Concordance for Sex and the Pseudoautosomal Gene Hypothesis Revisited: No Evidence of Increased Sex Concordance in a Nationwide Finnish Sample of Siblings With Paternally Derived Schizophrenia

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Objective: This study set out to determine, in a homogeneous sample with nationwide coverage in Finland, whether siblings treated for schizophrenia are more often of the same sex than expected by chance, and whether this is especially so when the disorder is transmitted by their fathers. **Method:** Finnish social and health insurance files as well as hospital discharge registers were searched for probands with schizophrenia from a birth cohort spanning 30 years. Nuclear families were identified by cross-linkage with the national birth register, and the sex distribution observed in multiply affected sibships was compared with expected distributions by maximum likelihood analysis. **Results:** In the subset of multiply affected sibships with one parent who had schizophrenia (84 fathers and 120 mothers), the observed sex distribution did not deviate from the expected pattern. However, a small and marginally significant excess of sex concordance emerged from the total sample of 1,942 sibships in which there were at least two affected members, irrespective of the parents' affection status. **Conclusions:** The results indicate that no above-chance sex concordance in sibships multiply affected with paternally transmitted schizophrenia is present in the genetically homogeneous population of Finland. In view of a virtually unbiased and complete ascertainment procedure and sample sizes one to two orders of magnitude larger than those in previous studies, the authors attribute prior findings of such a concordance to sampling artifacts or chance fluctuations and finally conclude that except for regional genetic isolates, there is no epidemiologic evidence that a gene accounting for substantial susceptibility to schizophrenia in a greater proportion of cases resides in the pseudoautosomal region of the sex chromosomes.

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The hypothesis that a gene in the pseudoautosomal region of the sex chromosomes might confer vulnerability to schizophrenia has drawn mainly on two previous findings in the epidemiology of this syndrome: an increased prevalence of aberrations in the number of sex chromosomes among institutionalized subjects with schizophrenia (1, 2) and the now 88-year-old observation that siblings affected with schizophrenia tend to be of the same sex more often than one would expect (3). The validity of both findings has, however, been questioned: the first because of the only moderate strength of the association in the reverse direction (since most carriers of sex chromosome numerical aberrations do not exhibit schizophrenia [4]) and the second mainly on methodological grounds (5), namely, incomplete and biased ascertainment of affected sibling pairs in samples of limited size. We therefore addressed the issue of increased sex concordance in affected sib-

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lings in a sample of 1,942 sibships with at least two members treated for schizophrenia ascertained through a combination of three case registers with nationwide coverage in Finland. Since the same set of registers served for the identification of families multiply affected with schizophrenia for the purpose of molecular genetic linkage studies, any epidemiologic finding of an increased sex concordance in the sampled population would directly bear on our a priori chances of establishing a positive finding of linkage between schizophrenia and the pseudoautosomal region in this panel of families.

How would an increased concordance for sex in sibling pairs with schizophrenia link to a tiny region of the sex chromosomes at the tip of their short arms? In meiosis correct pairing of autosomal chromosomes and the two X chromosomes of females is ensured by sequence homology, and crossing-over followed by exchanges of small DNA stretches by recombination may occur anywhere along their full length. In the X and the Y chromosomes undergoing meiosis in a male, however, sequence homology is largely restricted to the aforementioned region, to which a single obligatory crossing-over is confined, whereas the subsequent sex-specific region is devoid of recombinational events. Thus, a vulnerability-conferring gene residing in the sex-specific stretch of the X chromosome of an affected male would be transmitted only to his daughters, and a locus on the Y chromosome only to his sons, leading to perfect sex concordance of affected siblings. However, transmission of schizophrenia from an affected father to both his sons and his daughters (i.e., sex discordance of affected siblings) is too common to be reconcilable with this particular location of a single disease-associated gene of major effect. By contrast, if a disease-associated locus were to reside in the pseudoautosomal region, the degree in excess of expectations to which sex concordance of affected offspring of an affected male proband is observed would follow a gradient depending on its location: the farther the locus from the junction toward the tip of the chromosome, the greater the chances of its being separated from sex-determining loci in the sex-specific region by the obligatory crossing-over (6), and the lower the degree of observable increase of sex concordance in affected offspring of the male. In any case, transmission of a gene in the pseudoautosomal region from affected female probands would be expected to result in a 50:50 ratio of same-sex to opposite-sex affected offspring pairs (at least when equal numbers of affected male and female offspring are assumed).

Nongenetic mechanisms have been considered in explanation of previous findings of increased concordance for sex, namely, the tendency of same-sex sibling pairs to spend more time together than opposite-sex pairs, at least in childhood and adolescence. However, twin studies designed to gauge the influence of genetic and environmental factors on the susceptibility to schizophrenia assigned mostly a minor role to environmental factors, and among these the influence of shared environmental factors was poor compared with that of individual ones (7). On the other hand, it is hard to conceive of any genetic mechanism other than involvement of the pseudoautosomal region to account for an excess in sex concordance, and any proof or refutation of the latter would directly enhance or challenge the validity of the former.

