

NEWFOUNDLAND

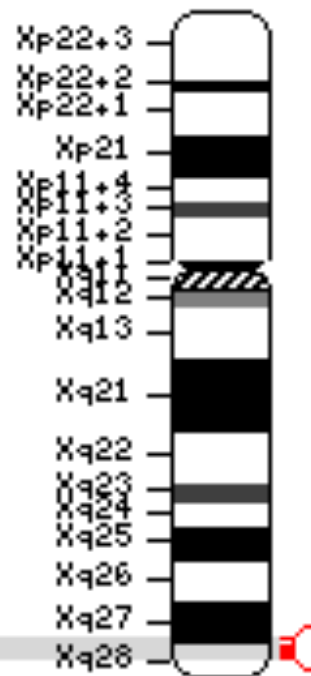
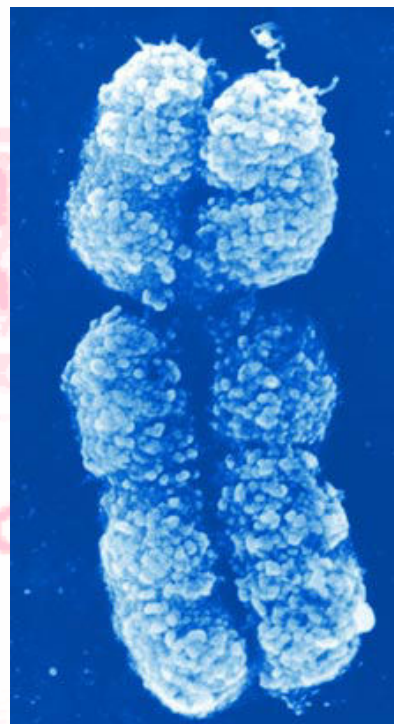
RESEARCH ARTICLE SCIENCE • VOL. 261 • 16 JULY 1993

A Linkage Between DNA Markers on the X Chromosome and Male Sexual Orientation

Dean H. Hamer, Stella Hu, Victoria L. Magnuson, Nan Hu, Angela M. L. Pattatucci

The role of genetics in male sexual orientation was investigated by pedigree and linkage analyses on 114 families of homosexual men. Increased rates of same-sex orientation were found in the maternal uncles and male cousins of these subjects, but not in their fathers or paternal relatives, suggesting the possibility of sex-linked transmission in a portion of the population. DNA linkage analysis of a selected group of 40 families in which there were two gay brothers and no indication of nonmaternal transmission revealed a correlation between homosexual orientation and the inheritance of polymorphic markers on the X chromosome in approximately 64 percent of the sib-pairs tested. The linkage to markers on Xq28, the subtelomeric region of the long arm of the sex chromosome, had a multipoint lod score of 4.0 ($P = 10^{-5}$), indicating a statistical confidence level of more than 99 percent that at least one subtype of male sexual orientation is genetically influenced.

X chromosome: Xq27~28 region



MEMO

LLEGE

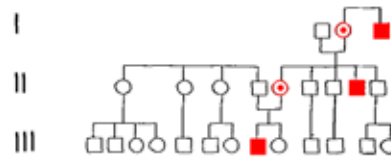
30
CENTS

X-linked male homosexuality

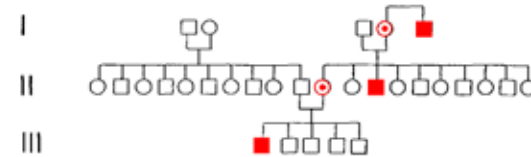
Fig. 3.

