BEHAVIORAL GENETICS

Can epigenetics explain homosexuality puzzle?

Study in twin brothers finds link between DNA methylation and sexual orientation

By **Michael Balter**

"Baby, I was born this way," Lady Gaga sang in a 2011 hit that quickly became a gay anthem. Indeed, over the past 2 decades, researchers have turned up considerable evidence that homosexuality isn't a lifestyle choice, but is rooted in a person's biology and at least in part determined by genetics. Yet actual "gay genes" have been elusive.

A new study of male twins, scheduled for presentation at a meeting of the American Society of Human Genetics (ASHG) in Baltimore, Maryland, this week, could help explain that paradox. It finds that epigenetic effects, chemical modifications of the human genome that alter gene activity without changing the DNA sequence, may have a major influence on sexual orientation.

The new work, from Eric Vilain's lab at the University of California (UC), Los Angeles, is "exciting" and "long overdue," says William Rice, an evolutionary geneticist at UC Santa Barbara, who proposed in 2012 that epigenetics plays a role in sexual orientation. But Rice and others caution that the research is still preliminary and based on a small sample.

A pride march in Belgrade last month. Scientists warn that the new findings should not be used to produce a test or "cure" for homosexuality.

PHOTO: REUTERS/CHRIS WATTIE

Researchers thought they were hot on the trail of "gay genes" in 1993, when a team led by geneticist Dean Hamer of the National Cancer Institute reported that one or more genes for homosexuality had to reside on Xq28, a large region on the X chromosome. The discovery generated worldwide headlines, but some teams were unable to replicate the findings and the actual genes have not been found—not even by a team that vindicated Hamer's identification of Xq28 in a sample size 10 times larger than his (*Science*, 21 November 2014, p. 902). Twin studies suggested, moreover, that gene sequences can't be the full explanation. For example, the identical twin of a gay man, despite having the same genome, only has a 20% to 50% chance of being gay himself.

That's why some have suggested that epigenetics—instead of or in addition to traditional genetics—might be involved. During development, chromosomes are subject to chemical changes that don't affect the nucleotide sequence but can turn genes on or off; the best known example is methylation, in which a methyl group is attached to specific DNA regions. Such "epi-marks" can remain in place for a lifetime, but most are erased when eggs and sperm are produced, so that a fetus starts with a blank slate. Recent studies, however, have shown that some marks are passed on to the next generation (*Science*, 24 January 2014, p. 361).

In a 2012 paper, Rice and his colleagues suggested that such unerased epi-marks might cause homosexuality when they are passed on from father to daughter or from mother to son. Specifically, they argued that inherited marks that influence a fetus's sensitivity to testosterone in the womb might "masculinize" the brains of girls and "feminize" those of boys, leading to same-sex attraction.

Such ideas inspired Tuck Ngun, a postdoc in Vilain's lab, to study the methylation patterns at 140,000 regions in the DNA of 37 pairs of male identical twins who were discordant—meaning that one was gay and the other straight—and 10 pairs who were both gay. After several rounds of analysis—with the help of a specially developed machine-learning algorithm—the team identified five regions in the genome where the methylation pattern appears very closely linked to sexual orientation. One gene is important for nerve conduction, whereas another has been implicated in immune functions.

To test how important the five regions are, the team divided the discordant twin pairs into two groups. They looked at the associations between specific epi-marks and sexual orientation in one group, then tested how well those results could predict sexual orientation in the second group. They were able to reach almost 70% accuracy, although the presentation makes clear that—in contrast to what a provocative ASHG press release about the study suggested—this predictive ability applies only to the study sample and not to the wider population. Just why identical twins sometimes end up with different methylation patterns isn't clear. If Rice's hypothesis is right, their mothers' epi-marks might have been erased in one son, but not the other; or perhaps neither inherited any marks but one of them picked them up in the womb.

In an earlier review, Ngun and Vilain cited evidence that methylation may be determined by subtle differences in the environment each fetus experiences during gestation, such as their exact locations within the womb and how much of the maternal blood supply each receives.

Such subtle influences are "where the action is," says psychologist J. Michael Bailey of Northwestern University in Evanston, Illinois. "Discordant [identical] twins comprise the best way to study this." But he and Rice caution that the study must be replicated with more twins to be fully credible. Sergey Gavrilets, an evolutionary biologist at the University of Tennessee, Knoxville, and a co-author of Rice's epigenetics model, adds that the study would also be "more convincing" if the team could link the regions showing epigenetic differences to testosterone sensitivity in the womb.

Vilain's team stresses that the findings shouldn't be used to produce tests for homosexuality or a misguided "cure." Bailey says he's not worried about such misuse. "We will not have the potential to manipulate sexual orientation anytime soon," he says. And in any case, he adds, "we should not restrict research on the origins of sexual orientation on the basis of hypothetical or real implications." ■