

# A Review of Xq28 and the Effect on Homosexuality

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## Abstract:

The cause of homosexuality remains a hotly contested debate to this day. Although the role of genetics has diminished over the past decade because of the popularity of environmental influences, it continues to be a relevant correlative possibility. Since its inception in the early 1990's from a study conducted by Dr. Dean Hamer, the genetic locus Xq28 has become amongst one of the most important genetic factors of sexual orientation. Subsequent studies attempting replication have improved on the original experiment although the initial measures and methods of experimentation may have biased the results of the findings. Consequently, contention between advocates for and against Xq28 continues over 15 years later with mounting evidence weakening the link of Xq28 and homosexuality. Even though the majority of genetic discussion revolves around Hamer's original findings, more recent genetic markers have also now been found which may show positive connections and provide the basis for further research.

## Keywords:

Homosexuality, genetics, Xq28

## Introduction

Sexual orientation is a critical part of a person's identity which can influence their decisions and actions during life. Once thought of as a paired trait, sexuality is now commonly described as a continuous spectrum of varying degrees of attraction to one sex or another (Pederson & Kristiansen, 2008). This has, however, led to difficulty in estimating homosexual prevalence in society. As social acceptance continues to grow for people with same-sex orientations there is a continued interest in the natural underlying causes. Many possible speculations have arisen, ranging from differences in neural anatomy to environmental factors (Hamer, Hu, Hu, Magnusson, & Pattatucci, 1993). The area from which perhaps the most interest has been garnered is in the role of genetics. Evidence regarding such a heritable correlation began with homosexual twin studies (Mustanski et al., 2005). Subsequent research has focused on mapping specific genetic components. Whether or not a genetic linkage can be verified is important in both the social and scientific understanding of sexual orientation. Homosexuality is and will be defined within these contexts as a sexual attraction and preference for other members of the same sex (Hamer et al., 1993). In keeping with the available studies, discussion and investigation focuses almost exclusively on male human homosexuality.

## Discussion of Measures/Methods in genetic studies

Over the past twenty years, much research and controversy has surrounded a possible correlation between homosexuality and a maternal sex-linked genetic marker, Xq28 (Paterson, 1998). In the first study to map this connection, participants were taken randomly via newspaper and magazine advertisements that catered to homosexual communities (Rice, Anderson, Risch, & Ebers, 1999). A problem arising from this method of collection is the selectivity of the sample as participants consist only of self-identified volunteers. An unrepresentative subset may consequently be taken because of such an unsystematic method (Bailey et al., 1999). Due to the added complexity for females who have two X-chromosomes, where one is randomly inactivated, the samples consisted only of men. Participants who had homosexual fathers or sons were also omitted to withhold influences by unknown Y chromosome contributions. This was conducted through pedigree analysis using family histories (Hamer et al., 1993). The homosexual criterion of participants was identified through taking sexual histories

and Kinsey scales, an approved ordinal self-rating scale ranging from 0 (exclusively heterosexual) to 6 (exclusively homosexual), where scores of 5 and 6 were chosen (Hamer et al., 1993). This bimodal treatment of homosexuality was justified by Hamer because of the overlap between various groups in the study created by the Kinsey method. Also, since scaling techniques risk obtaining false positives, the size of effect attributed on the outcome is an area of criticism (Bailey et al., 1999). The last criterion of sample selection was that the participants had to be in pairs of homosexual brothers (sibling pairs). This criterion helps legitimize an X chromosome linkage for homosexuality, as related males should have distinguishing marks in similar regions (Hamer et al., 1993). The DNA of the mothers was also sampled if it was available, to corroborate maternal transmission. After an initial analysis, a polymerase chain reaction of 22 predetermined areas of the sample DNA from the homosexual sibling pairs was conducted. Using these pairs is a more stable method to errors when compared to broader pedigree techniques (Hamer et al., 1993). The results demonstrated statistically significant markers at Xq28 (Hamer et al., 1993). Subsequent studies have used similar methods of data collection and measurement to analyze the accuracy of this connection.

