Gene enhancer in evolution of human opposable thumb

September 4 2008

Scientists have discovered a gene enhancer, known as HACNS1, that may have contributed to the evolution of the uniquely opposable human thumb, and possibly also modifications in the ankle or foot that allow humans to walk on two legs, according to a paper published in *Science* on Sept. 5, 2008.

This study is the first to provide evidence of the existence of human-specific gene enhancers, which are switches near genes in the human genome.

Dr. Shyam Prabhakar, first author of the paper and Senior Research Scientist at the Genome Institute of Singapore (GIS), said, "Opposable thumbs, manual dexterity and ankle or foot adaptations for walking on two legs are hallmarks of our species. We think we may have discovered one of the pieces of the genome that encodes some of these definitive human traits.

"This is just the first step – we need to characterize HACNS1 in more detail, and also test the hundreds of other HACNSs we have identified in the genome to figure out what role, if any, they play in making us human," he added.

The opposability of the human thumb is its unique ability to swing toward the palm and oppose the other four fingers to provide a tighter and more precise grip on objects.

The surprising complexity and abundance of enhancers, which turn on genes in the appropriate cells, have only recently been appreciated. Evolutionary changes in the DNA sequence of enhancers are thought to have triggered changes in human development that make us different from chimpanzees and other apes. Thus, the many observable differences between humans and chimpanzees, such as brain size, hair density, tooth patterns, pelvic structure and hand and foot modifications, could have arisen partly through changes in the way developmental genes are turned on.

The discovery provides significant insights into the genetic differences between humans and chimpanzees – the species that is approximately 99 percent similar to humans in terms of genetic composition. Apart from the obvious evolutionary interest, a more practical goal of such research is a more complete molecular understanding of the human body, leading eventually to a better understanding of human diseases and their treatments.

On a hunt for enhancers that could make us human, the authors of this study zoomed in on a genomic region they termed human-accelerated conserved non-coding sequence 1 (HACNS1).

HACNS1 showed statistical signatures of being an enhancer, and also had the most surprising amount of sequence change during human evolution of all the 110,000 such sequences identified in the human genome – it was by far the most striking candidate.

Remarkably, HACNS1 was found to play a unique human-specific gene-activating role in a region of the developing limb that eventually forms the junction of the wrist and thumb, and also extends partially into the developing thumb. A similar, though weaker activating role was also observed in the corresponding ankle/foot-forming regions of the developing hind limbs.

Highlighting the practical long-term goal of their joint project, Dr. James P. Noonan, last author and Assistant Professor at Yale University, pointed out, "Insights into human diseases and their treatments are often obtained through studies in non-human 'model organisms' such as mice. However, many human diseases are not reproducible in mice, and some diseases such as Alzheimer's and HIV/AIDS are not even known to exist in chimpanzees, our closest 'relatives'. Moreover, even if a disease is observable in a model organism, inter-species differences often cause treatments that appear to work when tested on, say, lab mice, to fail at the stage of human clinical trials. It is therefore imperative for human medicine that we fill in the gaps between our species and others by comprehensively characterizing human-specific genomic sequences and molecular processes. For this reason, it is important that we understand, at a molecular level, what it means to be human."

Principal Investigator at Singapore's Institute of Molecular and Cell Biology (IMCB), Associate Professor Venkatesh Byrappa added, "This is an elegant demonstration that changes in the gene regulatory region have actually led to a novel function unique to humans. These changes might be associated with morphological innovations that distinguish humans from other primates."

Source: Agency for Science, Technology and Research (A*STAR), Singapore