

The Discovery of the “Gay Gene”

In mid-1993, the West was told that a scientist had discovered a “gay gene” - a gene causing homosexuality. The details were confusing for non-scientists, but the headline stuck. For Mr. and Ms. Average Citizen, it seemed that homosexuality might be genetic.

Actually there was no “gay gene.” Even the scientist referred to, a gay man, Dr. Hamer of the United States National Institutes of Health, never claimed to have found a gene determining homosexuality. “We have not found the gene - which we don’t think exists - for sexual orientation,” he said.¹ However, he claimed to have found evidence that some male homosexuality was passed through female members of a family. More specifically, he claimed to have found a linkage between homosexuality in males and a small stretch of the DNA on the X-chromosome.²

Gene Linkage Studies

Hamer’s work falls into a category of research called “gene linkage studies.” There has been a surge of research in this field in the last decade and a half, each success inspiring another. The first most spectacular, was the discovery, early in 1993, of a gene responsible for Huntington’s disease. The gene had already been tracked down to chromosome 4, but it took six teams of workers at ten different institutions ten years to find where on chromosome four. Over the succeeding decade, researchers also identified genes causing cystic fibrosis, muscular dystrophy, and other diseases.

Biologists have had astonishing success mapping the human genome (on schedule and within budget!), and chromosomal genetic maps densely covered with regions identified by “markers” are now available to researchers in genetics. In one five year period near the end of last century, the genes corresponding to 1450 physical conditions were identified and their precise location on various chromosomes determined. Inspired by these successes, some scientists began talking optimistically of uncovering the genetic basis to human behaviors in the same way. This is what Hamer tried to do, and what other scientists, called behavioral geneticists, attempted to do before him, but with scant success. Some gene linkage studies of homosexuality are significantly motivated by a hope that if homosexuality can be shown to be sufficiently linked to biology, it will help erase social stigma.⁴⁻⁶

So, research linking human characteristics with genes is back in fashion after decades in the dogbox since the Nazi era.⁴

What Happens in Linkage Studies?

In linkage studies, researchers look for an extended family with an unusually high incidence of some behavior, such as bipolar disease, and then take samples of tissue from all available members and analyze the DNA, looking for segments in common using sets of tiny, synthesized DNA segments, called “markers” - an identical set for each person. These tiny markers are configured in such a way that they attach in a lock and key fashion to certain stretches of DNA that mirror the markers. Searching for one gene in 22,000 is worse than looking for a contact lens in a swimming pool, but, in this way, similar segments can be found in different people. If the same sequence is associated consistently with a given trait, then researchers assume it lies close to the gene that codes for it or actually is that gene. At that point, a linkage is said to have been shown.

The strength of linkage analysis is in studying physical diseases that have distinct symptoms and are caused by a single dominant gene. When they attempt to link behaviors to a single gene, they run into a volley of scientific scepticism, for several reasons.

First, no mainstream geneticist believes that behavior is linked to one single gene (see Chapter One). "It's very rare to find genes that have a specific effect," says Harvard biologist Balaban.⁴ Second, in the word of one writer for *Science*, "the field of behavioral genetics is littered with apparent discoveries that were later called into question or retracted."⁷ It was only in the first decade of the 21st century that some reliability became more characteristic of the field. Unfortunately the supposed SSA - genetic link was before that time.

Schizophrenia

About the time Hamer started his work trying to associate SSA with a section of the X-chromosome, linkage studies were rather dubious, but seemed worth pursuing. Studies on schizophrenia and alcoholism gave rather contradictory results.

The studies on schizophrenia blossomed with the completion of the human genome project. Many regions were found on various chromosomes which correlated strongly with schizophrenia, and studies on other family lineages, and other ethnicities often confirmed them, though there were puzzling lacks of confirmation from time to time. However the results for some regions of the DNA were so convincing finally that scientists began looking for specific genes within them. In August 2005, there were at least 25 chromosome regions under suspicion, and an equal number of genes on them being investigated. Of these there was strong evidence for involvement of 4 genes and "promising but not compelling evidence" for a fifth. Some of the results were described as "very robust". This was a good consensus to emerge from a welter of initially inconsistent studies. The work had progressed so far that some studies were starting to experiment with drugs which interacted with the products of the genes known to be involved.

