# Gene regulation, not just genes, is what sets humans apart

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The striking differences between humans and chimps aren't so much in the genes we have, which are 99 percent the same, but in the way those genes are used, according to new research from a Duke University team.

It's rather like the same set of notes being played in very different ways.

In two major traits that set humans apart from chimps and other primates – those involving brains and diet – gene regulation, the complex cross-talk that governs when genes are turned on and off, appears to be significantly different.

"Positive selection, the process by which genetic changes that aid survival and reproduction spread throughout a species, has targeted the regulation of many genes known to be involved in the brain and nervous system and in nutrition," said Ralph Haygood, a post-doctoral fellow in the laboratory of Duke biology professor Gregory Wray.

Haygood is lead author in a report on the research to be published online on Sunday, Aug. 12, in the research journal *Nature Genetics*.

His group looked at the regulatory sequences immediately adjacent to 6,280 genes on the DNA of chimps, humans and the rhesus macaque, a more distant primate relative that has 88 percent the same genes as humans. These regulatory stretches of DNA are where proteins bind to the genome to initiate a gene's function. And it is here that evolution has apparently fine-tuned the performance of genes, Wray said, resulting in

the dramatic differences in the human brain.

Though many studies have looked for significant differences in the coding regions of genes relating to neural system development and failed to find any, the Duke team believes this is the first study to take a genome-wide look at the evolution of regulatory sequences in different organisms.

Other studies have found significant differences between these species in the coding regions that govern the immune system, the sense of smell and the manufacture of sperm, but the coding regions of neural-related genes had shown very little sign of positive selection in these studies. Yet, as far back as 1975 when Mary-Claire King and Allan Wilson first said humans and chimps were 99 percent the same genetically, they had offered the suggestion that greater differences might be found in the regulatory regions.

The type of analysis performed by the Duke team couldn't be done until the macaque genome was published in 2005 because they needed a third, closely related relative to compare the regulatory sequences.

The mouse genome had been used as a reference point for comparing the coding sequences of humans and chimps, but the non-coding sequences have generally evolved much faster. "Mice wouldn't work for analyzing the non-coding sequences, because they're too different from humans and chimps," Haygood said.

While the biochemistry that cells use to turn food into energy is essentially the same across most animal species, the fine-tuning of how an organism deals with the different sorts of sugars and complex carbohydrates in its diet lies in the regulatory sequences, Wray said.

Chimps are fruit-eaters, for the most part, and would not last long away

from their fruit-rich forest. The sugars in their diet are relatively simple to break down and convert to cellular fuel. Humans, on the other hand, eat a wider array of foods, including many the chimps would simply not be able to digest like starchy root crops. The researchers found dramatic differences in the regulatory regions of their genes for breaking down more complex carbohydrates. It may be that parts of the human metabolism are cranked up to digest carbs down to simpler sugars.

“Regulatory changes have adapted to changing circumstances without changing the essential chemistry of metabolism,” Wray said. “This may set the stage for a more focused analysis of the human diet.”

Much is being written and hypothesized about how dietary changes have contributed to the current human pandemics of obesity and diabetes, and perhaps there will be some insights from understanding how these regulatory sequences have evolved, he said.

To do a genome-wide analysis of regulatory regions, Haygood and post-doctoral fellow Olivier Fedrigo had to adapt some of the statistical tools used for genome-wide analysis of coding regions. To be sure their results would be robust, they focused on just the most reliably accurate published DNA sequences in common between the three animals, discarding two-thirds of the genome to ensure accuracy. “With only three species, we had to be very stringent about quality,” Fedrigo said.

The researchers don’t think these findings will be of any help resolving questions about how and when the ancestors of humans and chimps diverged on the tree of life, but it’s safe to say that “most of this is ancient history,” Wray said.

Source: Duke University