- (■) Homosexual males
- (□) Nonhomosexual males
- (○) Nonhomosexual females
- (◉) Nonhomosexual females [inferred carrier]

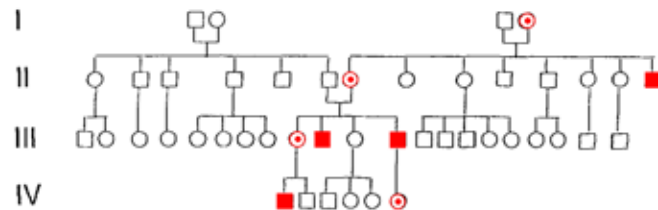
DH99002



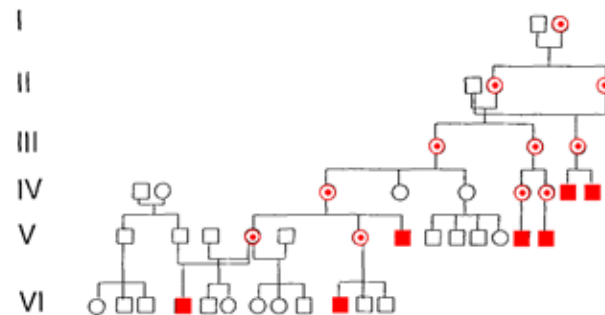
DH99017



DH321

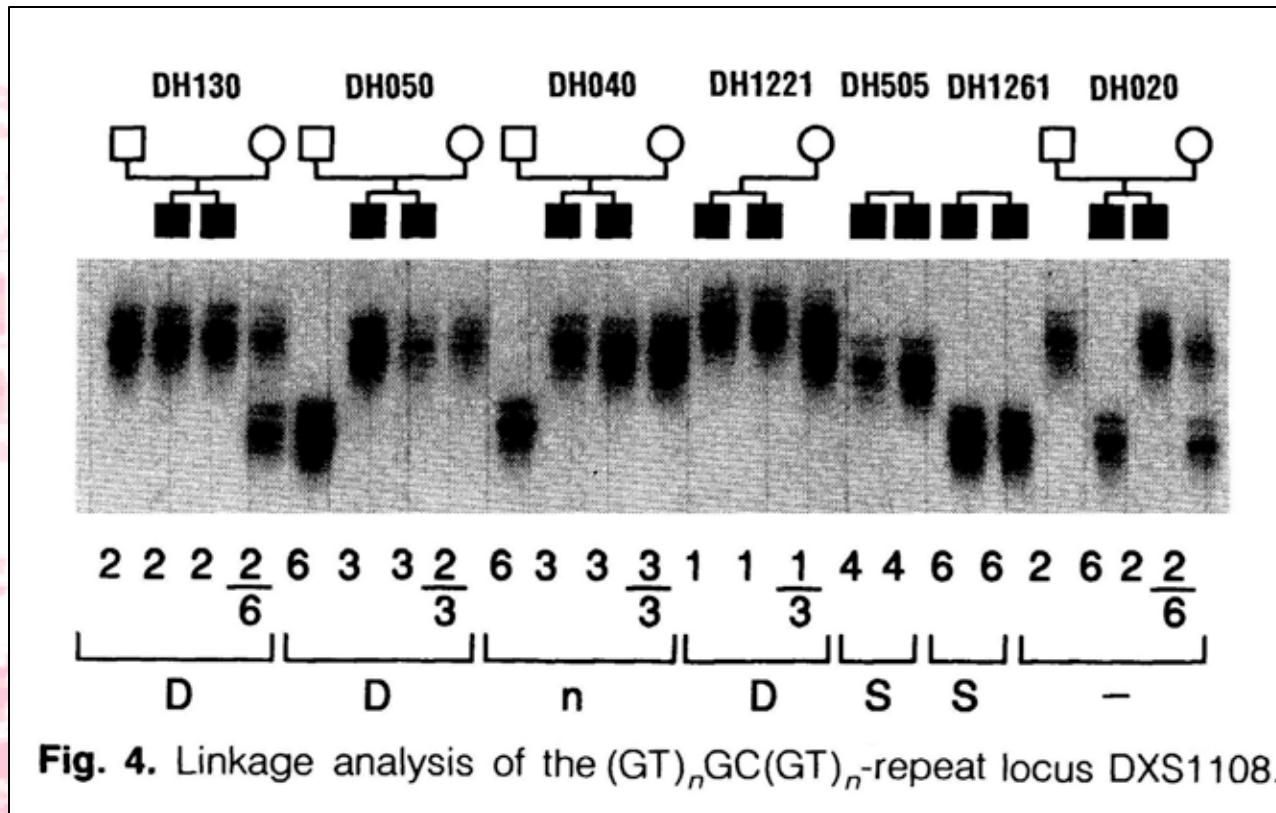


DH210

