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Point of View

Concordance by Sex in Sibling Pairs with Schizophrenia is Paternally Inherited

Evidence for a Pseudoautosomal Locus

TIMOTHY J. CROW, LYNN E. DeLISI and EVE C. JOHNSTONE

The hypothesis that the gene for schizophrenia is located in the pseudoautosomal region of the sex chromosomes predicts that same-sex concordance will occur in paternally rather than maternally derived pairs. In 120 families that included at least one sibling pair with schizophrenia, affected members were significantly more likely to be of the same sex when there was a history of illness on the paternal than on the maternal side, the difference remaining significant when parent of origin was assessed by three different methods. The finding is as predicted by the pseudoautosomal hypothesis: therefore a search for the gene should be focused on this small (three megabase) region of the genome. The ratio of same to mixed sex pairs in paternally-derived cases (approximately 3 : 1) suggests the gene is located in the centromeric one-third of the pseudoautosomal region.

A role for genes in the aetiology of schizophrenia is supported by twin and adoption studies (Gottesman & Shields, 1982), but neither the genomic locus nor the mode of inheritance has been identified. A locus on the sex chromosomes has not been widely entertained. Although sex linkage has been considered (e.g. by Slater, 1953*b*) for occasional pedigrees, a sex chromosomal locus for schizophrenia in general appears to be ruled out by approximately equal incidence in the two sexes and equal risk to the children of affected men and affected women. However, gender does influence the pattern of psychosis within families. Mott (1910) was the first to report a tendency for pairs of relatives with psychosis to be more frequently of the same than of mixed sex. The phenomenon was also noted by Myerson (1925) and Penrose (1942). Table I summarises published studies of psychotic sibling pairs; a 28% excess of same-sex pairs is present.

Sturt & Shur (1985) have drawn attention to various types of sampling bias, particularly those associated with incomplete or biased ascertainment, that might account for same-sex concordance. But such concordance is also seen in dizygotic twin pairs; in this case some of the ascertainment biases described by Sturt & Shur are not relevant and sampling errors can be checked by a comparison with same : mixed sex ratios in discordant pairs (Table II). A substantial same-sex excess in concordant pairs is still present.

It was previously suggested (Crow, 1983) that contagion might be a factor in the aetiology of schizophrenia, and that same-sex concordance could reflect an environmental influence, for example related to closer proximity of same-sex by comparison

TABLE I
Distribution by sex in sibling pairs with schizophrenia

	Schulz (1932)	*von Zehnder* (1941)	*Penrose* (1945)	*Tsuang* (1967)	*Totals*
Same sex	75	43	230	19	367
Mixed sex	56	29	192	9	286

Sign test (for the comparison with a 50 : 50 distribution) $z = 3.13$, $P < 0.001$.

TABLE II
Concordance for schizophrenia by sex in dizygotic twin pairs

	Slater (1953a)		*Rosanoff* et al *(1934/35)*		*Kallmann (1946)*		*Kringlen (1968)*		*Totals*	
	conc.	*disc.*	*conc.*	*disc.*	*conc.*	*disc.*	*conc.*	*disc.*	*conc.*	*disc.*
Same sex	11	50	10	43	34	262	6	84	61	439
Mixed sex	2	52	5	43	13	208	8	74	28	377

Same : mixed sex ratio = 2.17 (concordant), 1.16 (discordant). conc. = concordant; disc. = discordant. Sign test (for the comparison with a 50 : 50 distribution) $z = 3.8$, $P < 0.0002$.

with opposite-sex siblings. But analysis of age of onset of psychosis in siblings ruled out contagion and other post-natal environmental influences (Crow & Done, 1986). Therefore if concordance by sex is not an artefact and cannot be attributed to the environment, it may have a genetic explanation. Given the apparent absence of sex linkage, Penrose (1942) considered an influence of auxiliary (i.e. autosomal) genes for determining sex. An alternative explanation (Crow, 1987, 1988) is that the psychosis locus is in the pseudoautosomal region (Fig. 1).

