CHAPTER NINE

The "discovery" of the "gay gene"

In 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, Dean 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]

This chapter will look at these studies, but as discussed earlier, scientists now believe large number of genes are involved in behaviours. The studies on changes in histone proteins (Chapters One and Eight) suggest that thousands of genes may be involved in almost any trait and that their expression can be greatly impacted by environmental events and even social interactions. Gene patterns may be a recipe for bodies, but are not a reliable recipe for behaviours. Though much effort has been spent trying to find SSA genes, none have yet been found.

Gene linkage studies

Hamer's work falls into a category of research called "gene linkage studies."(There was a surge of research in this field for quite a while but because of the availability now of thorough "whole genome" scans, gene linkage studies are now becoming rather passé.)

The first most spectacular linkage study, 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 whereabouts on chromosome 4. Over the succeeding decade, researchers also identified genes causing cystic fibrosis, muscular dystrophy, and other diseases.

From 1990 to 1993 biologists had astonishing success mapping the human genome (on schedule and within budget!) and analyses are still being published. In one five year period near the end of the nineties, 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 behaviours in the same way. This is what Hamer tried to do, and what other scientists, called behavioural geneticists, attempted to do before him, but with scant success. Today there is much research trying to link such traits as schizophrenia or bipolar disorder with genes that cause them. Research looking for links between human characteristics and genes is back in fashion after many decades in the dog-box since the Nazi era.[3]

What happens in Gene Linkage studies?

In linkage studies for behaviour, researchers look for an extended family with an unusually high incidence of some behaviour, such as bipolar disorder, and then take samples of tissue from all available members and analyse 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 and contain a range of genes. Searching for one gene in 22,000 is worse than looking for a contact lens in a swimming pool, but, in this way, segments of DNA (also containing "irrelevant" genes) can be found in different people. If the same sequence is associated consistently with a given trait, then researchers assume the marker lies close to the gene that

codes for it, along with the other irrelevant genes. 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 *behaviours* to a single gene, they run into a volley of scientific scepticism, for several reasons.

First, no mainstream geneticist believes that behaviour 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.[3] Second, in the word of one writer for *Science*, "the field of behavioral genetics is littered with apparent [gene linkage] discoveries that were later called into question or retracted."[4] It was only in the first decade of the 21st century that gene linkage studies became more reliable. Unfortunately the supposed SSA—genetic link was publicised before that time. And, as mentioned, the most recent studies have moved beyond linkage studies to scans of the entire genome, in great detail.

In the next section we survey gene linkage studies that have tried to identify genes linked to schizophrenia, alcoholism and IQ, to put in perspective what is needed for success in gene linkage studies.

About the time Hamer sought to associate SSA with a section of the X-chromosome, linkage studies were scientifically dubious, but seemed worth pursuing. Similar gene linkage studies on schizophrenia and alcoholism had given rather contradictory results.

Schizophrenia

Gene linkage studies on schizophrenia blossomed with the completion of the human genome project. Using markers, many regions were found on various chromosomes which correlated strongly with schizophrenia, and studies on fresh family lineages and families from 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. By August 2005, at least 25 chromosome regions were thought to be involved, and an equal number of genes on them were 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 gene linkage studies. The work had progressed so far that some researchers started to experiment with drugs which interacted with the products of the genes known to be involved, in the hope of reducing the progress of schizophrenia. But this confidence proved to be completely ill-founded. By mid-2010 "whole genome" scanning had thrown the gene linkage results into embarrassing disarray. In "whole genome" scanning— rather than using markers which result in rough screening only—all the genes are scanned in extraordinary detail, nucleotide by nucleotide. (There are hundreds of nucleotides in a single gene, each made up of a nitrogen base, a sugar and phosphate.)

Enormous multicenter efforts scanning the entire genomes of 7662 subjects and 29053 controls in one study alone, in association with a second involving 3322 subjects 3587 controls, and a third involving 8008 subjects and 19077 controls, could not confirm any of the previous gene-linkage work, only labelling it promising. One million gene variants were examined, involving most common variations of DNA nucleotides. They found absolutely unequivocal evidence of a connection to variants in a gene on chromosome 6 linked to immunity, and to three other completely new genes, two called transcription factors (TCF4 and ZNF804A the latter a "zinc finger" protein because of its composition and shape) and the last, called neurogrannin, none previously suspected of being involved. The transcription factors were used by the nucleus to read the DNA sequence and neurogranin is a brain-specific protein connected with biochemical control of calcium. Like the fruit-fly case we described in Chapter One, why these genes should be important in schizophrenia is not at all obvious, and links will be very indirect.

The "whole genome" studies showed the unreliability of previous work involving gene linkages. Schizophrenia is certainly polygenetic because four genes were found and others suspected: but these significant genes found only account for 3% of schizo-

phrenia. The saga is recounted elsewhere.[5] This is a vivid illustration of how difficult this field is.