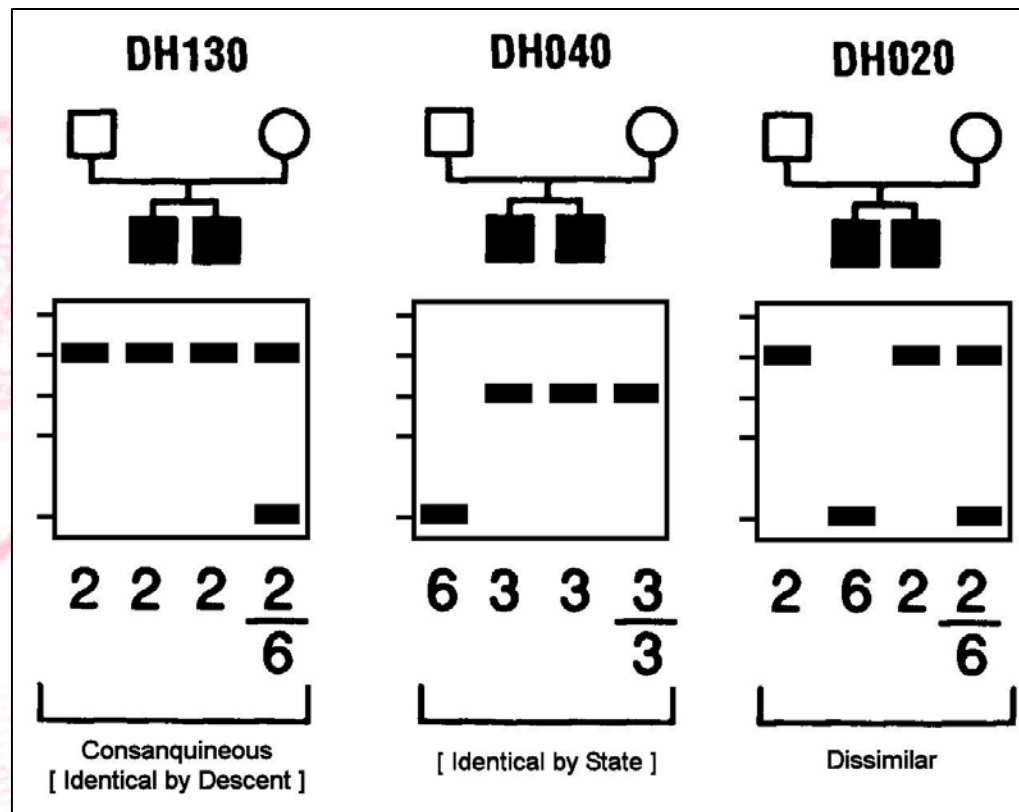


Identity by (S)tate & (D)escent

vs discordant (-) & un-informative (n) sites



Identity by Descent & State: consanguineous vs dissimilar X chromosomes



Trait assignment to RS region

Table 3. (D) concordant by descent
 (S) concordant by state
 (-) discordant
 (n) noninformative