In an attempt to overcome methodological obstacles in historic samples (3, 8–17) as reviewed by Crow et al. (18, 19), we tested in a nationwide sample 1) whether siblings with schizophrenia from multiply affected sibships were more often of the same sex, rather than opposite sexes, than expected from their sex ratio when their fathers but not their mothers were also affected with schizophrenia, 2) whether increased sex concordance extended to the nationwide sample irrespective of parents' status (as might be expected if a positive effect from hypothesis 1 were strong enough), and 3) whether concordance for sex would not deviate from expectations in any direction in sibships in which the mother but not the father was affected.

METHOD

Through inquiry to three independent case registers with nationwide coverage of Finland, we identified a total of 29,124 individuals from the birth cohort of 1940–1969 who had been diagnosed with and treated for schizophrenia, as indicated by at least one of the following: 1) registration in the social insurance files as a recipient of a disability pension because of chronic schizophrenia, 2) registration in the national health insurance files as a recipient of cost-free antipsychotic medication for schizophrenia, and 3) a listing in the national hospital discharge register as having a discharge diagnosis of schizophrenia (according to ICD-8 from 1968 to 1986 and DSM-III-R since 1987). Persons in the first registry routinely undergo independent diagnostic evaluation by a psychiatrist in the process of applying for a disability pension, for which everyone between 16 and 65 years of age with a chronic course of schizophrenia who is not able to maintain himself or herself by regular work is eligible, independent of sex and prior employment status. Dropouts from the second register, who would at the same time be missing from the third, include the few never-hospitalized persons who seek treatment in a private practice setting rather than with the extensive national health system and thereby risk loss of reimbursement for health maintenance costs. Although exact figures are unavailable, we believe that these instances are rare among persons with chronic schizophrenia. As there are no privately funded inpatient units in Finland, coverage of ever-hospitalized patients by the third registry is complete.

Personal diagnostic interviews with standardized schedules are impossible to conduct for such a high number of subjects; therefore, the reliability of registered diagnoses was checked by independent best estimate (20), with the use of DSM-III-R criteria, from all available medical records in a subsample of the probands (21). Of 75 registered cases, 57 (76%) of the probands retained a DSM-III-R diagnosis of schizophrenia, and for a further 12 probands, the diagnosed disorder was one of the conditions that, by cosegregation with schizophrenia in family studies, have been shown to be part of a genetic schizophrenia spectrum (schizoaffective disorder in seven cases; schizoid personality disorder in two; and schizophreniform disorder, delusional disorder, and schizotypal personality disorder in one case each). However, six probands (8%) had diagnoses that did not fall within the schizophrenia spectrum (four with a major affective disorder—although three of them had a psychotic affective disorder, a condition sometimes considered to be a further extension of the schizophrenia spectrum—and one each with reactive psychosis

and alcohol hallucinosis) and were thus wrongly included as cases of near-schizophrenia in the registers.

By means of the unique individual identification number every Finnish citizen receives upon birth, the identified cases—primarily independent observations—were cross-linked with the national birth register to establish nuclear families with several affected siblings, whose parents' data could then be rechecked for affection status with the set of three case registers. In this way, a nationwide panel of affected sibships with one parent, both parents, or none affected was identified, corresponding to the closest-relative approach (18) for determining lineality of transmission, but with the advantage of considering the same narrow disease category from the same data sources in the parents as in the probands.

Previous studies considered sibships with more than two affected members as a single observation of sex concordance when all affected siblings were of the same sex and of sex discordance when at least one of them differed in sex from the others (18). However, this sibshipwise strategy seems implausible, since it disregards the major instances of sex concordance in sibships where multiple affected members are of the same sex, but because of a single sibling of the opposite sex, the whole sibship enters the calculations only once as an observation of sex discordance. Most studies have therefore dissected those sibships with n affected members into all possible pairs (1+2+…+[n–1]=n[n–1]/2) and multiplied the resulting number of same-sex and opposite-sex pairs by 2/n to yield weighted pairs (22). These were considered as independent observations, yet despite the correction factor, multiple pairs from within the same sibship still involve the same meioses, a bias that has until recently also been overlooked in linkage studies of allele sharing among affected siblings. We circumvent this problem by regarding each meiosis (instead of sibling pairs) as the actual independent unit of observation, thus making use of the information contained in multiply affected sibships jointly instead of separately. A full likelihood analysis (23) is the appropriate strategy: the probability of the observed sex data is computed, given increased concordance for sex (with a parameter, δ, representing departure from the expected independence of sex of affected siblings) and also under the assumption of no deviation in sex concordance (null hypothesis: δ=1). The ratio of these probabilities indicates how much more likely increased sex concordance will be than the null hypothesis, given the observed data. The formal derivation of this likelihood analysis is as follows.

