Mix and match: the hunt for what makes us human

Genome studies are turning up exciting hints about what makes human brains unique. But scientists must now tackle a difficult question: how can they tell which leads point in the right direction and which are red herrings?

The new studies rely on genome sequence data from humans' closest relatives: other primates. A draft of the chimpanzee genome was released last year[1] and a draft sequence of the macaque genome is also publicly available. The data are enabling scientists to compare chimp, human and monkey DNA to search out signals that seem unique to people.

This approach is yielding pointers to the mechanisms that may have driven human evolution. Last week, researchers led by James Sikela of the University of Colorado Health Sciences Center in Aurora, announced the latest[2]. They looked for genes repeated more often in human DNA than in chimp genomes. They found that one gene contains a protein-coding domain that is repeated 212 times in people, compared with 37 repeats in chimps, 30 in macaques and one in mice and rats. And, significantly, this protein domain is present in human brain cells. It is also present in other tissues, but Sikela's team is excited because the domain is found in the neocortex, which is much larger in humans than in other primates.

"The fact that a huge explosion of this domain occurred in the primate lineages, and the fact that it is found in the brain, seems to make it a good candidate for cognitive function," says Sikela.

Investigating such 'copy-number polymorphisms' — gene repeats, deletions and other large-scale rearrangements — is one of the hottest areas of genomic research, says geneticist Evan Eichler of the University of Washington in Seattle. These sorts of structural variants have only recently been discovered, and it's possible that they could be a major driver of human evolution[3]. "One take-home message here is that duplications rock, and structural variation is very important," Eichler says.

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A broader question raised by Sikela's work and other recent studies is how to find out what, exactly, the newly discovered genes are doing. The easiest way to pin down an unknown gene's function — mutating it in an individual — isn't ethically acceptable in chimps or, of course, people.

One solution, says Sikela would be to mutate the relevant genes in mice, to see what happens to the rodents' brains. In a 2002 study, researchers at the Beth Israel Deaconess Medical Center in Boston, Massachusetts, found that they could enlarge mouse brains by inducing fetal mice to over-express the regulatory chemical β-catenin[4]. That suggested the chemical might regulate pathways that control human brain size.

Researchers can also scan tissue banks to find out when in human development genes are expressed. In a paper published on 16 August[5],

Muslim council phases in lunar calendar

The Muslim community in the United States has taken a small but significant step towards resolving one of the oldest disputes between Islam and science — the creation of a unified lunar calendar.

Islam, in common with Judaism, uses lunar dates worked out in accordance with the phases of the Moon. But despite major advances in lunar astronomy over the past few centuries, Muslims have never agreed a single lunar calendar. This may finally be about to change. At a meeting last month, the Fiqh Council of North America, a body of American Islamic religious scholars, agreed that religious festivals in the United States such as Eid, the end of the fasting month of Ramadan, will now be fixed according to a predetermined calendar.

In a statement on 28 August, Muzammil Siddiqi, chairman of the Fiqh Council, said: "Muslims will be able to plan their activities in advance, take time off from work or school. It will reduce a lot of chaos, hardship and confusion."

The timing of Islamic festivals in the United States will no longer rely on direct sightings of the Moon.

D. SANSONI/IMPACT PHOTOS

The move was welcomed in Britain by Zafar Iqbal who chairs the Islamic Calendar Committee of the Muslim Council of Britain, a coalition of some 400 mosques and community groups. Iqbal believes that the US decision will strengthen calls for Britain's estimated 1.6 million Muslims to adopt a unified calendar. "This is a very courageous decision," he says.

The US decision has its critics among both scientists and theologians, including members of the Fiqh Council itself. One member says he doesn't think the move will have universal appeal — especially among those who believe that it is a religious requirement for the beginning of each lunar month to be confirmed by a naked-eye sighting of the new Moon.

This need to see the new Moon dates from the time of the Prophet Mohammed in the seventh century. And there is a reluctance to switch from what people believe

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Researchers are comparing human and chimp genomes to find out what makes our brains so different.

a team led by David Haussler at the University of California, Santa Cruz, did just that. By comparing the human and chimp genomes, they found one gene that has evolved rapidly during the transition from chimps to people. They looked at embryonic tissue collected by collaborators in Belgium, and found that this gene is expressed at 7–19 weeks of human development, when neurons are known to be forming and moving throughout the brain.