## Discussion of Genes

The Xq28 locus has been the most scrutinized genetic region for homosexuality. It is suggested that a component in the Xq28 location with heritable maternal material influences homosexual predisposition. As such, related males (brothers, maternal uncles & cousins) should share an excessive amount of allelic material in that region (Rice et al., 1999). Although the terminal portion of Xq28 may code for homosexuality as indicated by the markers, it is difficult to establish any direct gene products. Even though the X-chromosome codes for relatively few genes, hundreds of candidate genes may still be coded for in that band (Hamer et al., 1993). Possible genes mapped within Xq28 may be associated with neural functioning, however, these are all in different sub-bands of the same locus (Wilke, Gaul, Klauk, & Poustka, 1997). There has yet to be a study large enough to confirm and isolate a specific gene product. As a result, relevant studies focus on the potential of Xq28 to correlate with homosexuality as opposed to the prospective products. Despite criticism, the Xq28 markers continue to be the strongest sex-linked candidates of homosexuality.

## Support for Xq28

Primary support for Xq28 is found in the original study by Dean Hamer, which linked 33 of 40 Caucasian homosexual sibling pairs (83%) with the distinct markers. A study done in the same year led by Stella Hu, with a similar team, also found a significant relationship. In addition to using homosexual sibling pairs, this study sampled heterosexual brothers to see if they had similar linkages in the Xq28 region. The results demonstrated that 67% of the homosexual pairs and only 22% of the heterosexual pairs shared any X-linked connection (Hu et al., 1995). Even though this confirms that heterosexual males lack certain Xq28 regions, the sample sizes were smaller, using only 32 homosexual pairs and 11 heterosexual pairs. The continued risk of obtaining unrepresentative samples remains a legitimate concern. This study was also the first to attempt and find similar outcomes in females. The results demonstrated no significant sharing of Xq28 markers in both heterosexual and homosexual sibling pairs (Hu et al., 1995). Within the study itself, there was acknowledgement that although this likely indicates different mechanisms for females, the sample sizes were too limited to make a more definitive statement (Hu et al., 1995). Another explanation for the findings is that the Xq28 locus might be recessive in females signifying that female homosexuality may not be influenced by sex-linked genes (Hu et al., 1995). Subsequently, Xq28 continues to only be a plausible factor of male homosexuality as females and heterosexual males show no excessive links. These findings along with pedigree analyses also confirm the lack of paternal transmission for Xq28 in women.

## Criticism of Xq28

A highly referenced study that contrasts with the significance of Xq28 was conducted by George Rice. The study was markedly similar to the original with the main exceptions being that the sample sizes were larger at 52 sibling pairs and taken from Canada, as opposed to Italy (Rice et al., 1999). The resultant data was determined to have only a 55% correlation found in Xq28 sharing (Rice et al., 1999). Comparatively to both Hamer and Hu's findings of 83% and 67% correlations, the final conclusion did not support Xq28 in a significant manner. This discrepancy is largely unaccounted for except a possibility that tighter controls in the previous studies may have been used to exclude potential candidates depending on homosexual relatives (Rice et

al., 1999). Still, because the variations between the studies were minimal, the reliability of the original findings can be legitimately questioned. In 1999, John Bailey's study was the first to attempt to garner a more representative subset through different sampling techniques. The study took two significantly larger samples than Hamer from an HIV clinic and a gay pride parade where they incidentally sampled male participants who would consent during that period (Bailey et al., 1999). Although there continues to be a sampling bias from this method, it has more validity than collecting volunteers through advertisements. Consequently, this study found no definitive support for Xq28 but reiterates that it does not exclude the possibility of a moderate linkage (Bailey et al., 1999).