If we assume that the siblings are not correlated by sex, then the likelihood of a given sibship is given by

$$L = \prod_{i=1}^{n} \phi^{M_i}(1-\phi)^{F_i}$$

where ϕ is the probability of a random affected person being male, and the product is taken over all sibships, i. The maximum likelihood estimate of ϕ can be shown to be the binomial proportion

$$\hat{\phi} = \frac{\sum_{i=1}^{n} M_i}{\sum_{i=1}^{n} (M_i + F_i)},$$

where M_i is the number of males in sibship i, and F_i is the number of females in the same sibship i. Under the alternative hypothesis, it is presumed that when the proband is male, there should be a reduced probability that remaining siblings are female, and thus the likelihood for a given sibship with a male proband is given as $L_{i,male}=\phi[\delta(1-\phi)]^{F_i}[1-\delta(1-\phi)]^{M_i-1}$, and with a female proband the likelihood would correspondingly be $L_{i,female}=(1-\phi)[\delta\phi]^{M_i}[1-\delta\phi]^{F_i-1}$. However, since the proband is typically unknown, one can determine the probability that a given sibship had a male proband as $\psi=M_i/(M_i+F_i)$. Thus, the overall likelihood for a given sibship with an unknown proband would be $L_i=\psi L_{i,male}+(1-\psi)L_{i,female}$, and when $\delta=1$, this is identical to the likelihood of the null hypothesis given above. A likelihood ratio test can then be performed by using the statistic

$$\Lambda = -2\ln \prod_{i=1}^{N} \frac{L_i(\delta = 1, \hat{\phi})}{L_i(\hat{\delta}, \hat{\phi})},$$

where ϕ and δ are estimated over all sibships jointly. This likelihood-based test follows a chi-square distribution, and it was considered to be one-tailed (with $p \leq 0.05$ indicating significance), since the core hypothesis on increased concordance for sex under paternal transmission makes a definite prediction about the direction of the effect

RESULTS

Of the 25,332 cases of schizophrenia (male-to-female ratio=1.46) in which the families could be identified, 3,338 were in sibships with two affected individuals, and a further 891 belonged to sibships with three or more affected members; there was a maximum of six affected individuals in three families and seven affected siblings in one instance (table 1). By simulation of at least 200 replicates of that data set, we estimated that any distortion of sex concordance below 0.9, a deviance milder than those found in previous work (δ in table 1), would essentially be identified with complete power (figure 1, curves for total sample).

Paternal Transmission

In eight of the affected sibling pairs and an additional triplet, both parents had a diagnosis of schizophrenia; these families were therefore excluded from the analyses by parental affection status. Only the fathers were affected in a further 86 sibships with multiple cases of schizophrenia, yet in two instances insufficient data on the mother were available, so we restricted the analysis to the 84 multiply affected sibships whose mothers proved to be not registered cases. However, there was no significant deviation from a random distribution of the sexes among affected siblings in this subset of families ($\chi^2=0$, df=1, p=0.50), and considering all 86 sibships would have in no way changed the result. To exclude the possibility that this null finding had arisen out of the insufficient power of our subsample, we simulated at least 1,000 replicates and found that given the effect size of previous work, where raw data on sibships with paternal transmission are available ($0.52<\delta<0.55$, calculated from reference 18), a distortion in sex concordance of that degree would have been identified more than 90% of the time, even under a conservative error rate of 0.1% (figure 1, curves for paternal transmission).

Full Sample

Since the core hypothesis of increased sex concordance of affected sibling pairs under paternal transmission could not be confirmed, it might be expected that the full sample of 1,942 multiply affected sibships ascertained irrespective of parents' diagnostic status would not show any significant deviation of sex concordance either. Surprisingly, we found mild evidence

TABLE 1. Composition of Samples Surveyed and Results of the Likelihood Ratio Test in Previous Studies of Sex Concordance in

