NATURE|Vol 457|12 February 2009

THE OTHER STRAND

Geneticists looked to the human genome to understand human evolution. But it's hard to interpret without considering the inheritance of culture, finds **Erika Check Hayden**.

Darwin200

Barely a decade after Charles Darwin published *On the Origin of Species*, he and his long-time correspondent Alfred Russel Wallace were engaged in a fierce debate. Darwin said that natural selection had shaped the human species just like any other. But Wallace disagreed, arguing that selection alone could not account for the exceptional capabilities of the human mind. "How could natural selection, or survival of the fittest in the struggle for existence, at all favour the development of mental powers so entirely removed from the material necessities of savage men?," he wrote[1].

Wallace lost out. By the mid-twentieth century most scientists had agreed that human bodies and minds were the product of genes that had evolved under the pressures of natural selection, just like everything else in the living world. One of the exciting prospects of reading the human genome was that it would reveal the ways in which this had happened — the marks left by evolution as it shaped humans into a species with language, learning and all sorts of other traits peculiarly interesting to it. "The idea was that if we could just identify those few critical genetic differences, we could explain the differences in cognition and language," says Todd Preuss of the Yerkes National Primate Center at Emory University in Atlanta, Georgia.

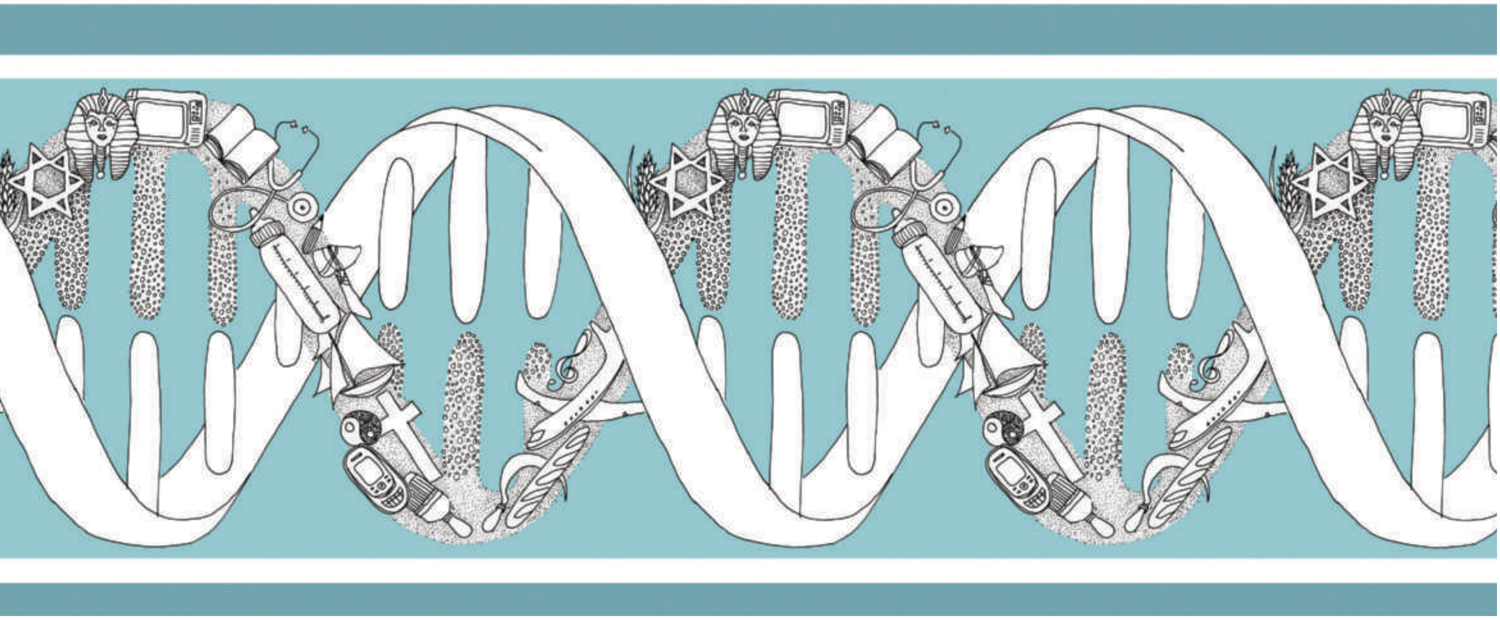
But today, nearly a decade after the human genome was sequenced, some geneticists are thinking again. Genomics has identified many sequences that are under selection, but it has not provided the simple read-out of human evolutionary history that some had hoped for. Scientists are having to rethink how genomes work, and are now pondering whether genes alone can explain the human animal. They don't think that human biology is incomplete without spirituality, as Wallace did. But they do wonder whether it is incomplete without culture. Because many complex skills and behaviours are being passed on through culture, some researchers are coming around to the view that the species has escaped the need to encode them rigidly in its genome. "Of course the mechanisms of selection are operating," says Ajit Varki, a specialist in human origins at the University of California, San Diego. But perhaps "we don't necessarily fix our behaviours, and we are letting some previously fixed behaviours deteriorate, because we can rely on cultural transmission", he adds.