In male meiosis a single obligatory crossing over takes place in a small segment of the distal short arms of the X and Y chromosomes (Burgoyne, 1986). Within this region homology of sequence between X and Y chromosomes is present (Goodfellow *et al*, 1983), and there is a gradient of sex linkage from the sex-chromosome-specific region out to the short-arm telomere (Rouyer *et al*, 1986). Genes within the region are transmitted in a manner that appears autosomal but has one additional characteristic. If a father carries a defective gene in this part of his X chromosome he is likely to have affected daughters, but if he carries the gene on the corresponding part of the Y chromosome his sons are at greater risk. Therefore affected individuals will be more often of the same sex than the 50:50 expectation. If the gene is at the telomere (where 50% recombination takes place), or when transmission is from the mother, no such effect is predicted. On account of the gradient of sex linkage the size of the concordance effect gives a clue to the location of the gene within this region.

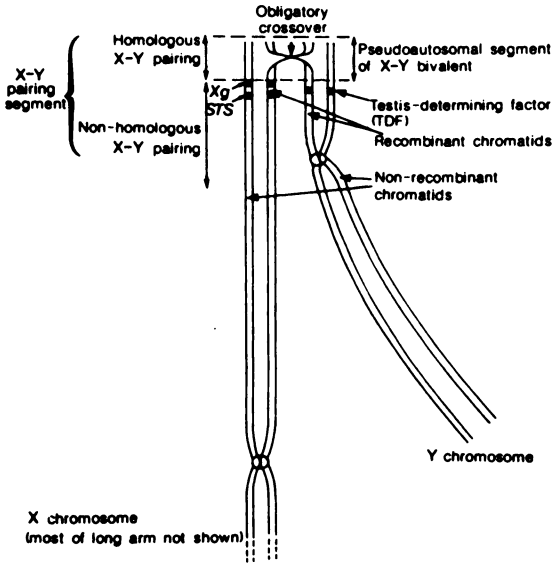

FIG. 1 Crossing over between X and Y chromosomes in male meiosis in the human pseudoautosomal region. Within this segment there is homology of genetic sequence between X and Y chromosomes. In male meiosis a single obligatory crossing over takes place as indicated: since this cross-over occurs within a confined region, recombination here is high relative to that within the region in female meiosis and in the rest of the genome. Because the position of the cross-over varies, a gradient of sex linkage exists within the region such that for genes located at the telomere (where there is 50% recombination) sex linkage is absent. By contrast, sex linkage (and concordance by sex) is greatest for genes located close to the pseudoautosomal limit. X_g = location of X_g blood group gene; *STS* = steroid sulphatase gene. (Reproduced by permission from Burgoyne (1986). Copyright ©1986 Macmillan Magazines Ltd.)

Method

We examined concordance by sex in two series of pairs of siblings with schizophrenia: (a) a series (79 sibships from 78 families) collected (from January 1985 to September 1988) across the United States with the help of the National Alliance for the Mentally Ill (NAMI) under the auspices of the Clinical Neurogenetics Branch of the National Institute of Mental Health and at the State University of New York at Stonybrook; and (b) a population-based series (41 families) collected under the auspices of the UK Medical Research Council at a district general hospital (Northwick Park Hospital; NPH) in north-west London.

Criteria for inclusion were (a) that each individual had suffered from a psychotic illness of sufficient severity to require hospital admission, and (b) that the illness met the criteria for a diagnosis of chronic schizophrenia or schizoaffective disorder by Research Diagnostic Criteria (RDC) (series 1) or fulfilled the St Louis criteria for schizophrenia, or on Present State Examination were placed in one of the CATEGO schizophrenic categories (series 2). Clinical features of 53 sets of siblings from the first series have been previously reported (DeLisi *et al*, 1987). A brief report of concordance by sex in the combined series has also appeared (Crow *et al*, 1989) without the detailed classification of family history employed here or the statistical correction in pairwise analysis discussed below.

In each series an attempt was made to identify other family members with major psychiatric illness by interview with multiple informants. Families were classified according to whether there was a history of illness on the maternal or paternal sides, by means of three alternative systems of classification:

(a) a 'hierarchical' system in which the parental origin of illness was designated according to the following order of priorities:
  (i) *schizophrenia* in a parent
  (ii) schizophrenia in a first-degree relative of a parent
  (iii) schizophrenia a second-degree relative of a parent
  (iv) *psychosis not otherwise specified* (NOS) in a parent
  (v) psychosis NOS in a first-degree relative of a parent
  (vi) psychosis NOS in a second-degree relative of a parent
  (vii) *affective disorder* in a parent
  (viii) affective disorder in a first-degree relative of a parent.