Size of Affected Sibship and Sex of Siblings	Previous Studies							
	Tsuang, 1965 (16)	Sturt and Shur, 1985 (5)	Crow et al., 1989 (18)		Collinge et al., 1991 (24)	Gorwood et al., 1992 (25)	d'Amato et al., 1992 (26)	Maier et al., 1993 (27)
			U.S.	U.K.				
One member								
F	0	0	0	0	0	0	0	0
M	0	0	0	0	0	0	0	0
Two members								
FF	6	1	6	12	8	5	4	14
FM	9	7	26	17	26	8	9	16
MM	13	2	33	5	37	14	5	10
Three members								
FFF	0	0	1	0	0	0	0	0
FFM	0	2	2	2	1	3	5	0
FMM	0	1	5	4	4	3	4	0
MMM	0	0	2	1	3	2	4	2
Four members								
FFFF	0	0	0	0	0	0	1	0
FFFM	0	0	0	0	0	1	0	0
FFMM	0	0	0	0	0	1	1	0
FMMM	0	0	1	0	1	0	0	0
MMMM	0	0	2	0	2	0	0	0
Five members								
FFFFF	0	0	0	0	0	0	0	0
FFFFM	0	0	0	0	0	0	0	0
FFFMM	0	0	0	0	0	0	0	0
FFMMM	0	0	0	0	0	1	0	0
FMMMM	0	0	0	0	0	0	0	0
MMMMM	0	0	0	0	0	0	0	0
Six members								
FFFFMM	0	0	0	0	0	0	0	0
FFFMMM	0	0	0	0	0	1	0	0
FMMMMM	0	0	0	0	0	0	0	0
MMMMMM	0	0	1	0	1	0	0	0
Seven members								
MMMMMMM	0	0	0	0	0	0	0	0
–2ln (likelihood ratio test)	2.76	0	0.65	0	1.26	0.74	0.29	3.32
p (one-tailed)	0.05	0.50	0.21	0.50	0.13	0.20	0.30	0.03
Distortion (δ)	0.57	1	0.84	1	0.79	0.78	0.85	0.60
Proportion of males	0.63	0.52	0.71	0.45	0.73	0.62	0.55	0.49

[a] For the previous studies, χ^2=9.03, df=9, p=0.10, for sex concordance in sibships with schizophrenia; for the previous studies and the total sample of the present study, χ^2=14.32, df=11, p=0.03, for sex concordance in sibships with schizophrenia.

of slightly increased sex concordance in the nationwide sample (δ=0.92, χ^2=3.36, df=1, p=0.03). To test how much this unexpected finding depended on the impact of a particular isolated community in northeastern Finland that has been targeted for molecular genetic studies because of a twofold greater prevalence of schizophrenia, a larger family size, and a population history suggestive of an internal genetic isolate (28), we excluded all cases from that community (166/4,229= 3.9% of cases from sibships with two or more affected members; table 1) and were left with no further evidence of increased sex concordance for the remaining larger part of Finland (δ=0.93, χ^2=2.23, df=1, p=0.07), whereas the internal genetic isolate alone would show some (δ=0.69, χ^2=3.06, df=1, p=0.04).

Maternal Transmission

In a subsample of 155 multiply affected sibships, the mothers but not the fathers were affected. However, since a Finnish mother is not obliged to reveal the identity of her newborn child's father to the registration authorities, the fathers' diagnostic data could not be traced sufficiently to exclude biparental transmission in several sibships. We therefore felt that it was safer to restrict this analysis to the 120 multiply affected sibships in whom schizophrenia could be definitely excluded by cross-checking with the case registers of their fathers. Again, the sex distribution of affected siblings did not differ from expectations under the null hypothesis (χ^2=0.57, df=1, p=0.23), independent of whether sibships with unclarified paternal affection status were excluded or not.

DISCUSSION

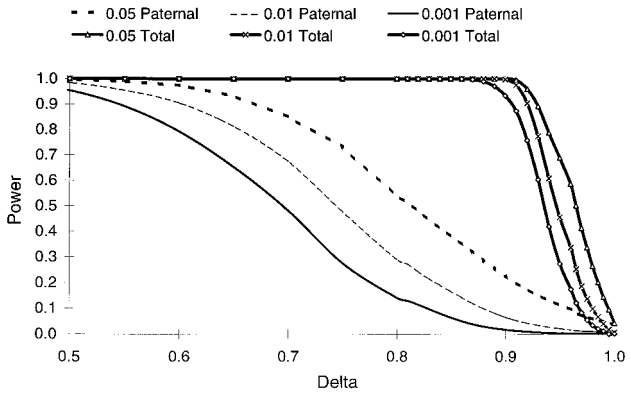
Concordance for Sex and the Pseudoautosomal Gene Hypothesis

The findings of increased concordance for sex in sibling pairs with schizophrenia obtained so far have been

Siblings With Schizophrenia and in the Present Study[a]

Present Study				
Sibships With Affected Father	Sibships With Affected Mother	Sibships in Total Sample	Sibships in Genetic Isolate	Sibships in Total Sample Minus Isolate
164	308	8,615	114	8,501
248	433	12,488	182	12,306
10	18	284	13	271
37	50	774	21	753
19	33	611	14	597
0	1	11	0	11
2	4	60	2	58
6	5	85	8	77
4	6	62	6	56
0	0	0	0	0
1	0	4	0	4
1	0	14	1	13
2	1	20	0	20
0	0	5	2	3
0	0	0	0	0
0	1	1	0	1
0	0	1	0	1
0	0	0	0	0
1	0	4	0	4
0	1	2	2	0
0	0	1	0	1
1	0	1	0	1
0	0	1	0	1
0	0	0	0	0
0	0	1	0	1
0	0.57	3.36	3.06	2.23
0.50	0.23	0.03	0.04	0.07
1	0.87	0.92	0.69	0.93
0.60	0.59	0.59	0.62	0.59