Proband ID #	Marker locus ABCDEFGHIJKLMNO Pq	RS	TUV
DH130	nDDDDnDnDnDnDn	nn	DDD
DH050	D n nnnDnmmn	Dn	nDD
DH040	n nDDnDnDnDnDn	DD	nnd
DH371	DD n DnDnDnmmn	Dn	nnd
DH1221	D DnDnDnDnDn	nd	DDD
DH070	DDD nd DDDnDnDn	DD	DDn
DH471	D n n DDDDD	Dn	nDD
DH060	nDn n DDDnDn	Dn	DDD
DH151	DnDnDn DnDnDn	Dn	nnd
DH170	n nDDnDnDn nn	DD	DDn
DH441	DD n nnd n nn	Dn	nnn
DH301	DDSSnDnDnS	S	nDn
DH411	SSSSSSSSSSSSSSSS	SS	SSS
DH1281	S SSSSSSSSSSSSSSS	SS	SSS
DH231	SSSSSS SSSSSSS	SS	SSS
DH1261	SSSS S SSSSSS	SS	SSS
DH1391	SS S SSSSSSSSSSSSS	SS	SSS
DH331	SSSSSSSSSSSSSSSS	SS	SSS
DH421	SSS SSSSSSSSSSSSS	SS	SSS
DH1131	SS S SSSSSSSSSSSSS	SS	SSS
DH311	SSSS SSSSSSSSSSSSS	SS	SSS
DH1081	SSS SSSSS SSSSSS	SS	SSS
DH321	SS S SSSS SSSSSS	SS	SSS
DH505	SSS SS S SSSSSS	SS	SSS
DH1171	SSS S S SSSSSS	SS	SSS
DH281	S SSSSSS	SS	SSS
DH461	SS S SSSSSS	SS	SSS
DH1191	SSS SS SSSSSS	SS	SSS
DH1381	SS SS SS S SS	SS	SSS
DH1331	SS S S S S S S	SS	SSS
DH1211	S SSSSSSSS	S	SSS
DH1061	SSS SSSSSS	S	SSS
DH1101	S SSSSSSSSSSSS	SS	SSS
DH391	n nnnn nnDD	n n	nnn
DH220	nDD	n n	n
DH020	DnDnD DD	nn	n
DH1041	SDDnDnDnDn S	S	Sn
DH1121	SSSSSSSS SSSS	SS	SS
DH1021	SSSSSSSSSSSS	SS	SS
DH1051	SS S SS S	S	S

Linkage Analysis

over 22 X-chromosome markers (A-V)

Table 2. Summary of linkage results. Linkage analysis was performed on 40 male homosexual sib-pairs; 22 X chromosome markers were used (30). The five marker loci on distal Xq28 are in boldface.

Locus	Location	AL*	HET†	Sib-pairs‡			z_1 §	$2\ln L(z_1)$	P¶
				[D]	[S]	[-]			
A. .KAL	p22	6	0.77	5	16	14	0.51	0.01	ns
B. .DXS996	p22	11	0.84	7	14	18	$\leq .5$	≤ 0	ns
C. .DXS992	p	8	0.87	6	13	19	$\leq .5$	≤ 0	ns
D. .DMD1	p21	9	0.78	3	10	23	$\leq .5$	≤ 0	ns
E. .DXS993	p11	6	0.80	3	14	17	$\leq .5$	≤ 0	ns
F. .DXS991	p	8	0.77	8	14	14	0.57	0.61	ns
G. .DXS986	q	10	0.71	7	20	10	0.65	2.11	ns
H. .DXS990	q	7	0.76	4	19	13	0.55	0.25	ns
I. .DXS1105	q	5	0.48	3	20	9	$\leq .5$	≤ 0	ns
J. .DXS456	q21	10	0.85	8	20	8	0.75	7.95	0.00241
K. .DXS1001	q26	10	0.82	8	16	13	0.60	1.09	ns
L. .DXS994	q26	5	0.75	7	17	13	0.55	0.26	ns
M. .DXS297	q27	5	0.70	5	21	8	0.71	4.25	0.01963
N. .FMR	q27	17	0.79	6	17	14	0.56	0.45	ns
O. .FRAXA	q27	8	0.72	4	17	13	0.56	0.38	ns
P. .DXS548	q27	6	0.67	7	20	7	0.73	5.21	0.01123
Q. .GABRA3	q28	4	0.35	2	23	3	0.74	2.39	ns
R. .DXS52	q28	12	0.79	9	22	6	0.81	11.83	0.00029
S. .G6PD	q28	2	0.36	4	24	2	0.85	6.38	0.00577
T. .F8C	q28	2	0.41	5	24	3	0.82	6.56	0.00522
U. .DXS1108	q28	6	0.71	8	22	4	0.85	12.87	0.00017
V. .DXYS154#	q28	10	0.71	8	22	5	0.83	12.84	0.00017
R/S/T/U/V	q28	0.99	0.99	12	21	7	0.82	18.14	0.00001

