Evidence for Homosexuality Gene

A genetic analysis of 40 pairs of homosexual brothers has uncovered a region on the X chromosome that appears to contain a gene or genes for homosexuality

How much of sexual orientation is determined by a person's genes, and how much by familial and cultural influences? That has proved to be an exceptionally controversial question. Several recent studies of twins and adoptive siblings have pointed toward a large genetic component in homosexuality, implying that a gene or genes should exist that create a predisposition for homosexuality, but there was no direct proof. Now, a team of geneticists at the National Cancer Institute has come closer to that proof.

On page 321, Dean Hamer and his colleagues Stella Hu, Victoria Magnuson, Nan Hu, and Angela Pattatucci report linking some instances of male homosexuality to a small stretch of DNA on the X chromosome. If the finding can be confirmed, it might eventually lead to a better understanding of the biological basis of homosexuality and of sexual orientation in general.

No one is breaking out the champagne just yet, however. The field of behavioral genetics is littered with apparent discoveries that were later called into question or retracted. Over the past few years, several groups of researchers have reported locating genes for various mental illnesses—manic depression, schizophrenia, alcoholism—only to see their evidence evaporate after they assembled more evidence or reanalyzed the original data. "There's almost no finding that would be convincing by itself in this field," notes Elliot Gershon, chief of the clinical neurogenetics branch of the National Institute of Mental Health. "We really have to see an independent replication."

Despite the caution, researchers familiar with the work say this study appears to have a very good chance of holding up because it avoids some of the methodological problems of earlier work. One way or the other, the verdict may be in before the end of the year since a replication can probably be performed quickly.

DARROW MONTGOMERY

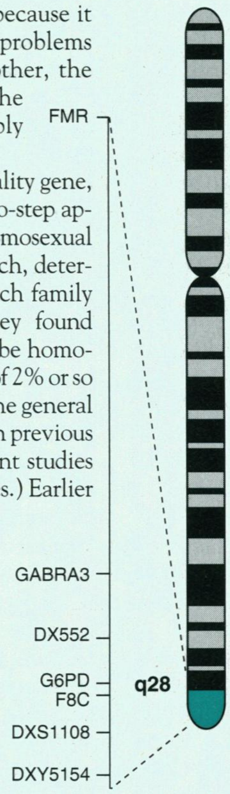
Gene team. Dean Hamer, and *(from left)* Stella Hu, Nan Hu, Angela Pattatucci, and Victoria Magnuson are studying the genetics of sexual orientation.

To look for a possible homosexuality gene, Hamer and his colleagues took a two-step approach. First they recruited 76 homosexual men and traced out pedigrees for each, determining which other members of each family were themselves homosexual. They found 13.5% of the gay men's brothers to be homosexual—much higher than the rate of 2% or so that the Hamer group measured in the general population. (While this is lower than previous estimates of 4% to 10%, other recent studies have come up with similar low figures.) Earlier studies had also found that brothers of homosexual men are more likely to be homosexual than are men in the general population.

But once Hamer and colleagues ventured outside the immediate family, they found something new. "When we collected the family histories," Hamer says, "we saw more gay relatives on the maternal side than on the paternal side." In particular, they found homosexuality to be significantly more common among maternal uncles of gay men and among cousins who were sons of maternal aunts than it is among males in the general population.

This implied that, for some male homosexuals at least, the trait is passed through female members of the family. And this in turn gave the researchers an obvious place to start looking for a homosexuality gene: the X chromosome, the only chromosome inherited exclusively from the mother.

To search for such a gene, Hamer recruited 40 pairs of homosexual brothers, took DNA samples from each, and performed a genetic linkage analysis using gene markers. The idea behind the analysis is simple: On average, each pair of brothers will have about half the DNA on their X chromosomes (and other chromosomes) in common. If both brothers are homosexual because they inherited a particular gene on the X chro-



X marks the spot. The markers indicated pointed to Xq28 as the possible gene site.