FIGURE 1. Power of the Likelihood Ratio Test for Concordance for Sex Among Siblings With Schizophrenia[a]



[a] Power of the likelihood ratio test for sibling concordance in the total study sample and in the subsample with paternal inheritance for various degrees of distortion in sex concordance (delta) and error probabilities (alpha) of 0.05, 0.01, and 0.001.

inconclusive (table 2). Only five studies tested for increased concordance for sex under paternal transmission. Whereas one of these studies (32) reported increased concordance under maternal rather than paternal transmission, contrary to expectations, the other four (18/19, 25, 27, 30) had positive findings, and despite small sample sizes throughout, two of these (18/19, 25) yielded significance suggesting a considerable excess of sex concordance. Given this large effect size in previous work, the approximately 10-fold larger subsample with paternal inheritance in the present study, and the results of our power calculations (figure 1), our failure to replicate must not have merely resulted from insufficient power but, rather, provides firm grounds for rejecting the core hypothesis. This conclusion proved insensitive to whether the traditional yet biased weighted-pairs procedure was applied (with subsequent goodness-of-fit chi-square testing of observed versus expected numbers of pairs, as done, for reasons of comparability across studies, for table 2) or the proposed maximum likelihood method unbiased for sibship size was used (table 1). It is therefore striking that, although it was absent from the subsample with paternal inheritance, a mild but significant excess of sex concordance appeared in the total sample. This vanished upon exclusion of cases from an internal genetic isolate that in itself showed evidence of increased concordance. However, at this point we remain cautious about concluding that increased concordance for sex as a hallmark of the pseudoautosomal gene hypothesis is present and limited to that particular isolate within Finland for two reasons: 1) unfortunately, there was no possibility for confirmation by testing the more rigorous core hypothesis, since only one multiply affected sibship from the isolate had an affected father, and 2), although there were good reasons to favor this particular internal isolate for molecular genetic studies throughout the genome (28), we had no prior evidence that it would behave differently with respect to the specific epidemiologic hypothesis tested in this study, and thus any other particular region in Finland might have equally warranted separate evaluation.

Thirteen studies since 1945 have tested for increased sex concordance among siblings with schizophrenia irrespective of parents' affection status, and even though the sample sizes were considerably larger than sizes of samples with paternal transmission, it is not surprising that the results disagree, given the variety of sampled communities, sex ratios, and diagnostic criteria, some including organic disorder (13) and clinical diagnoses of schizophrenia (16). Sturt and Shur (5) have drawn attention to a number of additional sources of considerable bias, most of which have not been successfully addressed by the majority of the studies summarized in table 2. With the exception of two family studies that screened consecutive psychiatric hospital admissions for multiply affected sibships (27, 32), ascertainment

TABLE 2. Studies on Sex Concordance in Sibling Pairs With Schizophrenia

Study	Number of Families	Number of Sibships	Number of Affected Individuals	Weighted Pairs		Weighted Sex Ratio (M/F)
				Concordant for Sex	Discordant for Sex	
Penrose, 1945 (13)	—	<422	<844[a]	230[a]	192[a]	0.92
Tsuang, 1967 (16)	—	28	56	19	9	1.67
Sturt and Shur, 1985 (5)	—	13	29	5	11	1.04
DeLisi et al., 1987 (29)	53	53	123	—[b]	—[b]	2.24[a]
Crow et al., 1989 (18)	119	120	267	85.2	61.8	1.74
Group a	78	79	178	62.2	36.8	2.57
Group b	41	41	89	23	25	0.86
Collinge et al., 1991 (24)	83	83	184	66.8	34.2	2.92
Group a	21					
Group b	46					
Group c	16					
Gorwood et al., 1992 (25)	39	39	97	33.1	24.9	1.54
d'Amato et al., 1992 (26)	—	33	83	27	23	1.24
Asherson et al., 1992 (30)	25	27	74	26.6	20.4	0.72[a]
Group a	7					
Group b	16					
Group c	2					
Ishida et al., 1993 (31)	—	77	154	40	37	—
Maier et al., 1993 (27)						
Group a	14	14	28	9	5	0.87
Group b	19	19	38	12	7	1.24
Group c	41	41	83	28	16	1.00
Wang et al., 1993 (32)						
Group a	20	24	48	17	7	—
Group b	24	25	62	23	14	—
Kendler et al., 1997 (33)	—	172	383	—	—	1.92[a]
Present study, 1998	—	1,942	4,230	1,249	1,051	1.58

[a] Not weighted.
[b] Sex distribution in individual sibships was not specified.

