Unravelling new complexity in the genome

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A major surprise emerging from genome sequencing projects is that humans have a comparable number of protein-coding genes as significantly less complex organisms such as the minute nematode worm Caenorhabditis elegans. Clearly something other than gene count is behind the genetic differences between simpler and more complex life forms.

Increased functional and cellular complexity can be explained, in large part, by how genes and the products of genes are regulated. A University of Toronto-led study published in the latest issue of *Genome Biology* reveals that a step in gene expression (referred to as alternative splicing) is more highly regulated in a cell and tissue-specific manner than previously appreciated and much of this additional regulation occurs in the nervous system. The alternative splicing step allows a single gene to specify multiple protein products by processing the RNA transcripts made from genes (which are translated to make protein).

“We are finding that a significant number of genes operating in the same biological processes and pathways are regulated by alternative splicing differently in nervous system tissues compared to other mammalian tissues,” says lead investigator Professor Benjamin Blencowe of the Banting and Best Department of Medical Research and Centre for Cellular and Biomolecular Research (CCBR) at the University of Toronto

According to Blencowe, it is particularly interesting that many of the genes have important and specific functions in the nervous system,

including roles associated with memory and learning. However, in most cases the investigators working on these genes were not aware that their favorite genes are regulated at the level of splicing. Blencowe believes that the data his group has generated provides a valuable basis for understanding molecular mechanisms by which genes can function differently in different parts of the body.

Blencowe attributes these new findings in part to the power of a new tool that he, together with his colleagues including Profs. Brendan Frey (Department of Electrical and Computer Engineering) and Timothy Hughes (Banting and Best, CCBR), developed a few years ago. This tool, which comprises tailored designed microarrays or “gene chips” and computer algorithms, allows the simultaneous measurement of thousands of alternative splicing events in cells and tissues. “Until recently researchers studied splicing regulation on a gene by gene basis. Now we can obtain a picture of what is happening on a global scale, which provides a fascinating new perspective on how genes are regulated,” Blencowe explains.

A challenge now is to figure out how the alternative splicing process is regulated in a cell and tissue-specific manner. In their new paper in Genome Biology, Dr. Yoseph Barash, a postdoctoral fellow working jointly with Blencowe and Frey, has provided what is likely part of the answer. By applying computational methods to the gene chip data generated by Matthew Fagnani (an MSc student) and other members of the Blencowe lab, Barash has uncovered what appears to be part of a “regulatory code” that controls alternative splicing patterns in the brain.

One outcome of these new studies is that the alternative splicing process appears to provide a largely separate layer of gene regulation that works in parallel with other important steps in gene regulation. “The number of genes and coordinated regulatory events involved in specifying cell and tissue type characteristics appear to be considerably more extensive than

appreciated in previous studies," says Blencowe. "These findings also have implications for understanding human diseases such as cancers, since we can anticipate a more extensive role for altered regulation of splicing events that similarly went unnoticed due to the lack of the appropriate technology allowing their detection."

Source: University of Toronto