COMPARATIVE GENOMICS

Gene Expression Differs in Human and Chimp Brains

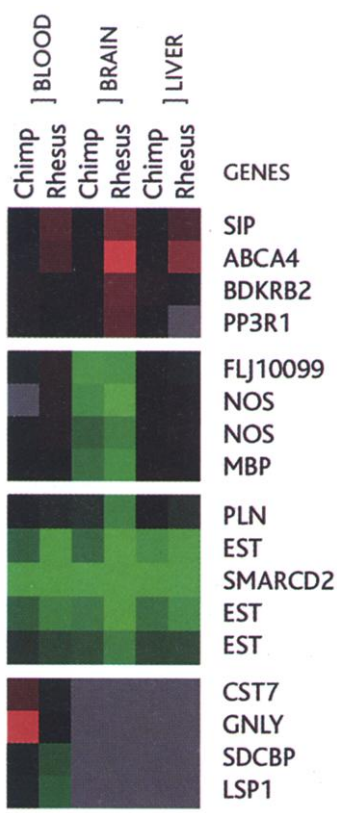
Greatly elevated levels of gene expression compared with chimpanzees and rhesus macaques could shed light on how our brains developed

TOKYO—Genetic variation may explain why humans differ from their primate cousins, but not in the way one might expect. Although the human genome differs only slightly—an estimated 1% to 2%—from those of the great apes, there are significant differences in how genes are expressed and regulated. New research suggests that those differences are most marked in the brain, a finding that offers possible clues to how humans developed their prodigious mental capacity.

"I'm not interested in what I share with the mouse; I'm interested in how I differ from our closest relatives, chimpanzees," says Svante Pääbo, a geneticist at the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany. Such comparisons, he argues, are the only way to understand "the genetic underpinnings of what makes humans human."

With the human genome virtually in hand, many researchers are now beginning to make those comparisons. At a meeting here last month,* Pääbo presented work by his team based on samples of three kinds of tissue—brain cortex, liver, and blood—from humans, chimps, and rhesus macaques. Pääbo and his colleagues pooled messenger RNA from individuals within each species to get rid of intraspecies variation and ran the samples through a microarray filter carrying 20,000 human cDNAs to determine the level of gene expression. The researchers identified 165 genes that showed significant differences between at least two of the three species, and in at least one type of tissue. The brain contained the greatest percentage of such genes, about 1.3%.

It also produced the clearest evidence of what may separate humans from other primates. Gene expression in liver and blood tissue is very similar in chimps and humans, and markedly different from that in rhesus macaques. But the picture is quite different for the cerebral cortex. "In the brain, the expression profiles of the chimps and macaques are actually more similar to each other than to humans," Pääbo said at the workshop. The analysis shows that the human brain has undergone three to four times the amount of change in genes and expression levels than the chimpanzee brain since the two split off from a common ancestor. "Among these three tissues, it seems that the brain is really special in that humans have accelerated patterns of gene activity," Pääbo says.

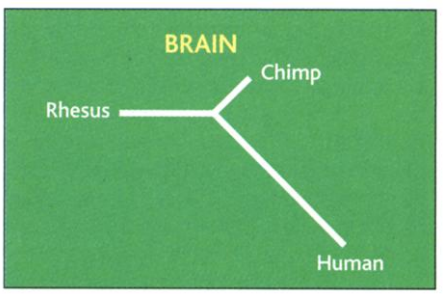


The color of thought? Green indicates that higher levels of gene expression were found in human brain tissue than in tissue from chimps and rhesus monkeys; red points to higher levels in chimps and monkeys. Black represents no difference, and gray areas were not measured.

The 200 workshop participants also heard about a biochemical difference that sets humans apart from our close cousins and, perhaps, influenced human brain development. "Beyond genomics and transcriptomics and proteomics, there is glycomics," says Ajit Varki, a glycobiologist at the University of California, San Diego (UCSD). Varki and his colleagues are looking at how the loss of an enzyme may have given humans an evolutionary advantage (*Science*, 23 March, p. 2340).