was unsystematic, mostly through retrospective—thus, incomplete—screening of hospital charts (25, 26), sporadic admissions by individual psychiatrists (24, 30) and treatment institutions stratifying their clients by sex, and self-reports in response to advertisements (18, 19, 29), which might be especially prone to selection bias. Sample sizes were generally low, and often sufficient statistical power was attained only by pooling small series of affected sibships from different countries (18, 19, 24) or even ethnic backgrounds (25, 26, 30) and combining diverse ascertainment procedures, diagnostic interviews, and manuals, at the expense of genetic and procedural homogeneity. If it was specified at all in previous reports, the time frame of sampling typically did not exceed 4 years (18, 24, 25, 27), which may have led to oversampling of affected male pairs among probands with recent onset (since age at onset of schizophrenia has been found to be lower in males than in females in most studies—yet not in this one [28]—so that a substantial proportion of mixed-sex pairs will have come to attention only after the intake period, when the female sibling will also have manifested the syndrome). At the other extreme of the age distribution, prevalence-based sampling within a narrow time frame may lead to overrepresentation of female probands concordant for schizophrenia (5), since they live longer than their male counterparts. Our study is so far the only one that has sampled a com-

Ascertainment Procedure and Study Location	Inclusion Criteria	Pairs for Whom Parent With Schizophrenia Was Known	Results
Consecutive psychiatric hospital admissions, Canada	Clinical schizophrenia, including organic paranoid	Condition not tested	Sex concordance significantly increased
66 sibships hospitalized for any mental disorder, U.K.	Schizophrenia, clinical	Condition not tested	Sex concordance not increased
Consecutive psychiatric hospital admissions, U.K.	Schizophrenia (ICD-8)	Condition not tested	Sex concordance not increased
Advertisement, U.S. (subsample from reference 18)	Chronic schizophrenia, schizoaffective (modified RDC)	Condition not tested	Sex concordance not increased
	Chronic schizophrenia, schizoaffective	9 paternal, 14 maternal	Nonsignificant overall excess of same-sex pairs; significant excess of same-sex pairs under paternal transmission
Advertisement, U.S.	RDC		
Hospital-based, U.K.	CATEGO		
Clinical observations among general hospital admissions, U.K. and across U.S.	Schizophrenia, schizoaffective requiring hospital admission (RDC)	Condition not tested	Nonsignificant 6.7% overall excess of same-sex pairs (calculated from table)
Psychiatric hospital records, central France and overseas department	Schizophrenia (DSM-III-R)	24.4 paternal, 11 maternal	1.7- to 3.2-fold excess of same-sex pairs under paternal transmission; nonsignificant 9.2% excess in overall sample
Subsample from reference 25	Schizophrenia (DSM-III-R)	Condition not tested	Sex concordance not increased
Psychiatrists' referrals for study of nuclear families with ≥ 2 cases	Schizophrenia, schizoaffective (RDC)	16 paternal, 20 maternal	Overall significant, under paternal transmission nonsignificant, excess of same-sex pairs
Wales			
U.K.			
Japan			
Hospital-based, Japan	Schizophrenia (DSM-III-R)	6 paternal, 13 maternal	Sex concordance not increased
Family study of 525 consecutive psychiatric hospital admissions, Germany	Schizophrenia (RDC)	6	Overall significant, under paternal transmission nonsignificant, excess of same-sex pairs for group c
	Schizophrenia (RDC), schizotypal personality (DSM-III-R)	10	
	Schizophrenia (RDC), schizotypal personality (DSM-III-R), all other psychotic disorders including psychotic affective (RDC)	16	
Family study of consecutive psychiatric hospital admissions, U.S.	Schizophrenia, schizoaffective (DSM-III-R)	19	Greater sex concordance under maternal than under paternal transmission
	Schizophrenia, schizoaffective, schizophreniform, schizotypal personality (DSM-III-R)	31	
Data from 39 public psychiatric hospitals, Ireland	Schizophrenia (DSM-III-R)	Condition not tested	Slight excess of same-sex affected sibling pairs interpreted as meager support for X-linkage
Nationwide case registers, Finland	Schizophrenia (ICD-8, DSM-III-R)	111 paternal, 144 maternal	Overall 3.4% excess, under paternal transmission 9.9% deficit, of same-sex pairs, both nonsignificant

plete birth cohort spanning 30 years, thus being broad enough to preclude selection for sex by prevalence-based sampling (since inclusion did not depend on whether probands were still alive at the moment of intake) or by a narrow time frame.

Each of these factors might have led to spurious evidence of increased sex concordance in previous studies, to which is added the widely applied practice of breaking down sibships with more than two affected members into weighted pairs (table 2). In fact, when the studies that reported the actual composition of sibships by sex were subjected to the unbiased maximum likelihood analysis (table 1), they no longer provided evidence for significantly increased sex concordance. Only upon addition of the much larger Finnish sample was significance attained, which leads to the somewhat paradoxical conclusion that previous studies may have upheld, for reasons of biased ascertainment and statistics, the presence of increased sex concordance where there was actually none, whereas the Finnish nationwide sample, one to two orders of magnitude larger and more robust with respect to these biases, would provide evidence for its existence (although possibly to a large degree derived from particular geographical pockets, as discussed above).

