WHAT MAKES US DIFFERENT?

Not very much, when you look at our DNA. But those few tiny changes made all the difference in the world

By MICHAEL D. LEMONICK and ANDREA DORFMAN

YOU DON'T HAVE TO BE A BIOLUMINIST OR AN anthropologist to see how closely the great apes—gorillas, chimpanzees, bonobos and orangutans—resemble us. Even a child can see that their bodies are pretty much the same as ours, apart from some exaggerated proportions and extra body hair. Apes have dexterous hands much like ours but unlike those of any other creature. And, most striking of all, their faces are uncannily expressive, showing a range of emotions that are eerily familiar. That's why we delight in seeing chimps wearing tuxedos, playing the drums or riding bicycles. It's why a potbellied gorilla scratching itself in the zoo reminds us of Uncle Ralph or Cousin Vinnie—and why, in a more unsettled reaction, Queen Victoria, on seeing an orangutan named Jenny at the London Zoo in 1842, declared the beast "frightful and painfully and disagreeably human."

It isn't just a superficial resemblance. Chimps, especially, not only look like us, they also share with us some human-like behaviors. They make and use tools and teach those skills to their offspring. They prey on other animals and occasionally murder each other. They have complex social hierarchies and some aspects of what anthropologists consider culture. They can't form words, but they can learn to communicate via sign language and symbols and to perform complex cognitive tasks. Scientists figured out decades ago that chimps are our nearest evolutionary cousins, roughly 98% to 99% identical to humans.

Illustration for TIME by Tim O'Brien
at the genetic level. When it comes to DNA, a human is closer to a chimp than a mouse is to a rat.

Yet tiny differences, sprinkled throughout the genome, have made all the difference. Agriculture, language, art, music, technology and philosophy—all the achievements that make us profoundly different from chimpanzees and make a chimpanzee in a business suit seem so deeply ridiculous—are somehow encoded within minute fractions of our genetic code. Nobody yet knows precisely where they are or how they work, but somewhere in the nuclei of our cells are handfuls of amino acids, arranged in a specific order, that endow us with the brainpower to outthink and outdo our closest relatives on the tree of life. They give us the ability to speak and write and read, to compose symphonies, paint masterpieces and delve into the molecular biology that makes us what we are.

Until recently, there was no way to unravel these crucial differences. Exactly what gives us advantages like complex brains and the ability to walk upright—and certain disadvantages, including susceptibility to a particular type of malaria, AIDS and Alzheimer's, that don't seem to afflict chimps—remained a mystery.

But that's rapidly changing. Just a year ago, geneticists announced that they had sequenced a rough draft of the chimpanzee genome, allowing the first side-by-side comparisons of human and chimpanzee DNA. Already, that research has led to important discoveries about the development of the human brain over the past few million years and possibly about our ancestors' mating behavior as well.

And next month, in the next few weeks, a team led by molecular geneticist Svante Pääbo of the Max Planck Institute for Evolutionary Anthropology, in Leipzig, Germany, will announce an even more stunning achievement: the sequencing of a significant fraction of the genome of Neanderthals—the human-like species we picture when we hear the word cave-man—who are far closer to us genetically than chimps are. And though Neanderthals became extinct tens of thousands of years ago, Pääbo is convinced he's on the way to reconstructing the entire genome of that long-lost relative, using DNA extracted, against all odds, from a 38,000-year-old bone.

Like side by side, these three sets of genetic blueprints—plus the genomes of gorillas and other primates, which are already well on the way to being completely sequenced—will not only begin to explain precisely what makes us human but could lead to a better understanding of human diseases and how to treat them.