The enzyme makes one form of a family of cell surface sugars called sialic acids. The UCSD team found that all mammals except humans have on their cell surfaces two variants, known as *N*-acetylneuraminic acid (Neu5Ac) and *N*-glycolylneuraminic acid (Neu5Gc). The researchers traced the lack of Neu5Gc in humans to a small mutation in a gene that, in other mammals, codes for an enzyme called CMP-Neu5Ac hydroxylase. This hydroxylase catalyzes the conversion of CMP-Neu5Ac into CMP-Neu5Gc by adding an oxygen atom. Without it, humans have none of the Gc variant and an excess of Ac.

Luckily, the acids are well preserved in bones. And the group found that whereas modern ape bones have a mixture of Neu5Gc and Neu5Ac, Neandertal fossils—and modern human bones—primarily have Neu5Ac. So the gene inactivation "appears to predate the common ancestor of humans and Neandertals but postdates the common ancestor with the great apes," Varki says. Because Neu5Gc is a binding target for certain pathogens, Varki speculates that the loss of Neu5Gc in early humans may have strengthened their immunity to certain diseases.



Changes. Branch lengths show relative amount of change in gene expression in the brain.

The connection to the brain comes in because even in mammals where Neu5Gc is common in most tissue, it is nearly absent in the brain. It is, of course, entirely absent in the human brain. In what Varki emphasizes is "pure speculation," he posits that getting rid of Neu5Gc may somehow have fostered improvements in the brain. Naruya Saitou, an evolutionary geneticist at the National Institute of Genetics in Mishima, Japan, calls the theory "a very provocative idea … worth examination."

The next step is to look at the effect of eliminating or overexpressing Neu5Gc in knockout and transgenic mice. Varki's group has also been studying a family of lectins called siglecs (for sialic acid–binding immunoglobulin-like lectins) that offer further clues. Although their function is not completely understood, siglecs are found in a wide variety of cell types, and all have an arginine residue that is needed to bind sialic acids.

One of Varki's postdocs stumbled onto something in human cells that looked very much like a siglec, but it was missing the arginine residue indispensable for sialic acid recognition. A comparison with great apes

CREDITS: MAX PLANCK INSTITUTE FOR EVOLUTIONARY ANTHROPOLOGY

*Genes and Minds Initiative Workshop on Ape Genomics, Tokyo, 14–15 March.

found that the ape version, which they provisionally named siglec zz, had the arginine residue, and it prefers to bind Neu5Gc. A single base-pair mutation is responsible for the loss of this arginine residue in the human version of siglec zz. "It is hard to imagine that these two [genetic differences] in sialic acid biology are not evolutionarily connected," Varki says.

But which one came first, and when? Varki suggests that it is unlikely the genetic mutation occurred first in Neu5Gc, followed by a precise "surgical strike" that hit the siglec zz arginine residue and left the rest of the molecule intact. Instead, he believes the first mutation was probably the loss of the arginine residue on human siglec zz, and that reduced, but did not eliminate, Neu5Gc binding sites. This may have then set the stage for the subsequent mutation in the hydroxylase.

For Caro-Beth Stewart, a molecular anthropologist at the University at Albany in New York, the research raises the possibility that what humans lost during evolution might be just as important as what they gained. Maybe, she quips, "we're just apes with lost functions." **–DENNIS NORMILE**

SOLID-STATE PHYSICS

Nanotube 'Peapods' Show Electrifying Promise

Take a microscopic buckytube, stuff it with buckyballs, and what do you get? Just possibly room-temperature superconductivity

SEATTLE, WASHINGTON—Materials that lose their electrical resistance at a whisper above absolute zero are too common to grab much attention nowadays. But when a French and Russian team reported that carbon nanotubes perform this trick, other researchers at the March meeting of the American Physical Society took notice.

The transition temperature—a measly 0.55 kelvin—isn't likely to entice engineers to spin the tiny all-carbon cylinders into superconducting wires. But calculations show that nanotubes filled with other materials could do much better, perhaps even superconduct at room temperature.

"It's impressive work," says David Tomanek, a nanotube expert at Michigan State University in East Lansing. "This is the first direct evidence that nanotubes superconduct." That's important, he continues, because other teams have already shown that crystals of fullerenes—carbon spheres informally known as buckyballs—can superconduct at temperatures as high as 52 K. And theory suggests that lining fullerenes up in wirelike rows would raise the threshold dramatically. Researchers in Japan and elsewhere have aligned fullerenes by packing them inside nanotubes like peas in a pod. Electronic interactions between the tubes and the fullerenes could further boost the superconducting temperature of fullerene wires, Tomanek says. Now the race is on to see if these peapods will superconduct at a high temperature.