HAMER *ET AL.*

mosome, the gene must lie somewhere in the shared sections of the chromosome, which can be identified by the gene markers. The researcher examines many pairs of brothers, looking for a stretch of DNA that all or most of them have in common. If such a stretch exists, then it probably contains the target gene.

When Hamer and colleagues performed their analysis, they found that such a shared stretch did indeed exist. Of the 40 pairs of brothers, 33 pairs shared a set of five markers located near the end of the long arm of the X chromosome in a region designated Xq28. It's unlikely the linkage between the markers and the homosexuality trait was due to chance, Hamer says. The linkage has a LOD score of 4.0—a technical measure that translates to a 99.5% certainty that there is a gene (or genes) in this area of the X chromosome that predisposes a male to become homosexual.

Hamer warns, however, that this one site cannot explain all male homosexuality. Although his pedigree analysis showed that the homosexuality trait is usually maternally inherited, he did see some families where the trait seemed to be passed paternally. And even among his 40 sets of brothers, chosen so that there was no evidence of the trait passing through male family members, seven sets of brothers did not share the stretch of Xq28 where the gene appears to lie. Instead, Hamer says, it seems likely that homosexuality arises from a variety of causes, genetic and perhaps environmental as well.

Still, researchers can hardly wait to get their hands on the gene in order to study just what it does. "It's very exciting," says Michael Bailey of Northwestern University in Chicago, co-author of a study 2 years ago that found half of the identical twins of gay men to be themselves gay. "If we can find a gene for sexual orientation, we can start to find out what the gene does."

The list of questions to be asked about

the gene is endless: What protein does it code for? Where does this protein act and what does it do? How does the gene in homosexuals differ from the corresponding gene in heterosexual men? Does the gene invariably lead to homosexuality in males, or are there heterosexual males who also carry the gene? And what does the gene do in women?

First, however, the results must be replicated. Hamer, who has already begun collecting data for a follow-up, says he's confident this homosexuality linkage will stand up better than some of the earlier work that attempted to link behavioral conditions to particular chromosomes. Several of those studies fell apart when the diagnosis changed for one or two key individuals—when, for example, a subject who had previously shown no symptoms developed manic-depression. By including only homosexuals, Hamer doesn't have to worry about "false negatives" —males who claimed not to be homosexual but who really were. And the use of 40 separate families makes it less likely that a mischaracterization could skew the result. Furthermore, earlier studies often relied on incomplete genetic maps, while Hamer used 22 markers that covered the X chromosome.

Hamer gets a vote of confidence from geneticist Jeremy Nathans of Johns Hopkins University, who says that Hamer's methods should make the study "more robust" and less likely than earlier work to break down upon further inspection, although he, too, warns that it must be replicated.

Another factor that inspires confidence in other scientists is Hamer's reputation as a very careful worker. For much of the past decade he focused on the genes that code for metal-binding proteins, mostly in yeast and mice. "He could easily have stayed in that field and had a very distinguished career," Nathans says. Instead, Hamer says he "decided to work on something more general, more human," and settled on the issue of genes that affect sexual orientation.

Assuming that Hamer's linkage study does hold up, as expected, he will find himself with another difficult problem on his hands—finding the male homosexuality gene that his data indicate is there, somewhere, in Xq28. It won't be easy. There are probably several hundred genes in that region, Hamer notes, most of them unidentified. The job will require assembling more and more families of homosexuals, analyzing the DNA with ever more markers, zeroing in on that one gene. And nobody has to tell Hamer that the search for the Huntington's disease gene, which finally ended earlier this year, dragged on for more than a decade after the gene had been traced to the tip of chromosome 4. But sooner or later, Hamer believes, someone will find this gene, and it might as well be him.

