Same gene, different results

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Courtesy MIT and World Science staff

Scientists are learning to their surprise that a single gene very often functions differently in different parts of the body.

Genes generally work by producing some molecule that serves a given function in the body. However, scientists have long known one gene can produce slightly different forms of the same molecule, by skipping or including certain alternative bits of genetic code.

The new research indicates this phenomenon, known as alternative splicing, is far more prevalent and varies more between tissues than previously believed. Nearly all human genes, about 94 percent, generate more than one form of their products, researchers reports in the Nov. 2 online edition of the research journal Nature.

“A decade ago, alternative splicing of a gene was considered unusual, exotic… it turns out that’s not true at all,” said Christopher Burge, senior author of the paper and a biologist at the Massachusetts Institute of Technology.

Burge and colleagues also found that in most cases the specific gene product depends on the tissue where the gene is expressed, or activated. The work paves the way for future studies into the role of alternative proteins in specific tissues, including cancer cells, he added.

Human genes typically contain several “exons,” or DNA sequences that code for amino acids, the building blocks of large molecules called proteins. A single gene can produce multiple sequences of amino acids, depending on which exons are included in the instructions that travel from the gene to a cell’s protein-building machinery.

Two different forms of the same protein, known as isoforms, can have different, even opposite functions. For example, one protein may activate pathways that induce cells to commit suicide when necessary. A close relative of the same protein may instead promote longer cell survival.

The researchers found that the type of isoform produced often depends strongly on the tissue. Certain protein isoforms that are common in the heart, for example, might be rare in the brain, so that the alternative exon functions like a molecular switch. Scientists who study splicing have a general idea of how tissue-specificity may be achieved, but much less understanding of why isoforms display such tissue specificity, Burge said.

One notable finding was that people’s brains often differ in their expression of alternative spliced mRNA isoforms, Burge and colleagues said. Isoform switching also occurs in cancer cells. One such switch involves a metabolic enzyme and contributes to cancer cells burning large amounts of sugar and growing more rapidly. Learning more about such switches could lead to potential cancer therapies, Burge said.