These ideas are not entirely new. In 1981, geneticists Marcus Feldman and Luca Cavalli-Sforza from Stanford University in California published models to show how human behaviour results from the interaction of biological and cultural evolution. What is new for genome scientists is the realization that they will not be able to interpret the evolutionary marks they have found in the human genome without considering behaviour and environment every step of the way.

Being human

The human species has a unique set of features, including a large brain in proportion to the rest of the body; the ability to communicate complex information through symbolic language; and physiological vulnerabilities to Alzheimer's disease, certain cancers and other conditions. Geneticists hoped to explain the evolution of these human attributes with the tools of comparative genomics — the side-by-side comparison of different species' genomes.

Varki was part of a group that pushed hard to sequence the genome of human's closest relative, the chimpanzee, arguing that any genetic differences between human and chimp sequences would lead straight to the heart of humanness. But the chimp sequence, published more than three years ago[2], hasn't delivered this. One comparison between humans, chimps and mice, for example, showed that the protein-coding sequences of genes expressed



K. LEMON

in the brain have changed very little across species[3].

A few genes are interesting exceptions. Selection seems to have favoured changes in *FOXP2*, a gene involved in human speech, after humans and chimps diverged between 4.6 million and 6.2 million years ago[4]. Geneticist Bruce Lahn from the University of Chicago in Illinois has proposed that *ASPM*[5] and *MCPH1*[6] — both of which are thought to be related to brain size — are under selection in humans. And then there is the gene encoding DUF1220, a "protein domain of unknown function" that seems to be under selection, that is active in the brain and has many more copies in humans than in other species[7]. But none of these genes alone is likely to explain a single human trait. "No real silver bullet has emerged to say, 'This is the human uniqueness gene', and there will never be one such gene," says Evan Eichler, a genome biologist at the University of Washington in Seattle. "It is the collective impact of all these genetic differences that make us human."

Some evolutionary research is leading away from protein-coding genes entirely. In 2006, a team of scientists led by David Haussler at the University of California, Santa Cruz, picked out 49 regions of the human genome[8] that had remained largely untouched throughout the evolution of fish, reptiles, birds and monkeys, and then went into mutational hyperdrive after ancestral humans emerged. The researchers found that the genomic address that has evolved faster than any other codes not for a protein, but for a small piece of RNA — human accelerated region 1 (HAR1) — that is expressed in brain cells during human fetal development. Beyond that, nobody knows what HAR1 does. Its sudden status as a belle at the evolutionary ball underscores the idea that selection could have acted most strongly on sequences outside the bounds of protein-coding genes, leaving Haussler and other researchers to work out what these sequences are doing, and why selection has acted on them. The picture could become even more complicated if, as some recent work has suggested, the statistical tests used to find genes under positive selection are themselves questionable[9]. "There are thousands and thousands of changes to our genomes that have occurred in the past few million years that are still hidden, and the vast majority of those will not be functionally consequential," Haussler says. "So it is an amazingly difficult, needle-in-a-haystack type of search."

