MedicalXpress

Multiple 'siblings' from every gene: Alternate gene reading leads to alternate gene products

July 11 2011

A genome-wide survey by researchers at The Wistar Institute shows how our cells create alternate versions of mRNA transcripts by altering how they "read" DNA. Many genes are associated with multiple gene promoters, the researchers say, which is the predominant way multiple variants of a given gene, for example, can be made with the same genetic instructions.

Their findings, which appear in the journal Genome Research, available online now, show how genes are read in developing and adult brains, and identify the changes in reading DNA that accompany brain development. Changes in how the cell reads the DNA create multiple RNA variants, which can lead to alternative forms of proteins (called isoforms). The Wistar researchers discovered numerous novel gene products, many of which are alternatively used during brain development. They found that genes linked to neurological disorders produce many variants/isoforms in the brain and that the isoforms produced in medullablastoma, a highly malignant form of brain cancer, were different for some genes from the isoforms found in normal adult brains.

"If a given gene is associated with multiple promoters, it creates multiple ways for a gene to be read in different cell-types or developmental stages. Consequently, each gene can produce a bunch of alternative products, like siblings of a family, who might probably do different things at different times (developmental stages) or different places (cells)," said Ramana Davuluri, Ph.D., associate professor in the Molecular and Cellular Oncogenesis Program at Wistar, and co-director

of Wistar's Center for Systems and Computational Biology. "Think of two brothers – for example, one a high-speed jet airline pilot and the other a much slower-paced bus driver. They both shuttle people around in vehicles, but imagine the damage they could do if they switch jobs for the day."

For example, Davuluri and his colleagues found several genes in developing brains that produce two or more transcript isoforms,. For many of these genes, while one isoform is produced in higher doses, the other isoform is completely absent in early development. This behavior is exactly the opposite for these same two isoforms in mature, adult brains. In cells taken from medulloblastoma tumors, the researchers saw the ratio of these isoforms to be more similar to developing brains than those of normal adults, which may be one way the tumor cells can grow abnormally."

"It is also a conceptual shift that may have a profound affect on how we look at diseases," said Davuluri, who is also the Philadelphia Healthcare Trust Professor at Wistar. "Our findings could serve as a warning that we need to pay attention to specific protein isoforms when we link a gene to a disease--we could be producing drugs to attack the protein product of, say, an oncogene, only to actually target the wrong protein isoform."

According to Davuluri, their findings demonstrate that our cells produce majority of alternative isoforms mainly by changing how they decide to start and end reading a gene at the outset. That is, different promoters tell the cell what version of a given gene to be read, and isoforms are not predominantly created through alternative splicing, as is largely thought to be the case in the scientific literature.

The Wistar researchers are able to make these complex associations through massive parallel (NextGen) sequencing, a technology that allows scientists to understand the content of DNA and how it operates. Vast

databases created with the sequencing data of multiple cells and cell types allowed the researchers to view the sum total of the mammalian genome (all of the genes contained in our DNA) and view them in the context of all the other "omes" that interact with our DNA. These include the transcriptome (the RNA molecules transcribed from DNA, which includes transcripts that encode proteins and those with other purposes); the promoterome (the known "gene promoter" sites within DNA); and the epigenome (how DNA-wrapping proteins can be altered to influence how the cell can access and read specific genes).

"Using genomics data generated by our laboratory and combining that with previously-published data, we were able to connect some otherwise unforeseeable dots," Davuluri said. "We no longer understand the workflow of our genes as simply one gene to one RNA to one protein, but as something much more complex."

Provided by The Wistar Institute