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ORIGINAL PAPER

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Non-concordance by gender for schizophrenia and related disorders in sibships

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Abstract We analysed gener-concordance rates among 29 prospectively sampled schizophrenic probands and their 39 affected and 71 unaffected siblings. We did not find any unusual concordance rates. We found no same-gender concordance particularly in siblings affected by schizophrenia and related disorders. We considered unaffected siblings in an additional attempt to make valid and unbiased comparisons between genders, but this reduced the number of informative sibships to 20. We stratified the siblings of probands by sibship and by the proband's gender in order to check gender distribution within families. The data do not support hypotheses that schizophrenia is pseudo-autosomal or male-female chromosomally transmitted.

Key words Schizophrenia · Sibships · Gender concordance

Introduction

Genetical factors are relevant to the aetiology of schizophrenia (Gottesman 1991). For decades there have been reports about a higher prevalence of same-gender sibling pairs than mixed-gender sibling pairs suffering from schizophrenia and related disorders (Mott 1910; Myerson 1925; Schulz 1932; von Zehnder 1941; Penrose 1942; Rosenthal 1962; Tsuang 1967; Crow et al. 1989; Crow 1991; Shimizu et al. 1991; Asherson et al. 1992; Gorwood et al. 1992; Maier et al. 1993; Wang et al. 1993).

Sturt and Shur (1985) and Curtis and Gurling (1990) argued that diagnostic heterogeneity, methodological errors in statistical analysis and incomplete biased sampling of probands or relatives (uneven gender ratios of probands) might account for the more frequent reporting of same-gender pairs. However, the sample sizes of studies that show a higher same-gender concordance are very impressive. Examples of such studies (sometimes with methodological shortcomings) are as follows:

1 In 1945 Penrose reported on 422 pairs of siblings in Ontario (Crow 1991).
2 Crow et al. (1989) sampled 120 pairs in the USA and London.
3 Shimizu et al. (1991) found a higher same-gender concordance in 118 sibships with affected parents in Japan.
4 Maier et al. (1993) studied 42 sibships that had been systematically recruited in Mainz, Germany.
5 Gorwood et al. (1992) sampled 39 sibships in 2 very different places: La Reunion, in the Indian Ocean, and Rouen, France.
6 Asherson et al. (1992) reported on 25 sibships from different countries (UK and Japan).
7 Wang et al. (1993) examined 24 pedigrees in Iowa.

We are aware of only two studies that have not shown a higher same-gender concordance in siblings affected by schizophrenia (Sturt and Shur 1985; Goldstein et al. 1990). These studies had small samples (13 and 21 sibships, respectively), but they recruited their probands in an unbiased and systematic manner, and covered all first-degree relatives.

Besides other genetical and psychological explanations for same-gender concordance (Rosenthal 1962), researchers have proposed the hypothesis that there might be a genetical locus relating to schizophrenia either in the pseudo-autosomal region of the gender chromosomes or on X-Y chromosomes in general (Crow et al. 1989; Crow 1992). The pseudo-autosomal hypothesis predicts that when fathers transmit the disorder, schizophrenia-concordant sibling pairs are more likely to be concordant by gender than when mothers transmit the illness. Some studies have observed this pattern (Crow et al. 1989; Gorwood et al. 1992), whereas others have not (Asherson et al. 1992; Maier et al. 1993; Wang et al. 1993). When molecular-

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Table 1 **a** Gender composition of sibships; **b** weighted affected sibling-pair analysis

