D. H. Hamer, S. Hu, V.L. Magnuson, N. Hu, and A.M. Pattatucci (1993). A Linkage Between DNA Markers on the X Chromosome and Male Sexual Orientation. <u>Science</u> 261:321



The Hamer Group, 1993 (Dean Hamer Front & center)

## **Background and Introduction**

The purpose of this experiment was to determine if sexual orientation in males is genetically influenced.

## **Previous Work**

#### Simon Levay

Simon LeVay suggested a link between the size of parts of the brain and sexual orientation.

#### **Pillard and Weinrich**

Study by R.C. Pillard and J.D. Weinrich

obtained information about the sexual orientation of the siblings of homosexual men

had them complete questionaires

22% of the brothers of homosexual men that they studied were homosexual or bisexual.

Suggested several ways their results could have been artificial:

- Recruiting bias by encouraging homosexual men with homosexual brothers to volunteer.
- Homosexual men more likely to recognize that their brothers were also homosexual, and vice versa.
- Some families of the heterosexual index subjects interviewed may have had homsexual brothers who identified themselves as heterosexual.

stated that the results they obtained did not suggest that homosexuality ran in families, or had a genetic or horomonal basis.

#### **<u>Bailey</u>** and Pillard

Carried out by J. Michael Bailey and Richard C. Pillard.

Recruted subjects through ads placed in gay publications in Midwestern and Southeastern USA.

Looking for homosexual or bisexual men with male cotwins, adoptive brothers or brothers who were not genetically related.

Conducted 1-2 hour interviews with subjects to determine sexual orientation, then contacted siblings.

Results:

- In 25 out of 50 (50%) surveys of confirmed homosexual men with a monozygotic twin, their twin was also homosexual.
- In 11 out of 46 (24%) of confirmed homosexual men with a dizygotic twin, their twin was also homosexual.
- In 6 out of 31 (19%) surveys of confirmed homosexual men with an adoptive brother, their brother was also homosexual.
- Concluded that their results indicated a substantial genetic influence on the sexual orientation of males.

There may have been an ascertainmant bias in their study in that they recruited only readers of the publications in which they placed ads.

# **Materials & Methods**

### **Experimental Overview**

Hamer *et al.* used pedigree analysis and <u>sib-pair linkage analysis</u> to determine the role of genetics in male sexual orientation:

Initial results suggested the possibility of a maternally-inherited trait in some individuals.

Possible causes for appearance of male-limited, maternally-inherited trait in pedigree:

- 1. X-linked gene (Hamer's prediction).
- 2. Maternal effects.
- 3. Decreased reproductive rates of expressing males.
- 4. Differential knowledge concerning maternal vs paternal family members.

DNA linkage analysis would distinguish X-linked inheritance from other causes:

- Linked inheritance of marker allele and homosexuality = locus increases probability of being homosexual
- No linked inheritance between marker allele(s) and homosexuality = loci do not increase probability

### Selection of participants and characterization of subjects

Two groups of homosexual males were sampled for this experiment:

- 1. Random group of 76 homosexual males.
  - Initial pedigree analysis to look for any inheritance patterns of the homosexuality trait.
- 2. 38 pairs of homosexual brothers that demonstrated possible maternal inheritance.
  - Pedigree and linkage analysis to locate possible loci on the X chromosome responsible for inheritance of homosexuality.

Subjects recruited through advertisements at HIV clinics and in homophile publications.

Sexual orientation of subjects was assessed using the Kinsey scales.

### **Pedigree Analysis**

Population prevalence of homosexuality = 2% = background rate of homosexuality.

Probability of homosexuality greater than 2% suggests an inheritance pattern.

Categories of male relatives (ie-brother, maternal uncle) with higher than 2% probability identified.

### **DNA Linkage Analysis**

DNA samples taken from 40 pairs of brothers (sib-pairs) and [some of] their mothers.

Typed each sample according to 22 markers spanning the X-Chromosome (1) (2).

At each marker loci, categorized each brother pair as one of the following:

- Concordant-by-descent (D)
- Concordant-by-state (S)
- Discordant (-)
- Noninformative (n)

Using likelihood ratio test, showed probability of brothers sharing a marker allele at each locus by descent:

- Probability close to 0.5 = no linkage
- Probability greater than 0.5 = linkage

Multipoint mapping used to visualize loci on X-Chromosome linked with homosexuality.

- Mapping based on LOD scores
- Region on chromosome with highest LOD score is likely region responsible for homosexuality trait

# **RESULTS**

Pedigree Analysis

Linkage Study

Multipoint mapping

## CONCLUSIONS

Hamer *et al.* suggested from this study that one form of male homosexuality is inherited maternally and that it is linked to a region of the X chromosome, Xq28.

There was nothing found in this study that indicated any linkage between sexual orientation and loci outside of the Xq28 region.

Hamer suggested the following reasons for the fact that 7 pairs of brothers did not inherit all of the markers (discordant) in the Xq28 region:

- The mother may have been homozygous at the locus related to sexual orientation
- There may have been recombination between the locus and a marker gene
- Genetic heterogeneity
- Non genetic sources

He did not conclude that this single genetic locus was completely responsible for the determination of sexual orientation in males.

# Impact

Due to the nature of this paper, there are obvious social and political implications. In addition, certain methods and techniques have been critically reviewed by other researchers. Independent groups attempting to reproduce Hamer's results have failed to find a link between homosexuality and Xq28. Below are a series of articles that detail some of the discussions, debates, and research following the publication of this paper.

1999 paper by Western University Researchers who failed to find linkage to markers on Xq28:<u>http://www.sciencemag.org/cgi/content/full/284/5414/665</u>.

Hamer's response to the above paper: http://www.sciencemag.org/cgi/content/full/285/5429/803a

1997 Science article describing an inquiry into possible scientific misconduct by Hamer: http://www.sciencemag.org/cgi/content/summary/275/5304/1251b.

Questions? email Lisa or Josh