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Points of View

Unsound Methodology in Investigating a Pseudoautosomal Locus in Schizophrenia

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We have reservations about accepting the conclusions made by Crow *et al* (1989), namely that there is evidence that susceptibility to schizophrenia may be transmitted by a pseudoautosomal locus. In our view the methodology of the study is unsound. Additionally the data presented by the authors, when analysed correctly, do not support their hypothesis.

Crow *et al* have broken one of the most important rules of segregation analysis – that the sampling of probands and families should not be biased. It is well known that schizophrenia is equally common in men and women, and yet the American sample studied is over 70% male. We have also noticed another bias in that there is an excess of maternally derived mixed-sex pairs. We can only speculate as to the source of these biases, but because both are related to the sex distribution of affected cases, the sample is clearly inadequate for the analysis carried out: segregation analysis requires that the system of ascertainment and hence the sample characteristics are not biased with respect to the dependent variable, which in this study is the sex of individuals suffering from schizophrenia.

Sturt & Shur (1985) have drawn attention to some of the methodological errors that should be avoided when attempting to assess whether sex concordance for schizophrenia is raised above that which might be expected by chance. The principal error which has affected previous studies of sex concordance is that the proband series were not composed of equal numbers of males and females. There is then a tendency attributable to chance for there to be an increased number of same-sex sibships. In fact some of the studies quoted by Crow *et al* as being in support of sex concordance suffered from this problem (see Sturt & Shur, 1985), whereas Sturt and Shur's own more carefully conducted study failed to show any excess of same-sex sibships.

The study of Crow *et al* contains some other methodological faults. There may be problems associated with using a rather broad and arbitrary definition of schizophrenia (hospitalisation and RDC or St Louis or CATEGO diagnosis), but the main problems are with the lack of a systematic method of ascertainment and lack of a rigorous method to assign diagnosis to the relatives of the proband sibships. This is particularly important because a paternal or maternal history of mental illness is one of the critical factors of the study. Although these methods are not fully described, it is obvious that the method of ascertainment used has produced a substantial bias, as evidenced by the large excess of male over female probands. The authors comment on this excess, and it is true that it is possible to correct for such an excess in subsequent analyses. Nevertheless the reader must remain unaware of other ways in which the initial sample may have been biased. By far the most cogent criticism of the methodology is the way in which diagnosis of relatives was performed. To do this it is essential that all possible steps are taken to eliminate bias in deciding on the source of the illness by using blind assessors, operationalised diagnostic techniques, and systematic investigation of all family members. In fact none of these techniques was used, and the authors say only that diagnosis was assigned to relatives by interview with multiple informants, and they omit to inform us of the diagnostic framework used (although it seems that this was possibly ICD-9).

We think also that inappropriate methods of analysis have been applied to the data, and that, correctly analysed, the data provide no support for the pseudoautosomal hypothesis. The pseudoautosomal hypothesis makes three predictions:

(a) in paternally derived families there will be an excess of same-sex sibships
(b) in maternally derived families the number of same-sex sibships will be that expected by chance
(c) taking all sibships together (which will comprise a mixture of paternally and maternally derived sibships, perhaps additionally with sporadic and autosomal cases) there will still be an overall excess of sex-concordant sibships.

In order to test their theory, Crow *et al* have mistakenly conflated the first two hypotheses and performed Fisher's exact tests to examine the following hypothesis:

> There will be relatively more sex-concordant sibships in paternally derived families, and relatively more mixed-sex sibships in maternally derived families.

TABLE I
Observed[1] and expected[2] concordance in same-sex and mixed-sex sibships

	Parental derivation by classification of family history						
	Hierarchical		*Unilateral*		*Closest relative*		*All subjects*
	Paternal	*Maternal*	*Paternal*	*Maternal*	*Paternal*	*Maternal*	
Same-sex pairs							
observed	17	12	15	12	22	16	63
expected	13.7	18.0	12.0	16.6	18.0	21.3	62.6
Mixed-sex pairs							
observed	7	23	5	20	11	25	57
expected	10.3	17.0	8.0	15.4	15.0	19.7	57.4
Significance (one-tailed binomial test)	NS	$P<0.05$	NS	$P<0.08$	NS	$P<0.07$	NS

The tests performed do significantly favour this hypothesis over the null hypothesis, but examination of the raw data shows that the main reason for this is that (especially after taking into account the large number of male cases) there is an excess of mixed-sex sibships in the maternally derived families (Table I). Using one method of determining parental derivation (the hierarchical method), this excess is significant at $P<0.05$, and with the other two methods $P<0.1$. This excess of mixed-sex sibships is in no way consistent with the pseudoautosomal hypothesis, and it is incorrect to use it in the Fisher's test to support this hypothesis.

Because the pseudoautosomal hypothesis makes the same prediction for the maternally derived families about the proportions of same-sex and mixed-sex sibships as does the null hypothesis, these families should be omitted from consideration. Instead, the paternally derived sibships should be studied alone, and the deviation of the observed proportion of sex-concordant sibships from expected can be tested as a binomial probability, taking into account the excess of male cases. When this is done there is no significant excess of sex-concordant pairs. Additionally, all the sibships can be pooled and an excess of sex-concordant pairs tested for (see point (c), above). There is no overall excess of sex-concordant sibships. When Sturt & Shur (1985) studied a systematically ascertained series of sibships, avoiding the methodological errors they enumerated, they also found no overall excess of sex-concordant sibships.

We believe that the hypothesis of pseudoautosomal transmission is, *a priori*, unlikely, and that the study of Crow *et al* does not provide appreciable support for it.

References

CROW, T. J., DELISI, L. E. & JOHNSTONE, E. C. (1989) Concordance by sex in sibling pairs with schizophrenia is paternally inherited – Evidence for a pseudoautosomal locus. *British Journal of Psychiatry*, **155**, 92–97.

STURT, E. & SHUR, E. (1985) Sex concordance for schizophrenia in proband-relative pairs. *British Journal of Psychiatry*, **147**, 44–47.

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In Reply . . . A Locus Closer to the Telomere?

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Curtis & Gurling quote with approval Sturt & Shur's (1985) critique of same-sex concordance with the implication that the phenomenon has been explained as ascertainment bias. While some of Sturt & Shur's points are valid, we note that these are not relevant to those series of dizygotic (DZ) twins