a.	No. of sibships	Gender composition (F = female; M = male)		**b.** Scores of affected pairs			
				Weighted		Expected	
		Affected	Unaffected	Same gender	Mixed gender	Same gender	Mixed gender
Male proband:							
Pairs	11	3 MF	FMMM, MMMMM FFMMMM	8	3	5.5	5.5
		8 MM	2 F, FFF, FFFFM FMM, FFFM				
Trios	3	2 MMF MFF	F, FFFFM F	2	4	3.4	2.6
Quartets	1	MFFF	MMMMMFF	1	1	1.2	0.8
Subtotal				11	8	10.1	8.9
Female proband:							
Pairs	10	7FM 3 FF	4 F, FM, FFMM F, FFFMM	3	7	5	5
Trios	3	FFF 2 FFM	FF FFMM	3.3	2.7	3.4	2.6
Quartets	1	FFFM	MMMM	1	1	1.2	0.8
Subtotal				7.3	10.7	9.6	8.4
All probands:							
Pairs	21			11	10	10.5	10.5
Trios	6			5.3	6.7	6.8	5.2
Quartets	2			2	2	2.4	1.6
Total				18.3	18.7	19.7	17.3

biological techniques have been used, results regarding the pseudo-autosomal hypothesis have often conflicted (Asherson et al. 1992; Wang et al. 1993), but some have supported it (Collinge et al. 1991; d'Amato et al. 1992).

In our analysis, we endeavoured to avoid the methodological shortcomings outlined above (Sturt and Shur 1985). We prospectively sampled sibships with schizophrenia and related disorders and their first-degree relatives. We used state-of-the-art clinical instruments and diagnostic criteria. Our sampling yielded an even gender distribution of probands and their relatives. Our analysis included proband's unaffected siblings.

Methods

We identified 29 hospitalised schizophrenic probands according to DSM-III-R in the Department of Psychiatry at the University of Vienna who had at least one sibling suffering from a non-affective, non-organic psychosis (schizophrenia, schizoaffective, schizophreniform or delusional disorders, atypical and brief reactive psychoses), schizotypal personality disorder or psychotic affective disorder (bipolar or major depression) (Kendler et al. 1993). Two experienced independent psychiatrists carried out blind consensus diagnoses according to DSM-III-R. All living adult first-degree relatives were examined, and all participants gave informed consent. Diagnoses in probands and relatives were based on best estimates from various data sources in accordance with DSM-III-R, including a personal interview using the *Schedule for Affective Disorders and Schizophrenia, Lifetime Version* (modified for the study of anxiety disorders) (Fyer et al. 1985), an unstructured psychiatric interview, a family-history evaluation, clinical data from medical records and a written case report. Data and diagnoses of other relatives were based on family-history evaluations and medical records (e.g. for determination of transmission models).

The probands comprised 15 females (mean age 31.3 years) and 14 males (mean age 34.1 years). The number of first-degree relatives of male and female probands did not differ significantly (χ^2 = 3.43; 1 degree of freedom). Female probands had 37 female and 35 male relatives, and male probands had 50 female and 46 male relatives. A total of six mothers and one father were affected (i.e. suffered non-organic, non-affective psychoses as described previously, schizotypal personality disorder or psychotic bipolar or unipolar affective disorder): schizophrenia (n = 1), schizo-affective (n = 1), schizophreniform (n = 1) and schizotypal personality disorders (n = 1) and atypical psychoses (n = 3) were all present; 51 parents were unaffected.

Among unaffected parents we found the following diagnoses: non-psychotic bipolar disorder (n = 1), alcoholism (n = 4) and depressive disorders not otherwise specified (NOS) (n = 2). The prevalence of psychosis in parents of multiply affected siblings (7 among 2 × 29 being affected represents > 12%) agrees with the prediction of published family studies (expectation of at least 10% of parents to be affected).

Of the 29 probands, 39 siblings (20 female and 19 male) were affected as follows: schizophrenia (n = 22), schizo-affective (n = 11), delusional (n = 1) and schizotypal personality disorders (n = 2) and atypical psychoses (n = 3); 71 were unaffected (38 females

Table 2 Gender-concordance data for pair-wise affected sibling pairs grouped according to parental transmission (Transmission was defined by the hierarchical method, see Crow et al. [1989])

	No. of sibling pairs	Weighted score	
		Same sex	Mixed sex
Maternal transmission			
Observed	13	5.33	4.66
Expected		5.26	4.74
		($\chi^2 < 0.5$, 1 degree of freedom; NS)	
Paternal transmission			
Observed	17	4.33	6.66
Expected		5.77	5.23
		($\chi^2 < 0.5$, 1 degree of freedom; NS)	
Unknown transmission			
Observed	21	8.66	7.33
Expected		8.16	7.84
		($\chi^2 < 0.5$, 1 degree of freedom; NS)	