"The idea was that if we could just identify those few critical genetic differences, we could explain the differences in cognition and language."
— Todd Preuss

Genome researchers once expected that most of the genetic differences between humans would be in single letters of DNA, a type of variation called a single nucleotide polymorphism, or SNP. But in the past few years, they have discovered that large chunks of the genome can be duplicated, deleted and otherwise rearranged differently between individuals. In a paper published this week[10], Eichler's team analysed the genomes of humans, chimpanzees, orangutans and macaques and found that a burst of duplications appears to have occurred in the last common ancestor of humans and chimpanzees. The question now is why? Such rearrangements risk disrupting essential genes and have been linked to human diseases such as autism and schizophrenia.

Varki and Eichler suggest that structural variations may also confer benefits by expanding the range of genetic diversity. The negative side effects might be outweighed by the advantages conferred by new genes or other beneficial arrangements. And the human genome might have been able to tolerate some of the potentially toxic variants thanks to clothing, tools, agriculture and other cultural innovations that allow individuals with these variants to survive. "By allowing individuals to be buffered against natural selection, perhaps culture allows a wider spectrum of genetic diversity to creep in," Eichler says. "Maybe the wider spectrum of diversity allows for more savants and autistic people in the same population."

Researchers have found that the human genome has accumulated more than its fair share of other potentially harmful genetic changes too — in protein coding regions, promoters and even the loss of entire genes. One explanation is that it is a remnant of the frequent population 'bottlenecks' in human history, in which small groups that migrated to new areas established new populations that all carried the founders' mutations. But another possibility, says statistical geneticist Gilean McVean at the University of Oxford, UK, is that the human ability to learn and adapt has eased the selection pressure that would weed out some of these changes. "When you look in the human genome, one of the things you see is that it has accumulated a lot of apparently bad mutations, and to some extent humans' inventive skills might have allowed that," he says. A modern example, he points out, might be the ability of humans to make spectacles to counteract poor vision.

Anthropologist and neuroscientist Terrence Deacon of the University of California, Berkeley, has long argued that culture could have "relaxed" human selection. Apes, for instance, have lost the ability to make vitamin C because the gene that facilitates this process has broken down. Deacon suggests that the availability of fruit eased the selection pressures working against individuals who couldn't make their own vitamin C, allowing the relevant gene to accumulate mutations but also making apes dependent on external sources for the nutrient. The relaxed selection created by human culture similarly could have allowed the evolution of more diversity and complexity, Deacon says, but it has also made humans more reliant on the innovations that freed them from selection in the first place. "We have produced symbolic communication and culture and technology, all of which play a part in shielding us from certain kinds of selective forces," he says.

Genetic burst

When scrutinizing the genome, some researchers see more dramatic evidence of culture's influence. In 2007, a team led by anthropologist John Hawks of the University of Wisconsin, Madison, and genome scientist Robert Moyzis of the University of California, Irvine, proposed that culture is hastening human evolution[11]. The team combed through a set of 3.9 million SNPs from European, African and other ancestral human populations, looking for those that bore a signature of positive selection: they were relatively young, common in individuals from the same population and different from those in the other populations. Such mutations are probably being 'swept' to abundance shortly after appearing because they lie in or near pieces of DNA that are beneficial in some way. The team found that a burst of these SNPs had appeared about 10,000 years ago, suggesting that selection has been causing very rapid genetic change since that time.

