleles is randomly and dynamically expressed only one at a time," says Sandberg. "And if one allele is being expressed, the other doesn't know about it. There's no coordination between two."

This explains in some measure why identical twins—products of nearly identical genomes—can be noticeably different from one another in their appearance and propensity for disease. Living things are, after all, built from cells, and each cell is in turn the product of the genes it expresses. Dynamic and random allelic expression can result in different blends of some traits, even in otherwise genetically identical people.

The finding also has significant implications for our understanding of some genetic diseases, such as neurofibromatosis, a painful disorder characterized by the systemic proliferation of non-cancerous neural tumors. It has long been a mystery why people who share the mutations that cause this family of diseases are so variably affected by it. The essential randomness of allelic expression might help account for those differences in this disease as well as in others.

More information: "Single-Cell RNA-Seq Reveals Dynamic, Random Monoallelic Gene Expression in Mammalian Cells" Science, 2014