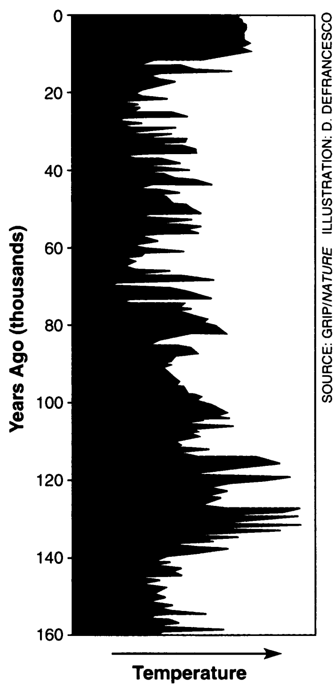
–Robert Pool

EARTH SCIENCE

Even Warm Climates Get the Shivers

To climate researchers, the intervals between ice ages—times like the present, when Earth warms and the ice sheets retreat—once looked like benign interludes in the harsh, unsettled climate of the last million years. No longer. That picture was shattered this week by the announcement that a detailed record of climate extracted from the Greenland ice sheet shows sharp, even "catastrophic" climate shifts during the two most recent interglacial periods. Over and over, for decades to thousands of years, Greenland cooled drastically from temperatures equal to or higher than today's, often to virtually ice-age conditions.

"The fantastic thing is that [the shifts] happen so fast, some of them within a few decades and some within a few years," says Willi Dansgaard of the University of Copenhagen, who with other members of the Greenland Ice-Core Project (GRIP) team reported the climate instabilities in two papers in the 15 July *Nature*. In that respect, the cold snaps are near-mirror images of the abrupt warmings that climate researchers have recognized in the record of glacial times (*Science*, 14 May, p. 890). But while many researchers suspect that instabilities in the great ice sheets played some role in those oscillations, the only obvious candidate for a trigger during warm periods is ocean circulation.



Spiky record. During the last interglacial *(lower band)*, sudden coolings struck.

The surprising news about warm climates comes from ice cored from deep in the 3-kilometer-thick Greenland ice sheet last summer by GRIP workers. They have now analyzed variations in climate-related properties across layers of ice laid down during the last interglacial (roughly 115,000 to 135,000 years ago) and the preceding interglacial, 100,000 years before that. One of the properties is the ratio of oxygen isotopes in the ice, which depends largely on the atmospheric temperature when the ice fell as snow.

Other climate records depict the last interglacial as uniformly warm, often 1 to 2°C warmer than today. But the more detailed GRIP record shows that the balminess of the last interglacial was interrupted on two occasions when, in less than a few centuries, temperatures in Greenland plunged from 2°C warmer than today to 5°C colder. The cold, equaling that of the mildest parts of the last ice age, persisted for 2000 years in one case and 6000 years in the other. The remainder of the 20,000-year interglacial in Greenland was peppered by shorter chills that set in even more suddenly. And some of those fluctuations were extreme, including a 14-degree, 70-year cooling that struck in a mere decade. Similar, though less extreme, instabilities show up in the preceding interglacial.

With little ice to blame as the trigger for many of these abrupt shifts, researchers are looking to the ocean. Periodic shutdowns in the northward flow of warm Atlantic water that warms the far northern North Atlantic, then sinks into the deep sea, have been invoked as a possible cause of climate oscillations around the end of the most recent ice age. The ice-age shutdowns may have stemmed from occasional collapses of the ice sheets into the ocean, but some researchers think this "conveyor belt" is also capable of turning off and on without any intercession from the ice. "You begin to look at the [ocean] circulation as very sensitive," says Richard Alley of Pennsylvania State University, who works on a parallel U.S. ice coring project.

Is such a switch waiting to flip in the current interglacial, now 8000 years old? A discovery from an Antarctic ice core suggests that recent climate may not be immune to tremors. At a meeting of the American Geophysical Union in May, Ellen Mosley-Thompson and her colleagues at Ohio State University reported that 2500 years ago—well within the current interglacial—the climate in central East Antarctica cooled halfway to glacial levels over several decades and didn't recover for almost seven centuries.

Otherwise, our own interglacial climate seems relatively steady. But GRIP scientists wonder whether, paradoxically, that might change in a warmer world. Perhaps the exceptional warmth of the last interglacial had something to do with its convulsive climate changes. As greenhouse gases build up from human activity, asks Dansgaard, "what is going to happen if and when the [present] climate gets warmer?" Perhaps more study of the ancient ice will tell.

–Richard A. Kerr