Alcoholism

Research on alcoholism had progressed to the stage where about 10 gene products had been fairly well implicated, some being enzymes which broke down alcohol and its products, others which were involved with drug receptor sites on cell surfaces, and neurotransmitters in nerves. Again the pattern which emerges is of multiple genes and multiple products and even variations in those gene products. One variety of an enzyme called alcohol dehydrogenase protects against alcoholism; another doesn't.

Gene linkage, although still sometimes quite elusive and inconsistent, had reached the point where it was worth searching, but one expected to find many genes contributing.

Intelligence

Plomin, a famous UK geneticist, embarked on a genome-wide search for regions and ultimately genes which might be associated with IQ. He thought this worth trying because studies suggested the genetic contribution to IQ is somewhere between 40 and 80%. He used an immense set of 1842 markers, and to accentuate any contrasts which might be present, chose subjects with IQ higher than 160 to compare with those of average 100. After all this work he ultimately found no clearly defined regions in the whole genome, although a few suggestive correlations.³ This is in marked contrast to the work on schizophrenia, and since 2001 there have been only a handful of IQ studies like that of Plomin's. They have not shown spectacular results. IQ is therefore very hard to link to genes though it undoubtedly will be eventually linked. But the links to individual genes are likely to be weak and indirect.

Hamer's Study - SSA

To find the homosexual gene or genes, Hamer and his colleagues first recruited seventy-six homosexual men, who identified themselves as predominantly or exclusively homosexual. They found 13.5 percent of their brothers to be gay, much higher than the 1% incidence of exclusive homosexuality in the general male population, and also a higher level of homosexuality in maternal uncles and the sons of maternal aunts.

They then recruited thirty-eight families in which there were two homosexual brothers, suspecting this would show more clearly the effect of homosexuality in male relatives on the maternal side. According to Hamer, 20 percent of male relatives were homosexual in this sample. Hamer then searched for a linkage on the X (female) chromosome (since males receive their single X chromosome exclusively from their mothers). He postulated, "If the X chromosome contains a gene that increases the probability of an individual's being homosexual, then genetically related gay men should share X chromosome markers close to that gene."² (Actually, it's normal for about 50 percent of brothers to share a particular sequence, as they will always have their father's Y chromosome, but, on average, half will have one of the mother's two X chromosomes and half the other. So it's only significant if the percentage of brothers sharing the sequence is well above 50 percent.) Hamer took forty pairs of gay brothers (thirty-eight from the sibling pairs, two from the first survey) and analyzed the DNA of the X chromosome with a series of twenty-two markers.

What did Hamer find? He claimed to have found a "statistically significant correlation" between the homosexual orientation and a genetic sequence on the tip of the long arm of the X chromosome, an area called "Xq28," in thirty-three cases out of the forty. That was 83 percent, well above the chance result of 50 percent. He summarized "We have now produced evidence that one form of male homosexuality is preferentially transmitted through the maternal side and is genetically linked to chromosomal region Xq28."² Hamer published his paper in *Science*, in July 1993, and immediately became a controversial figure in the scientific community. Numerous letters to *Nature*, for example, were mostly critical.

Shared Sequences Dissimilar

Hamer's paper gives the impression that all sixty-six men from the thirty-three pairs shared an identical sequence within the Xq28 region, but that's not exactly what the study showed. The sequences in any one pair of homosexual brothers were somewhat different from those shared by any other pair of homosexual brothers. In fact, each of thirty-three pairs of brothers shared exactly the same sequence only with his brother. One critic of the paper, Byne, remarks "No single, specific Xq28 sequence (the putative "gay gene") was identified in all sixty-six men."¹² It is possible that the same gene might be found in sequences which are not quite identical, but geneticists are uneasy with the idea.

Hamer and his team used the proper caveats in their paper: they didn't claim determinism, but rather influence and possibilities. They also said their finding needed replicating. But the editor of *Nature*, John Maddox, was clearly concerned the results might have to be retracted. He took the very unusual step of questioning Hamer's findings in an editorial.¹³ When asked about this by Hamer in a letter,¹⁴ Maddox replied that "two previous such interpretations (published in this journal) have proved unfounded."⁸ As we shall see, in retrospect Maddox was right.

