What makes us unique? Not genes so much as surrounding sequences

March 18 2010

The key to human individuality may lie not in our genes, but in the sequences that surround and control them, according to new research by scientists at the Stanford University School of Medicine and Yale University. The interaction of those sequences with a class of key proteins, called transcription factors, can vary significantly between two people and are likely to affect our appearance, our development and even our predisposition to certain diseases, the study found.

The discovery suggests that researchers focusing exclusively on genes to learn what makes people different from one another have been looking in the wrong place.

"We are rapidly entering a time when nearly anyone can have his or her

genome sequenced," said Michael Snyder, PhD, professor and chair of genetics at Stanford. "However, the bulk of the differences among individuals are not found in the genes themselves, but in regions we know relatively little about. Now we see that these differences profoundly impact protein binding and gene expression."

Snyder is the senior author of two papers — one in *Science Express* and one in *Nature* — exploring these protein-binding differences in humans, chimpanzees and yeast. Snyder, the Stanford W. Ascherman, MD, FACS, Professor in Genetics, came to Stanford in July 2009 from Yale, where much of the work was conducted.

Genes, which carry the specific instructions necessary to make proteins do the work of the cell, vary by only about 0.025 percent across all humans. Scientists have spent decades trying to understand how these tiny differences affect who we are and what we become. In contrast, non-coding regions of the genome, which account for approximately 98 percent of our DNA, vary in their sequence by about 1 to 4 percent. But until recently, scientists had little, if any, idea what these regions do and how they contribute to the "special sauce" that makes me, me, and you, you.

Now Snyder and his colleagues have found that the unique, specific changes among individuals in the sequence of DNA affect the ability of "control proteins" called transcription factors to bind to the regions that control gene expression. As a result, the subsequent expression of nearby genes can vary significantly.

"People have done a lot of work over the years to characterize differences in gene expression among individuals," said Snyder. "We're the first to look at differences in transcription-factor binding from person to person." What's more, by selectively breeding, or crossing, yeast strains, Snyder and his colleagues found that many, but not all, of

these differences in binding and expression levels are heritable.

In the Science Express paper, which will be published online March 18, Snyder and his colleagues compared the binding patterns of two transcription factors in 10 people and one chimpanzee. They identified more than 15,000 binding sites across the genome for the transcription factor called NF-kB and more than 19,000 sites for another factor called RNA PolII. They then looked to see if every site was bound equally strongly by the proteins, or if there were variations among individuals.

They found that about 25 percent of the PolII sites and 7.5 percent of the NF-kB sites exhibited significant binding differences among individuals — in some cases greater than two orders of magnitude from one person to another. (For comparison, the binding differences between the humans and the chimpanzee were about 32 percent.) Many of these binding differences could be traced to differences in sequences or structure in the protein binding sites, and several were directly correlated to changes in gene expression levels.

"These binding regions, or chunks, vary among individuals," said Snyder, "and they have a profound impact on gene expression." In particular, the researchers found that several of the variable binding regions were near genes involved in such diseases as type-1 diabetes, lupus, leukemia and schizophrenia.

The researchers confirmed and extended their findings in the Nature paper, which will be published online March 17. In this study, they used yeast to determine that many of the binding differences and variations in gene expression levels in individuals are passed from parent to progeny, and they identify several control proteins that vary — a study that would have been impossible to perform in humans.

"We conducted the two studies in parallel," said Snyder, "and found the

same thing. Many of the binding sites differed. When we mapped the areas of difference, we found that they were associated with key regulators of variation in the population. Together these two studies tell us a lot about the so-called regulatory code that controls variation among individuals."

More information:

* Kasowski, M., Grubert, F., Heffelfinger, C., Hariharan, M., Asabere, A., Waszak, S., Habegger, L., Rozowsky, J., Shi, M., Urban, A., Hong, M., Karczewski, K., Huber, W., Weissman, S., Gerstein, M., Korbel, J., Snyder, M., “Variation in Transcription Factor Binding Among Humans”, *Science*, published online 18 *March 2010. Zheng, W., Zhao, H., Mancera, E., Steinmetz, L., Snyder, M., “Genetic Analysis of Variation in Transcription Factor Binding in Yeast”, *Nature*, published online 17 March 2010.

Provided by Stanford University