*AL is the number of different alleles observed in 62 to 150 independent chromosomes. †HET is the calculated heterozygosity; $HET = 1 - \sum f_i^2$, where f_i = frequency of the i th allele. ‡[D] is the observed number of concordant-by-descent pairs; [S] is the observed number of concordant-by-state pairs; [-] is the observed number of discordant pairs; noninformative pairs are not included in this analysis. § z_1 is the estimated probability that two homosexual brothers share the marker locus by-descent (31). || $L(z_1)$ is the ratio of the likelihoods of the observed data at z_1 versus the null hypothesis of $z_1 = 1/2$ (31). ¶ P (one-sided) was calculated by taking $2\ln L(z_1)$ to be distributed as a chi-squared statistic at one degree of freedom; ns: $P > 0.05$. # Only the maternal, X-linked contribution was considered for this sex-linked locus (23).

LOD scores, long calculation

Let z_1 = the probability that a pair of brothers share a marker allele by-descent (z_1 is an unknown parameter that is estimated from the data),

$\Gamma(z_1)$ = the likelihood of the observed data at z_1

$\Gamma(1/2)$ = the likelihood of the observed data under the null hypothesis of $z_1 = 1/2$

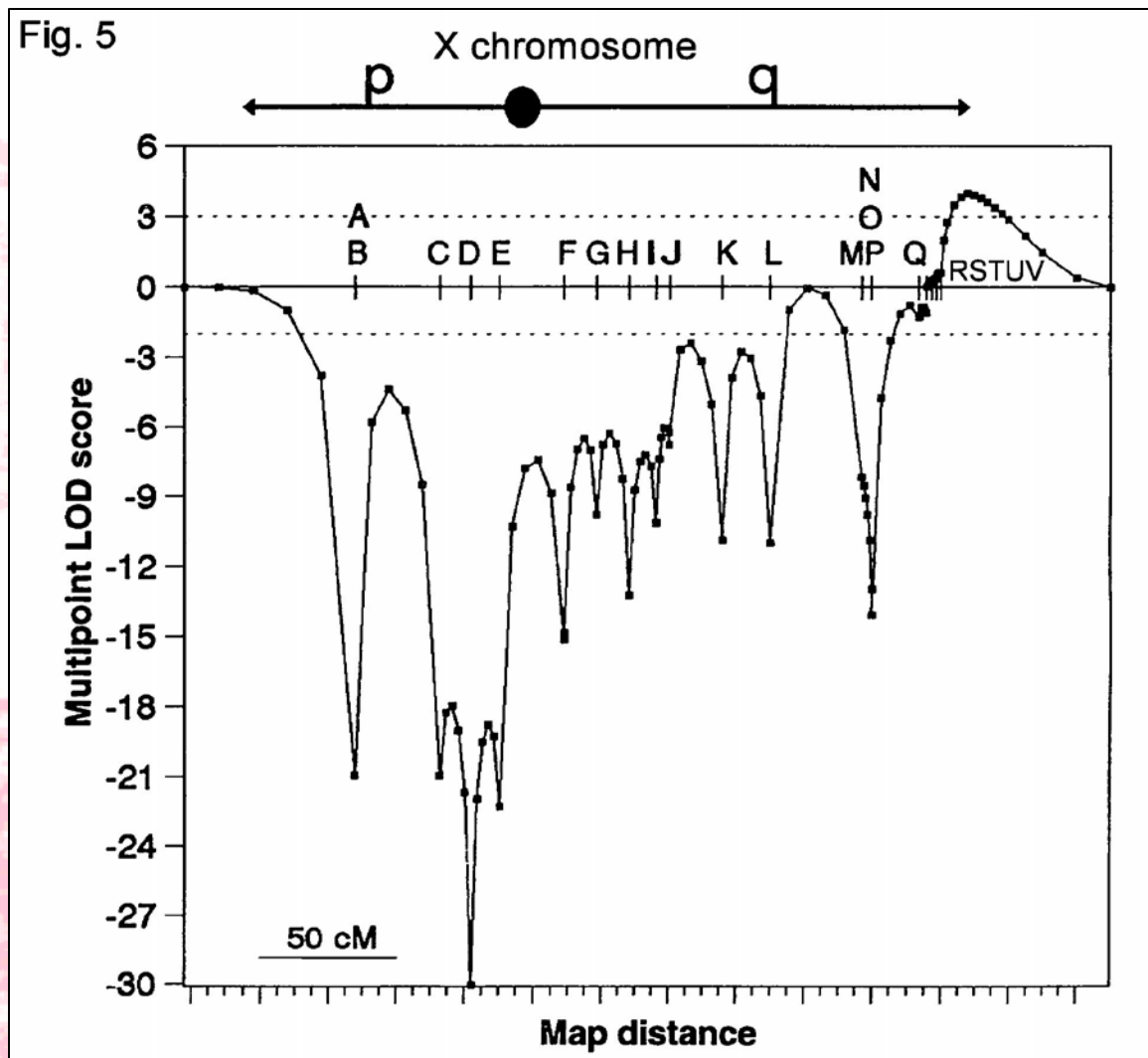
$L(z_1) = \Gamma(z_1)/\Gamma(1/2)$

$$2 \sum_{j=1}^N \ln[L_j(z_1)] =$$

$$2 \left(\sum_{j=1}^G \ln[(1 - z_1)/(1/2)] + \sum_{j=1}^D \ln[(z_1)/(1/2)] + \sum_{j=1}^S \ln\{f_j(z_1 + f_j - f_j z_1)/[f_j(1 + f_j)/2]\} \right) =$$