Another way to work out what brain genes do is to look for effects on human health, and to study patients with brain dysfunctions. In a study published on 13 August in *Nature Genetics*[6], Eichler's lab looked at duplications in the genomes of 290 patients with unexplained mental retardation. One patient had a deletion in the same region of the genome where Sikela's group found its new gene. "It doesn't prove anything, but it's interesting," Eichler says.

Finding the function of highly repetitive genes is especially challenging, he adds, because such genes are tricky to analyse correctly, and genome assemblers often miss them. So there are large gaps in our understanding of where duplications occur. Eichler is trying to remedy this with a project to sequence all the structural variations in a small group of people.

Other investigators say that it will be hard to make better sense of the new genome studies without more studies on apes. Because chimps are difficult to work with, and scarce, researchers don't really know much about how the structure and function of chimp brains compare with those of human brains, says Todd Preuss, a neuroscientist at the Yerkes National Primate Research Center in Atlanta, Georgia. That makes it hard to decipher the meaning of genetic disparities in the two species' brains, and that must change, he says. "We're all dressed up with no place to go — we've got all this wonderful information and we can't do much with it. The way to get around this is to study apes, and to start looking at the differences between human and chimp brain organization." ■

Erika Check

1. The Chimpanzee Sequencing and Analysis Consortium *Nature* **437,** 69–87 (2005).
2. Popesco, M. C. *et al. Science* **313,** 1304–1307 (2006).
3. Check, E. *Nature* **437,** 1084–1086 (2005).
4. Chenn, A. & Walsh, C. A. *Science* **297,** 365–369 (2002).
5. Pollard, K. S. *et al. Nature* doi:10.1038/nature05113 (2006).
6. Sharp, A. J. *et al. Nature Genet.* **38,** 1038–1042 (2006).

Mohammed required, regardless of whether a scientific approach might be more convenient — in fact doing so is seen by many Islamic scholars as coming close to committing a sin.

Usama Hasan, a lecturer in computer science at Middlesex University, UK, is an Islamic scholar and has collaborated with the Royal Observatory in London. He says that the council should have used a more accurate method to compile the calendar. The council opted for a method based on computing the position of the Moon relative to Earth and the Sun. But Hasan says that the technology now exists to predict whether the Moon will be visible in a certain place at a certain time, which comes closer to the requirements of Islamic tradition. "Seeing the Moon with the naked eye is a means to an end; it should not be seen as an end in itself," he says.

But the naked eye remains the method of choice throughout the Islamic world, and is one of the main reasons a unified calendar has so far proved elusive. According to this tradition, a new lunar month begins the morning after a sighting of the thin crescent Moon — some 24 hours after the birth of a new Moon.

That's difficult for countries in the Northern Hemisphere, because thick clouds often hide the crescent Moon. And in countries at higher latitudes, such as in Scandinavia, the crescent is invisible to the naked eye. When this happens, mosques in northern Europe and North America tend to follow decisions in other countries. Saudi Arabia and Pakistan are favourites, but even they often celebrate Islamic festivals on different days.

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Hasan is confident that the US decision will prompt a rethink in Saudi Arabia, where Moon-sighting causes frequent controversy. Saudi Arabia does have an Islamic calendar based on lunar tables, known as the *Umm al-Qura* calendar. This was developed by the King Abdulaziz City for Science and Technology, the country's science ministry, and is used for all non-religious purposes. But human sightings are still used to determine dates for religious festivals. Moreover, anyone can claim to have seen the Moon — the authorities are duty-bound to listen, and sometimes accept news of a sighting even if this does not agree with the dates in the lunar calendar.

This happened last year, when the Saudi government decided, with just ten days to go, to revise the date for the annual Hajj pilgrimage because of a claimed Moon sighting — even though astronomical calculations showed such a sighting to be impossible. The sudden change led to chaos in the organization of the three-day event, which attracts 2 million people from more than 150 countries.

Siddiqi, too, is hopeful that the use of lunar calendars will catch on, if only to rule out erroneous sightings. ■

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