Molecular genetic linkage and association studies with markers from the pseudoautosomal region directly challenge the pseudoautosomal gene hypothesis (table 3), yet results remained inconsistent not only among studies (positive in references 24, 26, and 36;

TABLE 3. Linkage or Association Studies on the Pseudoautosomal Region in Siblings With Schizophrenia

Study	Number of Families	Number of Sibships	Number of Affected Individuals	Ascertainment Procedure and Study Location	Inclusion Criteria	Genetic Model	Conclusions
Collinge et al., 1991 (24)	83	83	184	Clinical observations among general hospital admissions, U.K. and across U.S.	Schizophrenia, schizoaffective (RDC)	Nonparametric	Above-chance allele sharing of affected siblings at DXYS14 ($t=2.04$, $p<0.05$)
d'Amato et al., 1992 (26)	—	33	83	Subsample from reference 25, central France and overseas department	Schizophrenia (DSM-III-R)	Nonparametric; penetrance=0.6/0.3/0.002; frequency=0.018	Above-chance allele sharing at DXYS14 ($p<0.05$); no linkage at $\theta=0$ ($z=-5.7$), but $z=0.56$ at $\theta=0.25$
Asherson et al., 1992 (30)	6	22	44	Psychiatrists' referrals for study of nuclear families, Wales	Schizophrenia, schizoaffective (RDC)	Nonparametric; various penetrances and frequencies (0.04–0.1)	No above-chance allele sharing at DXYS14 ($p<0.04$); linkage excluded at $\theta=0$ ($z<-2$) for 16 models
Ishida et al., 1993 (31)	—	—	46	Hospital-based; 150 control subjects, Japan	Schizophrenia (DSM-III-R)	Association study	No differing allele frequencies at DXYS17, -28,-20, or MIC2
Wang et al., 1993 (32)	12	—		Family study of consecutive		Various penetrances including 0.01; frequencies=0.008 (dominant) and 0.1 (recessive)	Linkage excluded at $\theta=0$ ($z<-2$) for 10 models at seven loci; multipoint lod scores <-4
Group a			27	psychiatric hospital admissions, U.S.	Schizophrenia, schizoaffective (DSM-III-R)		
Group b			35		Schizophrenia, schizoaffective, schizophreniform, schizotypal personality, psychotic affective (DSM-III-R)		
Crow et al., 1994 (34)	85	—	—		Schizophrenia, schizoaffective (RDC)	Nonparametric; 60 age-dependent penetrance classes	No above-chance allele sharing at DXYS14 ($p\leq0.38$) or -17 ($p\leq0.35$); allele sharing and lod score at MIC2 suggestive of linkage with sex-specific region
Group a	23			Hospital-based clinicians' referrals, U.K., Ireland			
Group b	62			Advertisement, U.S.			
Barr et al., 1994 (35)	7	30	38	Large kindred from isolate, Sweden	Feighner and DSM-III	Penetrance=0.72/0.72/0.001; frequency= 0.02	No linkage with eight markers spanning the region
d'Amato et al., 1994 (36)	49	49	135	Extension of sample from reference 26, central France and overseas department	Schizophrenia (DSM-III-R)	Nonparametric; various penetrances and frequencies (0.003–0.097)	Above-chance allele sharing at DXYS14 ($p<0.03$), but not at four more loci; no clear evidence of linkage
Kalsi et al., 1995 (4)	23	—		Unspecified, U.K., Ireland			No linkage or above-chance allele sharing at DXYS14 and MIC2
Group a			95		Schizophrenia, nonaffective psychosis	Penetrance=0.73/0.73/0.005; frequency=0.0085	
Group b			112		Schizophrenia, schizoid personality, schizotypal personality, nonaffective psychosis	Penetrance=0.76/0.76/0.01; frequency=0.0085	
Maier et al., 1995 (37)	14	—	47	Family study of 525 admissions, Germany	Schizophrenia, schizoaffective (RDC)	Penetrance=0.55/0.55/0.10; frequency=0.01	No linkage to DXYS14 and DXYS41 ($z<-2$ at $\theta=0$)

negative in references 4, 30–32, 34, 35, 37) but also between phenotypic and genotypic evaluations within some of those studies (18 and 34, 26 and 36, 27 and 37, 30) that either genotyped a subsample (24, 26, 30, 32, 34, 36, 37) or a different, but by genetic background comparable, sample (31) than the one they screened for the phenotypic presence of increased sex concordance.

Distorted Sex Ratio: Bias or Valid Finding?