$$2 \left(G \ln(2 - 2z_1) + D \ln(2z_1) + \sum_{j=1}^S \ln[2z_1 + 2f_j - 2f_j z_1]/(1 + f_j) \right)$$

LOD score assignments: high scores in RS region of Xq28



LOD score analysis, simplified

Concordant	non-Concordant	ratio	odds ratio (0.8)	LOD	Chi Sq
0	40	0.00	0.00	-15.9	40.00
2	38	0.05	0.00	-14.7	32.40
4	36	0.11	0.00	-13.5	25.60
6	34	0.18	0.00	-12.3	19.60
8	32	0.25	0.00	-11.1	14.40
10	30	0.33	0.00	-9.9	10.00
12	28	0.43	0.00	-8.7	6.40
14	26	0.54	0.00	-7.5	3.60
16	24	0.67	0.00	-6.3	1.60
18	22	0.82	0.00	-5.1	0.40
20	20	1.00	0.00	-3.9	0.00
22	18	1.22	0.00	-2.7	0.40
24	16	1.50	0.03	-1.5	1.60
26	14	1.86	0.54	-0.3	3.60
28	12	2.33	8.71	0.9	6.40
30	10	3.00	139.38	2.1	10.00
32	8	4.00	2230.07	3.3	14.40
34	6	5.67	35681.19	4.6	19.60
36	4	9.00	570899.08	5.8	25.60
38	2	19.00	9134385.23	7.0	32.40
40	0	—	146150163.73	8.2	40.00

Marker	Concordant	non-Concordant	odds ratio (0.8)	LOD
A	16	24	0.00	-6.3
B	16	24	0.00	-6.3
C	20	20	0.00	-3.9
D	14	26	0.00	-7.5
E	20	20	0.00	-3.9
F	22	18	0.00	-2.7
G	24	16	0.03	-1.5
H	26	14	0.54	-0.3
I	28	12	8.71	0.9
J	30	10	139.38	2.1
K	32	8	2230.07	3.3
L	34	6	35681.19	4.6
M	36	4	570899.08	5.8
N	38	2	9134385.23	7.0
O	34	6	35681.19	4.6
P	30	10	139.38	2.1
Q	26	14	0.54	-0.3
R	22	18	0.00	-2.7
S	20	20	0.00	-3.9
T	16	24	0.00	-6.3
U	20	20	0.00	-3.9

LOD score assignments:
high scores in **RS** region of **Xq28**