Detecting superconductivity in empty nanotubes has been tough. In 1999, a group led by Mathieu Kociak and Helene Bouchiat at the University of Paris-South in Orsay reported in *Science* (28 May 1999, p. 1508) that ropes of 100 or so nanotubes could carry supercurrent between two superconducting electrodes. In superconductors, electrons pair up and travel through conductors without any electrical losses. In this earlier study, the electrons traveled in pairs through the nanotubes, but poor contact with the electrodes caused electrical losses that kept the experiment from confirming that superconductivity was taking place.

To prove that the nanotubes were truly superconducting, the researchers had to show that the electron pairs were not due to superconductivity in the electrodes. Kociak and his colleagues at the French national research agency CNRS and the Russian Academy of Sciences in Chernogolovka started with an array of metal pads made from a nonsuperconducting sandwich of aluminum oxide, platinum, and gold. After placing a batch of nanotube ropes atop a wire mesh suspended above the array of metal pads, the researchers blasted the ropes with a brief laser pulse. That shook loose some of the ropes, which fell atop the contacts below, in certain cases creating a bridge between two electrodes.

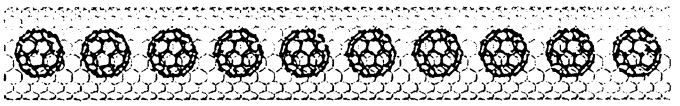
Then, using additional laser pulses, the researchers soldered the nanotubes to the metal pads to make clean electrical contact. Finally, they ran currents between selected metal pads to test the nanotubes' behavior.

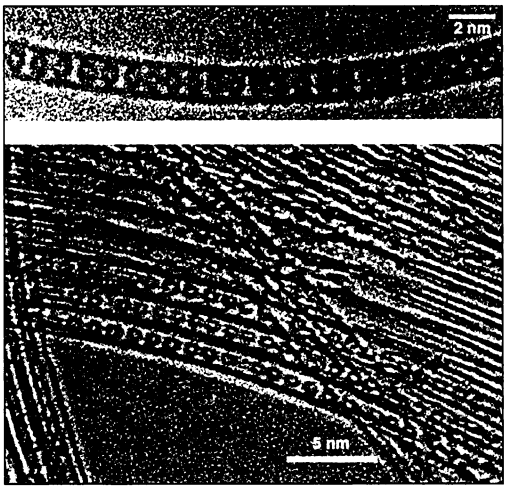
The painstaking work paid off: Measurements of both the electrical and magnetic behavior reported at the meeting and in the 12 March issue of *Physical Review Letters* show that the nanotube ropes were indeed superconducting.

Now the question is whether Kociak's team can pull off the same feat with nanotubes packed with fullerenes. The all-carbon spheres themselves became a big story in superconductivity last year when Bertram Batlogg and colleagues at Lucent Technologies' Bell Laboratories in Murray Hill, New Jersey, raised their superconducting temperature from about 9 K to 52 K by putting the spheres in the middle of a transistor. Turning on an electrical voltage between metals on either side of the transistors swiped electrons from the fullerenes in between. That opened up space for superconducting pairs of electrons in the material to hop around more easily, thereby raising the temperature at which it could superconduct.

According to Tomanek, theory suggests that placing the fullerenes in a wirelike arrangement could do even better: Lowering the number of immediate fullerene neighbors increases a quantum mechanical property known as the density of states—a situation favorable to a higher temperature superconductor.

"Fullerene peapods should give you room-temperature superconductivity," says Tomanek. However, he says, it could also lead to a type of magnetic behavior in the materials that would undermine superconductivity completely. The winner will likely be known in the next few months. **–ROBERT F. SERVICE**





Hot threads. Packing fullerene spheres into carbon nanotubes may boost their superconductivity threshold to high temperatures.

CREDITS: (TOP TO BOTTOM) JST AND NEC; D. LUZZI AND B. W. SMITH, *CARBON* **38**, 1751 (2000); B. BURTEAUX, D. LUZZI AND J. FISCHER, *CHEMICAL PHYSICS LETTERS* **310**, 21 (1999)