Table 3 Concordance of proband and siblings (informative sibships only)

Affected brothers	Affected sisters	Unaffected brothers	Unaffected sisters
Siblings of male probands (n = 12)			
(Estimate of degree of association 0.007 ± 0.46; NS)			
0	2	1	4
0	1	4	2
0	3	5	2
1	0	0	1
1	0	1	3
1	0	0	1
1	0	0	3
0	1	3	1
1	0	2	1
1	1	0	1
1	0	1	4
0	1	5	0
Siblings of female probands (n = 8)			
(Estimate of degree of association 0.025 ± 0.66; NS)			
0	1	2	3
1	0	2	2
1	0	0	1
1	0	0	1
1	1	2	2
1	2	4	0
1	0	0	1
1	0	1	1

and 33 males). These siblings, referred to in our analysis as "unaffected", included individuals with the following diagnoses: major depressive ($n = 2$) and depressive disorders NOS ($n = 2$), alcoholism ($n = 1$) and panic disorder ($n = 1$). Two sibships with the affected sibling of the index case being dead were included and one sibship with three affected sisters included one being dead. Reliable clinical data on these siblings were available.

In order to replicate studies by Crow et al. (1989, 1990), Gorwood et al. (1992), Asherson et al. (1992) and others, our statistical analyses were based on a pair-wise technique corrected to account for the number of members in each sibship (Suarez and Van Eerdewegh 1984). The number of same-gender pairs was compared with that expected in siblings of male and female probands separately and in the sample as a whole (Table 1b) and, respectively, in subsamples in which transmission was paternal, maternal or unknown (Table 2). Our sample showed even-gender distribution (Curtis and Gurling 1990). Paternal, maternal or unknown transmission was determined by the criteria described by Crow et al. (1989), within which the results for *hierarchical* categorisation are shown in detail. According to Crow et al. (1989) for the hierarchical categorisation a diagnosis of schizophrenia, psychosis NOS and affective disorder in parents and first- and second-degree relatives of a parent in a specified order of priorities defined the affection status. We also analysed *unilateral* and *closest-relative* categorisations (results not shown in detail), but this did not make a big difference to our results in Table 2. In the hierarchical categorisation we did not find a sibship with transmission from both sides, but we did in unilateral and closest-relative models.

Furthermore, we estimated the degree of association between gender and disorder using the methods and formulae described by Sturt and Shur (1985). We calculated them separately for relatives of male and female probands. A proband has to have at least one unaffected sibling and one sibling of each gender for the sibship to provide any information about familial gender-disorder concordance. Table 3 includes the 20 informative sibships. Because our sampling was focused on affected sibling pairs, separate tabulation for the parents of probands was not applicable (only seven affected parents). It was not necessary to correct for age in addition to the described method of stratification (Sturt and Shur 1985). The resulting estimate of the degree of association can be compared with a χ^2 distribution with 1 degree of freedom. Negative degrees of association indicate less-than-expected concordance by gender. In order to compare an observed distribution with an expected distribution, we applied χ^2 tests (two-tailed; $\alpha = 5\%$).

Results

Table 1 a shows the gender composition and sizes of all 29 sibships in our analysis, specified by gender of the proband. As shown in Table 1b, the distribution of same-gender and mixed-gender affected pairs observed, specified by gender of the proband, did not differ significantly from expectations (sample as a whole: $\chi^2 < 0.5$; 1 degree of freedom). Similarly, allocating the sibships to the hierarchical transmission categories of maternal, paternal or unknown does not result in a significant deviation from the expected gender-concordance in 51 affected sibling pairs (Table 2).

Furthermore, we applied the method of analysis described by Sturt and Shur (1985) to check for factors such

as unusual gender distributions within the families: There was no correlation among affected and unaffected siblings in 20 fully informative sibships (Table 3).