The frequent occurrence of male-to-female ratios well above 1.00 in different samples (table 2) deserves separate discussion, since it has been taken as evidence of ascertainment biased toward the dependent variable, the sex of proband pairs (38). Although ascertainment relied on nationwide registers with largely unbiased or even complete coverage of cases ever having occurred in the sampled birth cohort, our male-to-female ratio was greater than 1.00. However, in this case it is possible to exclude the possibility that the overrepresentation of males resulted from the peculiarities of exclusively ascertaining sibships with multiple affected members (this was what all previous studies except the one in reference 27 did), since a male-to-female ratio greater than 1.00 held true irrespective of the number of affected members per sibship in our sample (sibships with two affected: 1,996/1,342=1.49; three affected: 416/238=1.75; four affected: 112/60=1.87; five affected: 29/11=2.64; six affected: 10/8=1.25; seven affected: 6/1=6.00) and, most importantly, this also applied to sibships with a single case (12,488/8,615=1.45), which were ascertained in the same way as the subsequently studied multiply affected sibships (the only significant difference in sex ratio out of 21 pairwise comparisons was for single cases versus affected triplets [χ^2=5.34, df=1, p=0.02]). We are, on the other hand, not aware of any bias in favor of males that might have been introduced by the specific type of case registers we applied; as we have stated, the most suspect register in this study—the one for disability pensions—is in no way restricted to the workforce of the country. We therefore consider it most likely that a real predominance of males over females exists among persons with severe, treated schizophrenia, even under broad, register-based ascertainment procedures, and that the commonly held assumption of equal prevalence in the sexes does not apply. This is well in line with recent findings of a greater prevalence in males than in females from a similar register-based epidemiologic family study in Ireland (39), an environment with a comparable social structure, and with several other epidemiologic studies (40, 41) that confirmed the historic Kraepelinian notion cited by Crow et al. (19)—also shared by proponents of the neurodevelopmental theory (42)—that schizophrenia is predominantly a disease of young males.

Limitations of the Study

The limitations of this study include necessary restrictions in the diagnostic procedure. Unlike most studies with limited sample size, in this study it was not feasible to obtain standardized personal interviews with over 4,000 affected subjects from the 1,942 sibships with several cases of schizophrenia that were identified. Despite the structure and high quality of the national health system in Finland, a rate of 24% false positives for cases of schizophrenia among the registries emerged when the reliability of diagnoses in a subsample of probands was checked against the narrow criteria of DSM-III-R by a best estimate from all available medical records (21) (although this is only 4%–8% off the diagnostic range for a genetic schizophrenia spectrum). However, the same procedure applied to all 37 registered cases of schizophrenia that had arisen up to age 27 among the 11,017 members alive at age 16 in a 1966 birth cohort found no false positive cases at all (43). Whereas the first sample, reflecting a broader age range, was geographically limited to the small northeastern isolate targeted for more detailed study (28), the second covered the complete northern half of Finland, although it was restricted to one particular birth year. Earlier Present State Examination and CATEGO criteria-based interview data on first psychiatric hospital admissions in the southern capital region further indicate that the specificity of registered schizophrenia diagnoses can be substantial (44). While only a reliability exercise on a randomly drawn subsample would have provided representative data on diagnostic specificity in our nationwide sample, high local variability might still be expected whenever hundreds of clinicians contribute to nationwide registries in a nonstandardized manner. We did, however, attempt to control for changing diagnostic habits over time by splitting the total sample into two separate birth cohorts, one running from 1940 to 1959 and the other from 1960 to 1969, but this failed to yield different results (data not shown).

Another limitation relates to the fact that in sorting sibships by transmission of schizophrenia exclusively from one parental side, our registers were restricted to first-degree relatives, whereas other investigators (18), in addition to this "closest-relative approach," assessed family history information on second- and third-degree relatives (yet also conducted no personal interviews). However, in doing so, the spectrum of disorders by which transmission of schizophrenia through one parental lineage was traced included also affective disorder in a parent or second- or third-degree relative. Some family studies demonstrating an increased risk of unipolar depression in first-degree relatives of schizophrenic subjects (45, 46) seem to justify this practice, but that finding has not been confirmed in more recently studied samples (47, 48). Despite the possibility that we may have wrongly accepted sibships with one schizophrenic parent as showing unilineal inheritance when actually schizophrenia was also present in some second-degree relative on the other parent's side, this should be rare, given a disease-associated gene of major effect and at least moderate penetrance (the only scenario under which the tested hypothesis is valid), which would likely have led to some schizophrenia-related condition in the other parent, too. By focusing on families with schizophrenia in two successive generations, we probably selected for such high-penetrance families and thus safeguarded against inclusion of affected sibships with a significant genetic contribution from both parents. Also, in the studies in-

corporating family history information on higher-degree relatives, the closest-relative approach was no less sensitive to a finding of increased sex concordance than the two alternative modes tested (19).

Finally, as discussed at the beginning of this article, exclusion of a disease-related gene on the very tip of the sex chromosomes was impossible, as it would not lead to increased concordance for sex, but this limitation, though not always explicitly stated, applies to all epidemiologic studies on that subject.

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