Questionable Ethics

Hamer's work proved controversial, even within his own research team. One young researcher accused Hamer of omitting from the study results that would have made the findings non-significant. The accusation led to her dismissal from the research post and a complaint to the Office of Research Integrity (a U.S. watchdog on scientific ethics), which initially ruled there was a case to answer¹⁵ - but eventually in the late nineties dismissed the case. It was also disquieting that the funding under which the study proceeded was for Kaposi's sarcoma, present in gay populations, but nothing to do with the genetics of homosexuality. In the meantime, Hamer¹⁶ and colleagues replicated their study using a new population. This time they called in one of the world's leading genetic statisticians, Fulker, from Colorado. This time, the results were less impressive - 67 percent of homosexual brothers shared regions rather than 83 percent and the odds against it being a freak were again about twenty to one - just significant. However, they emphasized that the results applied only to their study group; that is, families with two homosexual brothers. When a linkage was attempted using homosexual men who had bisexual brothers, a correspondence of only 50 percent was found - no different from normal genetic sharing between siblings.

About this time another team found a very weak or negligible linkage. These findings have been presented at a conference and cited in published papers, though not themselves published. The work did confirm an excess of maternal relative homosexuality.

Hamer's study on the "gay gene" was contradicted in a study⁹ published in Western Ontario headed by researcher Rice, which found there was no trace of an association between homosexuality and the genetic region Hamer and his team had pin-pointed. Even when all the results from all the studies were combined, there was no significant association. Hamer argued that the Rice team result was inadequate because they did not select homosexual men with an excess of maternal homosexuality.

A further study has now appeared¹⁰ from the National Institutes of Health in Maryland, with collaborators from several parts of the US. The first author is Mustanski, and Hamer is included in the author list, though not leading the study.

According to the quoted statistical significance criteria in the paper, no part of the entire genome was linked with SSA in a statistically significant way. One peak on Chromosome 7 (region 7q36) approached statistical significance but is probably not significant. Although Hamer's original sample was reanalysed and showed significance for the Xq28 region, the combined larger sample did not. This strongly suggests the results of the Hamer work were an unfortunate statistical freak. In the paper a cited possible reason for the present results is "etiological heterogeneity". Translated into English this means "... it's more erratic than we thought..."

The combined studies could still be consistent with 10% genetic effect, as estimated elsewhere in our book, but the present best summary would be that no gene has been found, and this is in marked contrast to the work on schizophrenia and alcoholism which has found multiple genes. If there were a gene with an overwhelmingly strong influence it would have been found and confirmed by now.

Hamer is to be congratulated on his honesty in associating himself with this work that has caused a re-evaluation of his previous papers.

In a further interesting paper¹¹, Italian researchers describe an excess of homosexual male relatives on the maternal side, for homosexual men, supporting Hamer's previous papers. One quite unequivocal result is greater fertility on the female side, that is, among female relatives of homosexual men. If indeed homosexuality is linked to greater maternal line fertility, this could explain its persistence in the population. It rather seems as though the most probable finding to emerge from all the above work is some association of SSA with heightened homosexuality among maternal relatives, though this conflicts with a study by researcher John Bailey.

Our belief is that some genetic link with homosexuality will eventually be found, but prove to be quite weak.

As of late 2006 a Chicago research called Sanders was reinvestigating the links yet again and trying to recruit a sample of 1000 brothers. Perhaps this study will confirm some of the currently non-significant links Mutanski et al. found but the bottom line at the moment is that significant links have not been found.

Another paper by Hamer's group did not find a link between parts of the X-chromosome and the presence of lesbian SSA in families.

Summary

We can confidently predict half a dozen linkages will be "discovered" between genes and behavior each year. But the important lesson is this: any linkages probably affect only a small proportion of people to a very minor extent.

The scientific community realizes that "our genes do not make us do it". Hamer has always believed that. To give him the last word: "There will never be a test that will say for certain whether a child will be gay. We know that for certain."¹⁸ This means as clearly as anyone could state, that no-one is born gay.

Proponents of the view that homosexuality has psychological and sociological explanations have no difficulty with the possibility of genetic linkages to homosexuality. Any genetic link to a physical characteristic that might heighten a person's sense of gender nonconformity (the strongest known predictor of later homosexuality), could be held to be a contributing factor to later homosexuality. In a boy these might be, for example, genes related to slowness of build, lack of physical co-ordination (making a boy poor at sports), sensitivity. In a girl they might be factors like atypical physical strength, height, or weight. Links? Yes, but weak and indirect.

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