Over the last decade there has been continuing research in the consistency of the Xq28 link as well as deviations into other possible genes of interest. The first study to implement a complete genome scan for sexual orientation in males denotes several possible new genes and mild support for Xq28. In the genomic scan study, maximum likelihood of estimation scores were used for genetic analysis in which results higher than 1.8 were given significance (Kruglyak & Lander, 1995). The sample size was significantly larger than previous studies having a total of 456 homosexual individuals (Mustanski et al., 2005). The findings showed three new genetic markers of interest at 7q36, 8p12 and 10q26. The latter two loci have equal inheritance from maternal and paternal lines, suggesting more influence from autosomal instead of sex-linked genes (Mustanski et al., 2005). The region at 8p12 participates in the coding of Gonadotropin-releasing hormone which stimulates both luteinizing and follicle-stimulating hormones that are important in steroidogenesis (Adelman et al. 1986). 10q26 has been linked with some neural proteins in the brain (Mustanski et al., 2005). The most significant marker, 7q36, has coding regions for neurotransmitter and hormone gene products for the hypothalamus (Mustanski et al., 2005). This may suggest plausible relationships with neural gene products. These three genetic markers provide support for the idea of multiple gene interactions in homosexuality. Regarding support for Xq28, the markers had to be selectively controlled in this case to demonstrate a mildly significant score of 1.99 (Mustanski et al., 2005). Accordingly, Xq28 represents a more minor aspect of homosexuality than previously believed.

Some recent research has gone into the influences of various gene products such as sex hormones. Specifically, an analysis of gene CYP19, which aids conversion of andro-

gens into estrogen, showed no significant effects in male homosexuality (DuPree, Mustanski, Bocklandt, Nievergelt, & Hamer, 2004). Still, due to the strength of data from outside studies on animals, sex hormones and androgen receptors continue to be a viable path of interest for homosexual causation (Dupree et al., 2004).

## Conclusion

The inconclusive genetic findings present only possible explanations of genotypic information underlying homosexual expression. Since the results of the original Xq28 study have never been replicated to such a significant degree, the validity of the outcome has been weakened. It is quite evident in alternate studies that as sample sizes become larger and more selective (increasing statistical power) the visibility of such a relationship becomes diminished. Although Xq28 remains the most prominent sex-linked candidate, support has been shifting towards the more probable influence of autosomal genes (Mustanski et al., 2005). Currently, such new genes of interest potentially code for products such as neurotransmitters and prenatal hormones (Mustanski et al., 2005). Unfortunately there is no substantial evidence to suggest that these genes are related to homosexuality in a considerable manner. As no genetic link is strongly correlated enough to demonstrate causation, it is appropriate to assume that no single gene is responsible for homosexuality. Instead, it is a combination of different genes that provide a propensity towards homosexuality. Although abundant research has focused upon genetic influence, homosexuality may be solely a behavioural characteristic and subsequently the weight of the environment needs to be considered. Regarding the social environment, the idea that homosexual parents are prone to have a higher prevalence of homosexual children has been largely discredited (Morrison, 2007). It is illogical to deduce that homosexuals would have had any significant deviation from “normal” parenting methods. Using twin studies has provided evidence that sexual orientation can be impacted, in part, by non-shared environmental influences (Mustanski et al., 2005). It has proven very difficult to isolate what those unique factors could be. Nevertheless, the rich complexity of physical and social elements likely shape beliefs and characteristics to some degree. Consequently, more studies are still required to facilitate further understanding of genetic influence and which gene products, if any, can be strongly linked. Environmental studies should continue in the social context until more specific

genes can help identify possible physical factors. A focus also needs to center on female homosexuality, although it is more complex to study, it should not be ignored as a crucial part of this variant behavior. The recent autosomal genetic markers may provide a link between both sexes. Thus, as the current evidence suggests, regardless of future studies, it is likely a multitude of possible genes working in conjunction with environmental factors and triggers that produces homosexual behavior.

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