UC San Diego Health

UCSD Researcher Cites Human/Chimpanzee Genetic Differences That Offer Clues to Human Diseases

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The recently published Chimp Genome Sequencing project highlights the similarities between humans and our closest genetic cousins, the great apes. But a researcher at the University of California, San Diego (UCSD) suggests it is in the differences, rather than the similarities, that clues to understanding human disease might be found.

Two upcoming papers co-authored by Ajit Varki, M.D., Professor of Medicine at UCSD, describe genetic differences between the species: one, the discovery of the first human-specific protein that is also expressed in brain cells associated with human brain diseases; the second, a single oxygen atom difference that makes humans and chimpanzees resistant to each other's malarial parasites.

This research provides examples of how studying the evolution of humans and apes from a common ancestor may yield clues to explaining human and chimpanzee diseases. "Chimpanzees have long been thought of as a model for studying human diseases" said Varki. "In fact, what is most remarkable is that many of our diseases are rather different, either in incidence or in severity. Focusing on understanding these differences will eventually benefit both humans and chimpanzees".

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The First Known Human-specific Gene is Expressed in the Human Brain

Varki and colleagues at UCSD's Glycobiology Research and Training Center detail their finding of the first truly human-specific protein in the September 9 issue of *Science*.

Siglecs are molecules that serve as binding receptors for sialic acids, which are sugars found on the surface of all higher animal cells. Comparing human and chimpanzee genome sequences, the researchers noted that a human gene they had recently discovered called Siglec-11, was actually human-specific. The gene was generated by a mechanism called "gene conversion" that occurred in the human lineage sometime after our common ancestor with chimpanzees.

Nissi Varki, a professor of pathology at UCSD, found that while the protein encoded by the gene was expressed in human brain cells called microglia, it was not expressed in the brains of chimpanzees and other apes. "What's interesting is that microglia are also involved in Alzheimer's disease, multiple sclerosis and HIV-induced dementia, conditions that have so far not been reported in chimpanzees" said Varki, adding "This study raises more interesting questions than answers."

By defining this human-specific genetic change, scientists may eventually better understand such neurological disorders, and possibly why humans' brains are different from those of apes. The next step for the Varkis and their team is to explore the functional consequences and the mechanisms of brain expression. Causing Siglec-11 to be expressed in a mouse brains might help. "Meanwhile, another scientist might find a person with a neurological disease, and discover that patient has a genetic mutation of Siglec-11, helping us understand the functions of this gene in the normal human brain," he said.

A Single Oxygen Atom can Explain Differences in Human-Chimpanzee Malaria Susceptibility

It has long been known that chimpanzees don't get sick from the human malaria parasite *Plasmodium falciparum*, nor are humans infected with the malarial species that affects chimpanzees, called *Plasmodium reichenowi.* But until now, the reason for this surprising difference has been a mystery.

Just as humans and chimps have been shown to be very close genetic cousins, the two malaria parasites are genetically very similar. It is these two seemingly coincidental, but surprising, similarities that piqued the interest of Varki, and UCSD colleague Pascal Gagneux, Ph.D., a scientist in the Department of Cellular and Molecular Medicine who is also affiliated with the Zoological Society of San Diego,

A paper to be published in the September 6 issue of *Proceedings of the National Academy of Sciences (PNAS)* and currently on line at) They have now found that this difference of a single oxygen atom on sialic acids can shed light on the puzzling discrepancy in malaria susceptibility between the two species.

To find the difference between the two malarial parasites, the researchers focused on how each invaded their target red blood cells. Both *Plasmodium* species uses molecular "hooks" on their surfaces to latch onto the sialic acids on the red blood cell.

The researchers detected differences in the red cell binding capabilities between the two malaria species that could be explained by the differences in sialic acids. Thus, they argue that in the course of evolution, humans first became resistant to the malaria parasite infecting great apes by loss of the target molecule Neu5Gc. However, in the bargain they gained an excess of another

sialic acid called Neu5Ac, eventually facilitating the evolution of *P. falciparum*, a parasite that now causes more than 1.5 million deaths a year in humans.

Ajit Varki, M.D., is director of the Glycobiology Research and Training Center, Professor of Medicine and Cellular and Molecular Medicine, and associate dean for physician-scientist training at UCSD. He is an expert in Glycobiology, the study of glycans, cell-surface sugar chains attached to proteins and lipids, which have multiple roles in the development, organization and function of all organisms. Glycans have recently been found to be at the root of a growing list of human genetic disorders and infectious diseases. His studies in this field have led to his exploring evolutionary differences between humans and apes and their impact on human diseases.

Varki and Gagneux are both members of UCSD's Project for Explaining the Origin of Humans (http://origins.ucsd.edu/). They are also co-authors of a paper on the ethics of great ape research, published in the September 1 issue of *Nature* (see press release at: http://ucsdnews.ucsd.edu/newsrel/general/EthicsCaptiveApes.asp) Varki also co-authored a paper with Edwin H. McConkey of the University of Colorado, "Thoughts on the Future of Great Ape Research," published in the September 2 issue of *Science*. Here the researchers outline three reasons for substantially increasing such research in an ethically acceptable fashion: to understand the contribution of genomic DNA to the evolution of humans and apes; to improve our understanding of both species at all levels, from molecular to behavioral to states of diseases; and to help preserve populations of great apes.

In addition to Dr. Varki, contributors to the first *Science* article include Toshiyuki Hayakawa, Takashi Angata, and Amanda Lewis (all from UCSD) and Tarjei S. Mikkelsen, from the Broad Institute of the Massachusetts Institute of Technology and Harvard University. (Mikkelsen was also the first author of the Chimpanzee Genome Project, recently published in *Nature* magazine.)

In addition to Varki and Gagneux, contributors to the *PNAS* paper include Maria J. Martin at UCSD, Julian C. Rayner, Division of Geographic Medicine at the University of Alabama at Birmingham, and John W. Barnwell with the Division of Parasitic Diseases, Center for Disease Control and Prevention in Atlanta.

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