**FIRST GLIMMERINGS**

**SCIENTISTS DIDN'T NEED TO WAIT FOR THE CHIMP GENOME TO BEGIN SPECULATING ABOUT THE ESSENTIAL DIFFERENCES BETWEEN HUMANS AND APES, OF COURSE. THEY DIDN'T EVEN NEED TO KNOW ABOUT DNA. MUCH OF THE VITRIOL DIRECTED AT CHARLES DARWIN A CENTURY AND A HALF AGO CAME NOT FROM HIS IDEAS ABOUT EVOLUTION IN GENERAL BUT FROM HIS INSULTING BUT LOGICAL IMPLICATION THAT HUMANS AND THE AFRICAN APES ARE DESCENDED FROM A COMMON ANCESTOR.**

As paleontologists have accumulated more and more fossils, they have compiled data on a long list of anatomical features, including body shape, bipedalism, brain size, the shape of the skull and face, the size of canine teeth, and opposable thumbs. Using comparative analyses of these attributes, along with dating that shows when various features appeared or vanished, they have constructed increasingly elaborate family trees that show the relationships between apes, ancient hominids and us. Along the way they learned, among other things, that Darwin, even with next to no actual data, was closer to being right in his intuition that apes and humans are descended from a single common ancestor—and, surprisingly, that the ability to walk upright emerged millions of years before the evolution of our big brains.

But it wasn't until the 1960s that details of our physical relationship to the apes started to be understood at the level of basic biochemistry. Wayne State University scientist Morris Goodman showed, for example, that injecting a chicken with a particular blood protein from a human, a gorilla or a chimpanzee provoked a specific immune response, whereas proteins from orangutans and gibbons produced no response at all. And by 1975, the then new science of molecular genetics had led to a landmark paper by two University of California, Berkeley, scientists, Mary-Claire King and Allan Wilson, estimating that chimpanzees and humans share between 98% and 99% of their genetic material.

**ZEROING IN ON THE GENES**

**EVEN BEFORE THE CHIMP GENOME WAS PUBLISHED, RESEARCHERS HAD BEGUN TEASING OUT OUR GENETIC DIFFERENCES. AS LONG AS 1998, FOR EXAMPLE, GYCOBIOLOGIST AJIT VARKI AND COLLEAGUES AT THE UNIVERSITY OF California, San Diego, REPORTED THAT HUMANS HAVE AN ALTERED FORM OF A MOLECULE CALLED SIGNS ACCID ON THE SURFACE OF THEIR CELLS. THIS VARIANT IS CODED FOR BY A SINGLE GENE, WHICH IS DAMAGED IN HUMANS. Since SIALIC ACIDS ACT IN PART AS A DOCKING SITE FOR MANY PATHOGENS, SUCH AS MALARIA AND INFLUENZA, THIS MAY EXPLAIN WHY PEOPLE ARE MORE SUSCEPTIBLE TO THESE DISEASES THAN, SAY, CHIMPANZEE ARE.**

A few years later, a team led by Pääbo announced that the human version of a gene called **FOXP2**, which plays a role in our ability to develop speech and language, evolved within the past 200,000 years—after anatomically modern humans first appeared. By comparing the protein coded by the human FOXP2 gene with the same protein in various great apes and in mice, they discovered that the amino-acid sequence of the human variant differs from that of the chimpanzee in just two locations out of a total of 715—an extraordinarily small change that may nonetheless explain the emergence of all aspects of human speech, from a baby's first words to a Robin Williams monologue. And indeed, humans with a defective FOXP2 gene have trouble articulating words and understanding grammar.

Then, in 2004, a team led by Hansell Stedman of the University of Pennsylvania identified a tiny mutation in a gene on chromosome 7 that affects the production of myosin, the protein that enables muscle tissue to contract. The mutant gene prevents the expression of a myosin variant, known as **MYH16**, in the jaw muscles used in biting and chewing. Since the same mutation occurs in all of the modern human populations the researchers tested—but not in seven species of nonhuman primates, including chimps—the researchers suggest that lack of MYH16 made it possible for our ancestors to evolve smaller jaw.
Katrina, which hit the same week, the publication of a rough draft of the chimp genome in the journal *Nature* immediately told scientists several important things. First, they learned that overall, the sequences of base pairs that make up both species' genomes differ by 1.23%—a ringing confirmation of the 1970s estimates—and that the most striking divergence between them occurs, intriguingly, in the Y chromosome, present only in males. And when they compared the two species' proteins—the large molecules that cells construct according to blueprints embedded in the genes—they found that 29% of the proteins were identical (most of the proteins that aren't the same differ, on average, by only two amino-acid substitutions).

