



'Ome Run: Mapping Brain Transcripts, Cells, and Processes

16 October 2008. In the dark ages—before thousands of fluorescent microarray spots lit the way—researchers had to painstakingly measure transcriptional changes one gene at a time. Now a single chip can profile thousands of genes. Out of this comes a list of transcripts that go up, down, or stay the same. But how does the list relate to biology? One approach to sorting out this type of data appears in the October 12 Nature Neuroscience online. Researchers led by Dan Geschwind and Steve Horvath at the University of California, Los Angeles, report a whole-transcriptome approach that identifies gene expression networks or patterns. Applying the analysis to whole brain samples, they have been able to tease out gene modules that correspond to specific functions or cell types, giving the researchers perhaps the first comprehensive view of transcriptional organization in the brain. And because the modules are related to structure and function, the approach has the potential to extract real meaning from pathology-driven transcriptional changes, such as those that might occur in Alzheimer disease. “With a comparative network analysis, you can look at the Alzheimer’s brain and ask how the network is perturbed. Then, rather than getting a simple laundry list of genes, it would show you the underlying biological processes that are deranged,” said Geschwind.

Earlier this year Geschwind’s lab reported that their modular approach detects differential expression between AD and control samples (see [ARF related news story](#)). The current paper goes further, showing that in normal samples there is a profound organization to the brain transcriptome. First author Mike Oldham and colleagues used microarrays to measure transcript levels in samples of tissue from human brain. They used weighted genome coexpression network analysis (WGCNA), a statistical approach developed at Horvath’s lab, to identify genes that are co-regulated. From one data set (samples of human cortex taken from 67 persons), they identified 19 coexpression modules. Comparing across data sets, they found many of the same modules in a second set of cortex samples, in samples of caudate nucleus, and in cerebellum samples, suggesting that the coexpression relationships are preserved across different brain regions. Six modules were identified in all four sample sets, five in three sets, and six in two. “What we have done is provide a map that describes the organization of the transcriptome within specific brain regions,” said Oldham.

What does this tell us about the regulation of transcription in the brain? “This means that there are consistent underlying sources of variation in microarray data that are generated from whole tissue samples from specific human brain regions,” said Oldham. The question, then, is what contributes to that consistency and that variation. To address this, the authors looked at properties of the modules themselves and the genes they contain. Several of the genes in module M9, for example, are involved in myelination, while genes in M15 include astrocytic genes involved in glutamate transport. The data suggest that the modules relate to structure and function. Comparing module content with gene expression data from purified cell populations, the researchers found distinct modules highly enriched for markers of oligodendrocytes, astrocytes, and neurons. Given those correlations, the work suggests that valuable transcriptome information on individual cell types can be obtained from whole tissue analysis. “Conventional wisdom has said that you lose information about cellular specificity when you generate microarray data from these kinds of tissue samples. But we are showing that a lot of these genes that are coexpressed in fact map back to specific cell types in the brain,” said Oldham.

This approach has two major applications, Oldham suggested. First, it provides a new means for annotating gene function, including the vast number of genes for which little is known. A case in point is C11ORF9, an open reading frame on chromosome 11. Oldham and colleagues found that this gene is consistently coexpressed with canonical oligodendrocyte genes in multiple brain regions. “This is telling you that that gene is probably going to be important for oligodendrocyte function,”

said Oldham. The authors also used this “guilt-by-association” argument to obtain some new insights into adult neurogenesis. They found one module from analysis of the head of the caudate nucleus that contains markers of both astrocytes and immature neurons. The caudate nucleus contains the subventricular zone (SVZ), a site of neurogenesis, and the researchers found that 10 of the strongest members of the module were preferentially expressed there. In contrast, *ALDH1L1*, recently identified as a specific marker of astrocytes, is robustly expressed in the parenchyma but not the SVZ, and neither is it a member of the neurogenic module.

The second major application is in comparative analysis, such as between disease and control samples. “We have effectively introduced a new quantitative basis for comparing gene expression with disease states using what we call differential network analysis,” said Oldham. Geschwind suggested that this approach could help researchers get a better handle on the underlying pathology in Alzheimer and other diseases. “A differential analysis may show 500 or 1,000 transcripts that are altered in the hippocampus of AD samples. But how do you tell what’s important, what are the most central genes and what are the peripheral ones?” he said. This type of analysis could help because each gene can be scored with a “membership” value that predicts how important that gene is to the module. “This approach allows you to move much more rapidly from whole genome expression analysis to hypothesis generation,” said Geschwind.

One potential caveat to this type of analysis is that genes in different cell types could be coordinately expressed, which could potentially lead to spurious assignment of genes to cell types. Geschwind actually see this type of crosstalk as a plus. “You could pick up co-regulation, but if you have enough data I believe it is likely that you will get to the level of the individual cell,” he said. In fact, he thinks modules that link different cells together may be some of the most informative. “Not every module is going to correspond to a cell. Some may correspond to an entire process occurring in a circuit of cells, or to interplay between neurons and glia at the synapse. In fact, in my mind those would be some of the most exciting modules,” he said.—Tom Fagan.

Reference:

Oldham MC, Konopka G, Iwamoto K, Langfelder P, Kato T, Horvath S, Geschwind DH. Functional organization of the transcriptome in human brain. *Nature Neuroscience* 2008, October 12 advanced online publication. [Abstract](#)