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In this system one step in the diagnostic sequence from schizophrenia through psychosis NOS to affective disorder was considered equivalent to one step in the sequence from parent to first- and second-degree relative of parent. Thus affective disorder in a parent, psychosis NOS in a first-degree relative, and schizophrenia in a second-degree relative of a parent were considered equivalent. Thus if affective disorder was present in the mother and psychosis NOS in the father's brother, the family was designated bilateral.

(b) a 'unilateral' system in which parental origin was designated when illness (as defined in any of the above categories) was present on one but not on the other side

(c) a 'closest relative' system in which parental origin was designated by the relative closest in the chain, from parent to first-degree and then second-degree relative of a parent, to be affected by any of the above categories of illness.

In each case some families were classified as having illness on both or on neither parental sides (Tables III and IV). Classification by the 'unilateral' system minimises the number of families that are allocated to either paternal or maternal categories and maximises those in the 'both' category, while the 'closest relative' system has the opposite effect. The 'hierarchical' system can be used to examine the influence of particular illnesses (e.g. schizophrenia or affective illness) in preceding generations (Table VI), and the relationship of the affected individual (Table VII), on the pattern of inheritance in the sibling pairs.

Figure 2 illustrates the way in which the three methods of classification are applied in a pedigree that is allocated to a different category by each method.

In a number of sibships more than two individuals were affected. Analysis by sex was carried out both sibshipwise (i.e. by determining whether or not all affected individuals in a sibship were of the same sex) and pairwise (assessing individual pairs within each sibship). The latter provides more information by taking into account the fact that each meiosis is an independent event. However, it is necessary to correct for the fact that there are not as many independent events (i.e. births of a sibling) as the total of all possible pairs within a sibship. A 'weighted-pairs' correction (Suarez & van Eerdewegh, 1984) was therefore applied. In these families each individual pairing was multiplied by a factor of $2/n$ where n is the number of affected members. Thus in a family with four ill siblings there are six possible pairs but each of these pairs is given a value of 2/4 (i.e. ½).

Results

The sex distribution and classification of family histories by the three systems is given in Table III. Both series include a number of sibships with more than two affected members, in three cases with four, and one with six affected individuals.

A noteworthy finding is that even with the classifications that maximise usage of family history information, a high proportion of families (at least 24% in the NAMI series and over 40% in the NPH series) have no relatives beyond those in the sibship itself with recognised psychiatric disorder. The distribution by sex of these pairs in the two series is different – 10 : 8 : 1 mm : mf : ff in the NAMI series and 2 : 9 : 7 in the NPH series, according to the 'closest relative' classification.

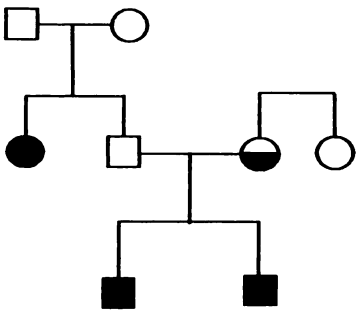

FIG. 2 A pedigree to illustrate the method of classifying sibships with respect to parental origin of illness. In this family parental origin is classified differently by each of the three systems – by the 'hierarchical' system it is paternal because schizophrenia in a first-degree relative of a parent takes precedence over affective illness in a parent; by the 'unilateral' system it is 'both', because there is illness on both paternal and maternal sides; and by the 'closest relative' system the sibship is classified as maternal on account of the depressive illness of the mother. (□ male, ○ female; ■ ● schizophrenia, ⊖ unipolar depression.)

Allocation of sibships to the categories 'paternal', 'maternal', 'both' and 'neither' (Table IV) indicates that with each of the three systems of classification there is an excess of same-sex over mixed-sex pairs in the paternally derived sibships. The excess (15 : 5) is greatest with the 'unilateral' system. The ratio of same-sex to mixed-sex pairings is significantly greater in paternally than maternally derived pairs ($P < 0.008$ to $P < 0.02$, Fisher's exact test).