The genetic differences between chimps and humans, therefore, must be relatively subtle. And they can't all be due
simply to a slightly different mix of genes. Even before the human genome was sequenced back in 2000, says biologist Sean Carroll of the University of Wisconsin, Madison, "it was estimated that humans had 100,000 genes. When we got the genome, the estimate dropped to 25,000. Now we know the overall number is about 22,000, and it might even come down to 19,000."

This shockingly small number made it clear to scientists that genes alone don't dictate the differences between species; the changes, they now know, also depend on molecular switches that tell genes when and where to turn on and off. "Take the genes involved in creating the hand, the penis and the vertebrae," says Lovejoy. "These share some of the same structural genes. The pelvis is another example. Humans have a radically different pelvis from that of apes. It's like having the blueprints for two different brick houses. The bricks are the same, but the results are very different."

Those molecular switches lie in the noncoding regions of the genome—once known dismissively as junk DNA but lately rechristened the dark matter of the genome. Much of the genome's dark matter is, in fact, junk—the residue of evolutionary events long forgotten and no longer relevant. But a subset of the dark matter known as functional noncoding DNA, comprising some 3% to 4% of the genome and mostly embedded within and around the genes, is crucial. "Coding regions are much easier for us to study," says Carroll, whose new book, The Making of the Fittest: DNA and the Ultimate Forensic Record of Evolution, delves deep into the issue. "But it may be the dark matter that governs a lot of what we actually see."

What causes changes in both the dark matter and the genes themselves as one species evolves into another is random mutation, in which individual base pairs—the "letters" of the genetic alphabet—are flipped around like a typographical error. These changes stem from errors that occur during sexual reproduction, as DNA is copied and recombined. Sometimes long strings of letters are duplicated, creating multiple copies in the offspring. Sometimes they're deleted altogether or even picked up, turned around and reinserted backward. A group led by geneticist Stephen Scherer of the Hospital for Sick Children in Toronto has identified 1,576 apparent inversions between the chimp and human genomes; more than half occurred sometime during human evolution.
When an inversion, deletion or duplication occurs in an unused portion of the genome, nothing much changes—and indeed, the human, chimp and other genomes are full of such inert stretches of DNA. When it happens in a gene or in a functional noncoding stretch, by contrast, an inversion or a duplication is often harmful. But sometimes, purely by chance, the change gives the new organism some sort of advantage that enables it to produce more offspring, thus perpetuating the change in another generation.

WHAT THE APES CAN TEACH US
A STRIKING EXAMPLE OF HOW GENE DUPLICATION MAY HAVE helped propel us away from our ape-like origins appeared in Science last month. A research team led by James Sikela of the University of Colorado at Denver and Health Sciences Center, in Aurora, Colo., looked at a gene that is believed to code for a piece of protein, called DUF1290, found in areas of the brain associated with higher cognitive function. The gene comes in multiple copies in a wide range of primates—but, the scientists found, humans carry the most copies. African great apes have substantially fewer copies, and the number found in more distant kin—orangutans and Old World monkeys—drops off even more.

Another discovery, first published online by Nature two months ago, describes a gene that appears to play a role in human brain development. A team led by biostatistician Katherine Pollard, now at the University of California, Davis, and Sofie Salama, of U.C. Santa Cruz, used a sophisticated computer program to search the genomes of humans, chimps and other vertebrates for segments that have undergone changes at substantially accelerated rates. They eventually homed in on 49 discrete areas they dubbed human accelerated regions, or HARs.