Alcoholism

Modern gene-linkage studies of alcoholism have progressed to the stage where about 10 genes have been implicated, but inconsistently, and about 20 papers a year are being published. Even if all studies are combined, their significance is dubious. So even after lots of work no genes have been clearly identified. Alcoholism genes are proving even more elusive than those for schizophrenia

Intelligence

Plomin, the well known UK geneticist, embarked on a gene linkage search for regions and ultimately genes which might be associated with IQ (researchers these days much prefer the symbol "g" meaning general intelligence.) He thought this worth trying because other linkage studies suggested the genetic contribution to IQ was somewhere between 40 and 80 %. He used a large 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.[6]

Later in 2010, Plomin and co-workers reported a detailed "whole genome" scan of a considerably larger sample—several thousand individuals. After three stages of work they found 9 significant associations between high IQ and genes, but each was only just significant ($p < 0.05$) and may well not be replicable. They commented wryly that the genes "…remain tantalizingly beyond our current reach."[7] IQ is therefore very hard to link firmly to genes. It undoubtedly will link eventually, but the links to individual genes are likely to be weak and indirect.

Hamer's Study—SSA

Compared with the scale and outcomes of the work above, efforts which have attempted to link genes with SSA now seem small, naive and hyper-optimistic. Moreover, Chapter Ten shows the

genetic contribution to SSA is relatively low compared with, e.g intelligence, making success even less likely. However we review some of the historic efforts.

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.

To find the homosexual gene or genes, Hamer and his colleagues first recruited 76 homosexual men, who identified themselves as predominantly or exclusively homosexual. They found 13.5 % 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 38 families in which there were two homosexual brothers, suspecting this would show more clearly the effect of homosexuality. Hamer then searched for a linkage on the X (female) chromosome[2] (since males receive their single X chromosome exclusively from their mothers).

Hamer 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". Hamer published his paper in *Science*, in July 1993, and immediately became a controversial figure in the scientific community. Numerous letters to the journal *Nature*, for example, were mostly critical.

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 not be reliable. He took the very unusual step of questioning Hamer's findings in an editorial.[8] When asked about this by Hamer in a letter,[9] Maddox replied that "two previous such interpretations (published in this journal) have proved unfounded."[10] As we shall see, in retrospect Maddox was right.

In the meantime, Hamer[11] and colleagues replicated their study using a new population. This time, the results were less impressive—only just statistically significant, but the replication was promising.

Hamer's study on the "gay gene" was then contradicted in a gene linkage study [12] published in Western Ontario, headed by researcher Rice. It found 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 Hamer and Rice 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.

Then a "whole genome" study[13] appeared from the National Institutes of Health in Maryland, with collaborators from several parts of the US. It was much larger than any preceding gene linkage study. The first author was called Mustanski, and Hamer was included in the author list, though not leading the study.

According to the results in the paper, no part of the entire genome was statistically significantly linked with SSA. One peak on Chromosome 7 (region 7q36) approached statistical significance but the result will probably not survive replication.

Although Hamer's original sample was re-analysed and confirmed his original finding of significance for the Xq28 region, the larger combined (Hamer and Rice) sample did not. This strongly suggests the apparently significant 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..."

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

However, using a different method, the Rice team[14] then could not replicate the Mustanski results. This seems like the typical linkage difficulties re-occurring.

In a sociological study of homosexual subjects, Italian researchers [15] describe an excess of homosexual male relatives on the maternal side, supporting Hamer's previous papers. One quite unequivocal result is greater fertility on the female side, that is, among female relatives of homosexual men. It rather seems the most probable finding to emerge from all the above work is some association of SSA with homosexuality in a maternal relative, though this conflicts with a study by well-known researcher Bailey. This could suggest various genetic mechanisms, but all such studies were non-random samples, and conclusions from these are always doubtful.

As at mid 2010 a Chicago researcher called Sanders was reinvestigating the genetic links yet again and reportedly working on a sample of 1000 SSA brothers. Perhaps this study will confirm some of the currently non-significant links Mustanski et al. found, but in view of the huge sample numbers which were needed to confirm the association of genes with schizophrenia, and the lack of reliability of previous work, it looks unlikely the effort will succeed.

Hamer's group attempted another SSA-gene linkage study but did not find a link between parts of the X-chromosome and the presence of lesbian SSA in families.

We have mentioned epigenetic (non-DNA) influences in earlier chapters (Chapters One and Eight.) However no distinctive histone patterns for SSA people have yet been found. We also showed in **Figure 2**, that homosexuality is probably too common to have an epigenetic cause.

As at mid 2010, no homosexual genes or other genetic explanations are known, either for male or female. At least ten times the present effort would need to be expended in further work, and even then the results might be unimpressive.

Summary

The scientific community realises 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."[16] 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 non-conformity (the strongest known predictor of later homosexuality), could be held to be a contributing factor to later homosexuality. In a boy these might be, e.g genes related to slightness of build or poor

physical co-ordination (making a boy poor at sports). In a girl they might be factors like atypical physical strength, shape, height, or weight. Links? Yes, but weak and indirect.

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