The researchers then tested whether evolution had sped along like this throughout human history. If so, then the different ances-


DLILLC/CORBIS


M. SHAH / GETTY IMAGES

Comparisons between the genomes of chimps and humans have revealed some sequences that are under selection.

tral populations should have fairly similar genomes because many mutations and their surrounding regions would have swept throughout the human genome before these populations diverged. But current human populations are much more genetically diverse than this hypothesis predicts, so Moyzis and Hawks have concluded that evolution must have ramped up over the past 40,000 years. They chalk some of this acceleration up to human population growth, which exposed the species to more new mutations and created more raw material for selection. But the other reason, Hawks thinks, is culture — because although the physiology of humans has not changed much in the past 40,000 years, their expansion and migration means that lifestyles, languages and technologies certainly have.

"By allowing individuals to be buffered against natural selection, perhaps culture allows a wider spectrum of genetic diversity to creep in."
— Evan Eichler

Although not everyone agrees with Hawks's claims, the best understood example of recent human evolution does seem to fit. Genetic mutations that allow adults to digest lactose, a sugar found in milk, have emerged independently in different populations in response to the same cultural innovation — cattle domestication[12]. "I don't see culture as an alternative to genetics, I see culture as being the explanatory factor for these genetic changes," says Hawks. "There is no explanation for change without the gene–environment interaction."

Hawks and others are now looking for the beneficial sequences connected with the selected SNPs. But these sequences are hard to pinpoint, and even harder to connect up with a specific human trait. "We know that genes involved in immunity, genes involved in brains, these are showing signals of adaptation in a way that suggests [these traits] have been important," says McVean. "But that's kind of obvious — you only have to look at our biology or our physiology or behaviour to see that."

To Varki and others, the absence of sequences that underlie specific human behaviours could itself testify to the importance of human culture. According to the 'Baldwin effect', named after the American psychologist who proposed it in the late 1800s, behaviours crucial to survival will often become 'hard-wired' into the genome to ensure that they are not lost. But most human skills are not hard-wired: people who have never lived in the Arctic would have a difficult time figuring out how to hunt a seal, skin it and stretch its hide to build a kayak. But if they moved there, they could quickly learn.

The human species has spent most of its history wandering through and creating new environments, and specific skills or resources can quickly become obsolete. So it might have been helpful to cement into DNA the social and intellectual capacities to learn, but leave out the specific instructions for building a kayak. "It is good to make learning more rapid and to improve memory," says geneticist Eva Jablonka of Tel Aviv University in Israel, "but it is not good to specify it too precisely because this memory and learning allows you to cope with a wider range of environments for which you cannot be prepared genetically."

If genes and culture are evolving together, then some difficult questions start to arise — in particular, about whether human evolution is dividing the species. Surveys of human diversity have shown that people can be classified into genetically similar groups that correlate with their geographic ancestry. And Jonathan Haidt of the University of Virginia in Charlottesville has proposed that genetic differences between these groups could underlie variations in traits such as aggression, thriftiness and spontaneity. "Each [human] niche has its own microclimate with its own adaptive pressures," says Haidt, who was impressed by Hawks' work. "The discovery of much more rapid genetic evolution leads directly to the prediction that we will find dozens or hundreds of genetically based ethnic divergences in traits, many of which will have some moral significance." No such ethnically linked divergence has been found to exist, but Haidt points to a hypothesis that selection has boosted the average IQ of the Ashkenazi Jewish population because of its historical reproductive isolation and history of working in the financial trades[13].

Agriculture, tools and other cultural innovations may have allowed mutations to accumulate in the human genome.

P.-A. PETTERSSON/GETTY IMAGES; ATLANTIDE PHOTOTRAVEL/CORBIS

Altered state

Most geneticists disagree with Haidt. They point out that occupations, conflicts and other aspects of culture have changed so rapidly during human history that the selective pressures associated with them would have not had time to fix changes in the genome. And Jablonka returns to her point that it is more evolutionarily advantageous for the human species to stay adaptable than to cement personality traits in the genome of different groups. "It would not only be detrimental," she says, "it cannot happen in a species that is all the time having to adapt to the changes it is creating in the world."