Discussion

Sturt and Shur (1985) described various methodological problems associated with carrying out gender-concordance studies. Besides sampling systematically to obtain an even distribution of gender in probands and relatives, the methodological advantage of the statistical analysis proposed by them and also used during our study is the inclusion of all of the proband's siblings, irrespective of affection status, to check for putative biases induced by variations in the sizes of sibships and by an unbalanced gender ratio. In so doing one can examine individual intra-familial gender distributions. The major disadvantage of this method is that sibships are only informative if they have at least one affected and one unaffected sibling and, in addition, at least one sibling of each gender. Thus, this method substantially reduces the number of informative affected sibling pairs.

Our study did not provide evidence of a higher rate of same-gender sibling pairs with schizophrenia and related disorders. This replicated the findings of Sturt and Shur (1985), formerly criticized because of their small sample size (Crow et al. 1990). Together with similar statistical methodology, both studies give us more representative findings: 33 rigorously sampled probands had 151 affected or unaffected siblings and were included in the analyses as fully informative sibships. Besides these 33 informative sibships, together both studies have now selected, investigated and analysed an additional 170 individuals from sibships and 200 parents.

The results of these studies, together with the results obtained by Goldstein et al. (1990) (21 sibling pairs), contrast with other series of multiply affected sibships, which are distinguished by enormous sample sizes of several hundred and exhibit same-gender concordance (Crow et al. 1989; Crow 1991; Shimizu et al. 1991). Some of them have methodological shortcomings (Sturt and Shur 1985; Curtis and Gurling 1990). But in contrast to the two studies which did not find a higher same-gender concordance in schizophrenics, according to current knowledge (Kendler et al. 1993) we used a broader definition of affection status in siblings (including schizotypal personality disorder and psychotic affective disorder).

Sampling systematically, Maier et al. (1993) applied statistical techniques to allow for the differing effects of age on each gender, parental origins and unaffected siblings. They tested three different schizophrenia disease models. They only detected significant same-gender sibling concordance in 42 sibships when they included affective disorders with psychotic features in addition to schizophrenia, schizo-affective disorders and unspecified functional psychoses (a model similar to ours). Schizophrenia disease models, excluding psychotic affective disorders, gave insignificant results. The authors discuss this finding in terms of how the two narrow disease models failed to deliver significant results because the number of identified sibships with multiply affected members was too low (14 and 19 siblings affected). But they found all disease models suggestive of the same observation of an excess of same-gender concordance. Not showing evidence of deviations of gender-ratios from expectations, our study included 29 (Table 1) or 20 (Table 3) affected sibships and 51 affected sibling pairs (Tables 1 and 2). The numbers are in-between those of the study by Maier et al. (1993), but in contrast we did not find even a tendency towards unusual gender-concordance rates.

We tried to replicate the results of other observers of higher gender-concordance rates in schizophrenic siblings by applying their methods of analysis (Crow et al. 1989; Crow et al. 1990; Collinge et al. 1991; Asherson et al. 1992; Gorwood et al. 1992), however, in doing so we were unable to consider the unaffected siblings of probands. The results also did not show any evidence of higher rates among same-gender sibling pairs. Particularly in sibships displaying paternally derived transmission, the rate of gender-discordant sibling pairs was as high as expected by chance.

It can be argued that differences in age at onset between males and females might be a putative reason for the divergency of results (Maier et al. 1993). Male schizophrenics show an earlier age at onset than females. But we sampled an equal number of male and female probands, with a relatively high mean age in males (34.1 years), but a lower mean age in females (31.3 years). Furthermore, the majority of siblings had already passed most of the period of risk and there was an equal number of male and female relatives. In the calculation of same-gender concordance in siblings of male probands (Table 1), we did not find a significant result, although one could find a tendency toward higher same-gender rate.

We primarily applied a sampling strategy for affected siblings. This should not affect the results, because to find hospitalised affected siblings we had to first screen all the single probands. Family history of secondary cases was carefully assessed with patients and relatives during the time of hospitalisation of all the single probands.

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