The excess of same-sex pairs in the paternally derived sibships is independent of the method of classification of family history. However, there is an excess of males in the series (167 : 100) that relates particularly to the NAMI cases (127 : 51) but is absent from the NPH sample (40 : 49). Presumably it arises from the method of collection by recruitment through a mailed newsletter to the NAMI membership. Perhaps this elicited a response that included an excess of more seriously affected individuals who are likely to be of earlier onset and male. Such an excess could explain an excess of same-sex (male) over mixed-sex pairs, but it cannot account for the difference in same : mixed sex ratios in the maternally and paternally derived pairs, particularly the deficit of mixed sex pairs among the latter.

Each sibship including more than two affected individuals carries more information than has been used in the above analysis. To obtain as accurate as possible an estimate of the size of the concordance-by-sex effect, a pairwise analysis was conducted with the weighted-pairs correction.

The analysis (Table V) indicates that whereas the ratio of same-sex to mixed-sex pairs in the maternally derived sibships is less than but approaching unity, the ratio in the paternally derived sibships is consistently greater (2.4–3.5). As in the sibship analysis (Table IV), the paternal excess is relatively insensitive to the method of designating parental derivation.

TABLE III

Distribution by sex of affected individuals in relation to parental derivation of illness according to three classifications of family history

	Hierarchical				*Unilateral*				*Closest relative*				*Totals*
	pat.	*mat.*	*both*	*none*	*pat.*	*mat.*	*both*	*none*	*pat.*	*mat.*	*both*	*none*	
NAMI series (total no. of sibships, 79; total no. of individuals, 178)													
2m	8	8	4	13	8	8	7	10	10	10	3	10	33
2f	2		3	1	1		4	1	3	1	1	1	6
mf	3	10	5	8	2	9	7	8	5	12	3	6	26
2m, 1f	1	1	1	2	1	1	2	1	2	1	1	1	5
1m, 2f		2				2				2			2
3m	1		1		1		1		1	1			2
3f		1				1				1			1
3m, 1f				1				1				1	1
4m	1		1		1		1		2				2
6m	1						1		1				1
Totals	17	22	15	25	14	21	23	21	24	28	8	19	
All male	11	8	6	13	10	8	10	10	14	11	3	10	
Mixed sex	4	13	6	11	3	12	9	10	7	15	4	8	
All female	2	1	3	1	1	1	4	1	3	2	1	1	
NPH series (total no. of sibships, 41; total no. of individuals, 89)													
2m	2	1	1	1	2	1	1	1	2	1	1	1	5
2f	2	2	1	7	2	2	1	7	3	2		7	12
mf	3	6		8	2	5	2	8	4	6		7	17
2m, 1f		3		1		2	1	1		3		1	4
1m, 2f		1		1		1		1		1		1	2
3m				1				1				1	1
Totals	7	13	2	19	6	11	5	19	9	13	1	18	
All male	2	1	1	2	2	1	1	2	2	1	1	2	
Mixed sex	3	10		10	2	8	3	10	4	10		9	
All female	2	2	1	7	2	2	1	7	3	2		7	
Totals for both series (total no. of sibships, 120)													
All male	13	9	7	15	12	9	11	12	16	12	4	12	
Mixed sex	7	23	6	21	5	20	12	20	11	25	4	17	
All female	4	3	4	8	3	3	5	8	6	4	1	8	

pat., paternal; mat., maternal; m, male; f, female.

TABLE IV

Concordance by sex in sibships with schizophrenia classified by family history according to three systems

Classificatory system	*Paternal*	*Maternal*	*Both*	*Neither*	*Totals*
'Hierarchical'[1]					
same sex	17	12	11	23	63
mixed sex	7	23	6	21	57
'Unilateral'[2]					
same sex	15	12	16	20	63
mixed sex	5	20	12	20	57
'Closest relative'[3]					
same sex	22	16	5	20	63
mixed sex	11	25	4	17	57

1. $P=0.008$; 2. $P=0.01$; 3. $P=0.02$. All values by Fisher's exact two-tailed t-test. For comparison of maternally v. paternally derived sibships.

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TABLE V
Pairwise analysis of concordance by sex using a weighted-pairs correction

	Hierarchical		*Unilateral*		*Closest relative*	
	Paternal	*Maternal*	*Paternal*	*Maternal*	*Paternal*	*Maternal*
Same sex	24.66	17.66	18.66	17	31	22.66
Mixed sex	7.33	25.33	5.33	22	13	27.33
Same : mixed Sex ratio	3.36	0.69	3.50	0.77	2.38	0.83
Fisher's exact *P* (two-tailed)	0.002		0.009		0.02	

Hierarchical analysis allows the influence of type of psychiatric illness (Table VI) and proximity of affected individual in preceding generations (Table VII) to be assessed.

