

Gene activity in the brain depends on genetic background

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Researchers at the Allen Institute for Brain Science have found that the same genes have different activity patterns in the brain in individuals with different genetic backgrounds. These findings may help to explain individual differences in the effectiveness and side-effect profiles of therapeutic drugs and thus have implications for personalized medicine. The study is available in this week's online early edition of the *Proceedings of the National Academy of Sciences*.

In this study, the authors compared where in the [brain](#) each of 49 different pharmaceutically related [genes](#) is expressed, or turned on, in seven genetically distinct groups of mice with known genealogical relationships. By analyzing 203 distinct brain areas over 15,000 thin sections of tissue, they precisely mapped where these genes are active, down to the level of individual cells. The genes all encode molecular targets of well-known pharmaceuticals, such as antidepressants, antipsychotics and pain relievers including Prozac, Immitrex, and Aricept.

More than half of the genes examined showed striking, localized differences in expression patterns between the different genetic groups, or strains, of mice. For example, the dopamine D2 receptor gene—which encodes a target of action of Zyprexa, a drug used for schizophrenia and bipolar disorder—is active in a memory-related area called the entorhinal cortex in one strain of mice, but not in two others. Because different parts of the brain have different functions, variations in the localization of gene activity likely have functional implications.

"It is clear that to understand how genes translate to behavioral and other differences between individuals and species, we need to look beyond just the inherited sequences of the genes themselves," said Allan Jones, chief executive officer of the Allen Institute for Brain Science. "Our results show that genetic background—the specific blend of gene variants comprising an individual genome—can influence how the activity of a given gene is regulated and where it is expressed."

Taken all together, the data from the study demonstrate that closer genetic relatives exhibit fewer differences in gene expression patterns, whereas more distant relatives show greater variation. Interestingly, the researchers found that the expression variations between genetic strains were more likely to be found in areas of the brain that evolved more recently. These regions are most commonly linked to higher order functions such as cognition, social behavior, learning and memory.

"This study shows how large-scale datasets can be used to reveal fundamental biological patterns that would likely be missed otherwise," said Jones. "It is likely that many important differences between individuals and species may result from combinations of many small but clear differences in gene expression."

Jones added, "Our ongoing Allen Human Brain Atlas project, which will provide gene expression data across the brains of multiple donors, will help researchers translate these results from an animal model to a human system."

More information: JA Morris et al. "Divergent and nonuniform gene expression patterns in mouse brain," *PNAS*, published online October 18, 2010, [doi: 10.1073/pnas.1003732107](https://doi.org/10.1073/pnas.1003732107)

The data in this study are openly available to the public as the Mouse Diversity Study via the ALLEN Brain Atlas data portal at [www.brain-](http://www.brain-map.org)

map.org or directly at mousediversity.alleninstitute.org

Provided by Allen Institute for Brain Science

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