

# Gene Expression and Splicing Vary Widely from One Tissue to the Next

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(PhysOrg.com) -- Genes talk to themselves and to each other to control how a given cell manufactures proteins. But variation in the control of the same gene in two different tissues may contribute to certain human traits, including the likelihood of getting a disease, said a team of geneticists and neuroscientists at Duke University Medical Center.

Using a genome-wide screen to look for single-nucleotide changes, the researchers found that the expression of a given gene -- the amount of protein it is producing -- can vary widely. They also found that genetic variation leading to alternative splicing, a process that can create different proteins from the same gene, might in general be more relevant to disease than the effects of genetic variation on the general amount of gene expression.

The major conclusion is that researchers should look directly at brain tissue if they are studying neuropsychiatric diseases like epilepsy or Alzheimer's disease, for example, said senior author David Goldstein, PhD, professor of molecular genetics and microbiology and director of the Center for Human Genome Variation at Duke's Institute for Genome Sciences and Policy (IGSP).

"This is not something that has generally been done," Goldstein said.

"People have been looking at gene expression and splicing in blood cells, because these are easy to obtain and work with, yet they are trying to ask what the implications might be for diseases that do not affect the tissue they are studying."

The bottom line, he says, is "biology is more complicated than that. A genetic variant might influence the expression of a gene or the type of protein that is made because of splicing changes, in brain cells but not in blood cells, or in blood cells but not brain cells."

First author Erin Heinzen and the team investigated two tissues types -- blood and brain -- because they expected to find differences. The work was published in the Dec. 22 online version of *PLoS Biology*.

"I was surprised because I didn't expect the differences to be as dramatic as they were, between the tissues," Heinzen said.

The team used a genome-wide screen to look for single-nucleotide changes that associated with splicing and gene expression. Less than half of the single-unit changes showed effects in both tissue types, which provided strong evidence for distinct genetic control of splicing and expression in the two tissue types.

Heinzen said that she expects the findings of tissue specificity to apply to all types of tissue. "It really shows that we need to build up a very comprehensive picture of how genetic variation influences gene expression in specific tissues." The work needed could be a massive undertaking, she said.

The study also looked at genes associated with Type 1 diabetes, the form of the disease that in most cases begins in childhood. The scientists found that some of the Type 1 diabetes associations appear to be explained by the effect of single-nucleotide changes related to splicing. "What that suggests is that some of the disease changes have an underlying cause that has to do with splicing, but not the control of gene expression. It suggests that genetic control of splicing might in general be more relevant to disease than effects on expression."

While several groups of scientists have begun showing the ways that splicing is highly regulated in a tissue-specific manner, "our work showed that genetic variation influences that in a way that is relevant to disease."

Goldstein said this might mean that the overall amount of proteins a gene produces -- a gene's expression -- could change perhaps without having severe consequences. "However, if you change the forms of the proteins that a gene makes, more of this form of protein, less of this form, that matters more. That is what splicing variations do," he said.

Often scientists look at measures of the activity of a gene by the sheer quantity of protein that is produced. "This study focuses attention on looking at not just quantity, but also the quality -- the exact types of protein that are made by that gene," Goldstein said.

Overall, he said, the study findings will "reorient our attention toward what is happening in specific and relevant tissues. At the same time, we're looking at the way that genetic variation influences the types of proteins that are made, as opposed to just the abundance."

Provided by Duke University

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