Until researchers understand the evolutionary basis for human behaviour it will be easy to argue over such ideas but hard to rule them out. So geneticists are moving away from evolutionary just-so stories that are based on single genes and embracing the complexity of the cultural and biological contexts in which humans and their genes operate. Daniel Geschwind of the University of California, Los Angeles, for instance, is analysing how genes interact with each other in complex networks. If one gene in the brain occupies a central node in the human network but a peripheral one in chimps, then it is a strong hint that the gene's function has changed in some meaningful way too. This type of approach should help solve the problem that researchers have run up against repeatedly in genomic analyses: how to determine which human characteristic, or phenotype, is affected by a genetic sequence under selection.

Cognitive psychologists have found in recent decades that some phenotypes once thought to be uniquely human — such as the development of moral codes, or the ability to recognize that other individuals have minds of their own — are seen in other animals. And work by Michael Tomasello of the Max Planck Institute for Evolutionary Anthropology in Leipzig, Germany, has suggested that human-specific phenotypes may be very subtle. His group found that young chimps, orangutans and toddlers performed about the same on tests designed to assess 'physical' intelligence, such as retrieving a piece of food that had been hidden under a cup and then moved. But the children were better at 'social' intelligence tasks, such as copying an experimenter's actions to retrieve a treat stuck in a tube[14].

Preuss says that such precise dissections of human-specific traits are still quite rare. "If you go beyond the bland expression of 'advanced cognition' and try to talk about cognitive mechanisms and abilities, we don't really know that much," he says. This means that there is a glut of genomic data but a paucity of crucial information from other fields that would help to make sense of it. "We need to start connecting this genetic world to the traditional anthropological approaches," agrees Hawks, who sees genomics as an inspiration to start collecting and sharing data on an equivalent scale in his own discipline.

Long before the next centennial of Darwin's birth, these data might have closed the book on human evolution. If they do show that culture has shaped the evolution of humans in a way that has no counterpart elsewhere in the animal kingdom, then perhaps Wallace will earn some posthumous credit: this was more than natural-selection-as-usual. But culture cannot have had so strong a role in human evolution without itself being influenced by the results. In the words of Wallace, understanding this interplay will require all of the "mental powers so entirely removed from the material necessities of savage men". ■

Erika Check Hayden is a senior reporter for *Nature* based in San Francisco.

1. Wallace, A. R. in *Contributions to the Theory of Natural Selection. A Series of Essays* (Macmillan, 1870).
2. The Chimpanzee Sequencing and Analysis Consortium *Nature* **437,** 69–87 (2005).
3. Clark, A. G. *et al. Science* **302,** 1960–1963 (2003).
4. Enard, W. *et al. Nature* **418,** 869–872 (2002).
5. Mekel-Bobrov, N. *et al. Science* **309,** 1720–1722 (2005).
6. Evans, P. D. *et al. Science* **309,** 1717–1720 (2005).
7. Popesco, M. C. *et al. Science* **313,** 1304–1307 (2006).
8. Pollard, K. S. *et al. Nature* **443,** 167–172 (2006).
9. *Nature* **457,** 543 (2009).
10. Marques-Bonet, T. *et al. Nature* **457,** 877–881 (2009).
11. Hawks, J. *et al. Proc. Natl Acad. Sci. USA* **104,** 20753–20758 (2007).
12. *Nature* **444,** 994–996 (2006).
13. Cochran, G., Hardy, J. & Harpending, H. *J. Biosoc. Sci.* **38,** 659–693 (2006).
14. Herrmann, E., Call, J., Hernàndez-Lloreda, M. V., Hare, B. & Tomasello, M. *Science* **317,** 1360–1366 (2007).

See Editorial, page 763, and online at www.nature.com/darwin.