The region that changed most dramatically from chimps to humans, known as HARI, turns out to be part of a gene that is active in fetal brain tissue only between the seventh and 19th weeks of gestation. Although the gene’s precise function is unknown, that happens to be the period when a protein called reelin helps the human cerebral cortex develop its characteristic six-layer structure. What makes the team’s research especially intriguing is that all but two of the HARs lie in those enigmatic functional noncoding regions of the genome, supporting the idea that much of the difference between species happens there.
of thousands of years. A discovery published online by Nature last month suggests Neanderthals may have made their last stand in Gibraltar, on the southern tip of the Iberian Peninsula, surviving until about 28,000 years ago—and possibly even longer.

The Neanderthals weren’t nearly as primitive as many assume, observes Eddy Rubin, director of the Department of Energy’s Joint Genome Institute in Walnut Creek, Calif. “They had fire, burial ceremonies, the rudiments of what we would call art. They were advanced—but nothing like what humans have done in the last 10,000 to 15,000 years.” We eventually outcompeted them, and the key to how we did so may well lie in our genes. So two years ago, Svante Pääbo, the man who deconstructed the FOXP2 language gene and has done considerable research on ancient DNA, launched an effort to re-create the Neanderthal genome. Rubin, meanwhile, is tackling the same task using a different technique.

The job isn’t an easy one. Like any complex organic molecule, DNA degrades over time, and bones that lie in the ground for thousands of years become badly contaminated with the DNA of bacteria and fungi. Anyone who handles the fossils can also leave human DNA behind. After probing the remains of about 60 different Neanderthals out of the 400 or so known, Pääbo and his team found only two with viable material. Moreover, he estimates, only about 6% of the genetic material his team extracts from the bones turns out to be Neanderthal DNA.

As a result, progress is maddeningly slow. And while he can’t reveal details, Pääbo says he’ll soon be announcing in a major scientific journal the sequencing of 1 million base pairs of the Neanderthal genome. And he says he has 4 million more in the bag. Rubin, meanwhile, is also poised to publish his results, but refuses to divulge specifics. “Pääbo’s team has significantly more of a sequence than we do,” he says. “Some of the dates will differ, but the conclusions are largely similar.”

Although Pääbo admits that he still hasn’t learned much about what distinguishes us from our closest cousins, simply showing how he can reconstruct significant DNA sequences from such long-dead creatures is an important proof of concept. Both he and Rubin agree that within a couple of years a reasonably complete Neanderthal genome should be available. “It will tell us about aspects of biology, like soft tissue, that we can’t say anything about right now,” Rubin notes. “It could tell us about disease susceptibility and immunity. And in places where the sequence overlaps that of humans, it will enable us to compare a prehistoric creature with chimps. Someday it may even be possible to insert equivalent segments of human and Neanderthal DNA into different laboratory mice in order to see what effects they produce.

**WHAT IT ALL MEANS**

In fact, even the most ardent proponents of genome-comparison research acknowledge that pretty much everything we know so far is preliminary. “We’re interested in traits that really distance us from other organisms,” says Wisconsin’s Carroll, “such as susceptibility to diseases, big brains, speech, walking upright, opposable thumbs. Based on the biology of other organisms, we have to believe that those are very complex traits. The development of form, the increase in brain size, took place over a long period of time, maybe 50,000 generations. It’s a pretty complicated genetic recipe.”

But even the toughest critics acknowledge that these studies have enormous potential. “We will eventually be able to pinpoint every difference between every animal on the planet,” says Lovejoy. “And every time you throw another genome, like the gorilla’s, into the mix, you increase the chances even more.”

Some of the differences could have enormous practical consequences. Since his discovery that human cells lack one specific form of sialic acid, which was accomplished even before the hu-

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**RESURRECTED**
Pääbo is decoding DNA extracted from the bones of Neanderthals that died tens of thousands of years ago.