In each case the numbers are small. They suggest that paternal transmission of concordance by sex is at least as pronounced when there is a diagnosis of schizophrenia in the preceding generations as when parental origin is determined on the basis of other diagnoses (Table VI), and that the effect is relatively independent of the relationship of the individual on whose illness parental origin is assigned (Table VII).

Discussion

The finding that siblings who have inherited psychotic illness from their father are more often of the same sex than those inheriting illness from the mother is what would be expected if the gene were located within the pseudoautosomal region. Other explanations for same-sex concordance (e.g. that it results from shared psychological environment (Rosenthal, 1962) or 'auxiliary' sex-determining genes (Penrose, 1942)) have been offered but would not have predicted dependence upon paternal rather than maternal inheritance. The excess of males in the NAMI series could lead to concordance by sex in the series as a whole, as pointed out by Sturt & Shur (1985), but it cannot explain the relevance of the sex of the transmitting parent. One possibility, compatible with observations in the literature (Crow, 1988), is that in some cases the disease is preferentially transmitted from father to son. Such transmission suggests a locus on the Y chromosome, but this is consistent with equal incidence in the two sexes in general only if the gene is within the pseudoautosomal region.

Underlying the above analysis is the assumption that the mode of transmission is dominant, that is the gene originates either on the paternal or the maternal side. However, in a surprising proportion of families (31% overall) no cases of psychiatric illness were detected outside the sibship. Had the sibships been smaller and included only one affected member, the case might well have been described as 'sporadic' and therefore non-genetic (Goldin *et al*, 1987), or attributed to new mutation. This would have been an error – on the contrary, the distribution in these families is consistent with recessive transmission. Such a mode of transmission for schizophrenia was previously proposed, for example by Kallmann (1946). However, not infrequent occurrence in parent–child pairs (see e.g. Penrose, 1968) suggests a dominant gene.

TABLE VI
Concordance by sex in relation to type of illness in parent or parental relative

Diagnosis in relative	*Parental origin*	
	Paternal	*Maternal*
Schizophrenia		
same sex	8	3
mixed sex	1	11
Psychosis NOS		
same sex	6	4
mixed sex	5	6
Affective disorder		
same sex	4	5
mixed sex	1	5

TABLE VII
Concordance by sex in relation to proximity of illness in parents and their relatives

Affected relative	*Parental origin*	
	Paternal	*Maternal*
Parent		
same sex	6	6
mixed sex	3	12
First-degree relative of parent		
same sex	7	5
mixed sex	3	9
Second-degree relative of parent		
same sex	5	1
mixed sex	1	1

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Book (1953) and Slater (1958) postulated an 'intermediate' mode of transmission, that is, manifestation in all homozygotes (recessive) but in only a proportion of heterozygotes (dominant transmission). The present findings are consistent with such a concept but its molecular meaning is obscure.

Since there is a gradient of sex linkage within the pseudoautosomal region (Rouyer *et al*, 1986) the ratio of same to mixed sex in the paternally derived pairs gives an indication of the location of the gene within this region. Concordance by sex will be maximal (i.e. paternally/derived pairs of siblings will always be of the same sex) with a gene at the boundary of the pseudoautosomal region (i.e. closest to the centromere) whereas at the telomere, where there is 50% recombination in male meiosis, concordance by sex will be absent. The numbers are small but the ratio (2.4–3.5 : 1, Table V) suggests a location relatively low within this segment, perhaps in the centromeric one-third. It should be noted that if there is heterogeneity, that is if some cases of schizophrenia are linked to loci elsewhere, or if there are errors in designating parental origin of illness, this will reduce the ratio. Therefore the gene may be close to the pseudoautosomal limit.

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Timothy J. Crow, PhD, FRCP, FRCPsych; Eve C. Johnstone, MD, FRCP, FRCPsych; *Division of Psychiatry, Clinical Research Centre, Northwick Park Hospital, Harrow HA1 3UJ*; Lynn E. DeLisi, MD, *Department of Psychiatry, State University of New York at StonyBrook, StonyBrook, New York, 11756, USA*