British Journal of Psychiatry (1994), **165,** 117–123

Correspondence

Contents: Epilepsy in adults with Down's syndrome/ Pseudoautosomal linkage in schizophrenia/Obstetric complications in schizophrenia/Early responses to electroconvulsive therapy/Electroconvulsive therapy and brain damage/Volunteers to help Bosnian refugees/Cognitive function and fall-related fractures/ Alcoholism in Kuala Lumpar General Hospital/A man who does not use his arms

Epilepsy in adults with Down's syndrome

SIR: McVicker *et al* (*BJP*, April 1994, **164,** 528–532) have shown that late-onset seizures in people with down's syndrome are associated with dementia. The reported overall prevalence of 9.4% of seizure disorders in Down's syndrome is similar to that observed (10.2%) in the Leicester Down's syndrome cohort (Collacott, 1994) of 344 adults. The incidence of seizure disorders was 0.28 per 100 people per year in those aged less than 20 years. The incidence fell to a nadir of 0.09 in those aged 30–39 years, and then rose to maximum of 0.71 in those aged 50–59. Late-onset seizures were associated with clinical dementia. However, the use of the Adaptive Behaviour Scale demonstrated that seizures occurred when the dementing process was well advanced.

The similarity of the findings from two total population studies from different geographical areas of the UK is of considerable interest. Late-onset seizures in people with Down's syndrome indicate dementia unless proven otherwise.

COLLACOTT, R. A. (1994) Epilepsy, dementia and adaptive behaviour in Down's syndrome. *Journal of Intellectual Disability Research,* **37,** 153–160.

R. A. COLLACOTT
S-A. COOPER
Department of Psychiatry, University of Leicester

Pseudoautosomal linkage in schizophrenia

SIR: Crow *et al*'s account of the investigation of linkage between schizophrenia and sex chromosome pseudoautosomal markers (*BJP*, February 1994, **164,** 159–165) suffers from a flaw that the authors fail to mention: namely that the positive results can be attributed to the fact that their sample is biased towards an excess of same-sex male schizophrenic sibling pairs. Such a sample will produce spuriously positive lod and sibling pair linkage scores with markers near the pseudoautosomal boundary. Furthermore there are insufficient details about the analyses given in the paper to permit independent replication on further data sets.

The weakly positive lod scores reported are derived from a sample which has been used previously for the study of same-sex concordance (Crow *et al*, 1989) as well as linkage analysis (Collinge *et al*, 1991). We (Curtis & Gurling, 1990) drew attention to the excess of affected males in this sample of sibships. In reply, Crow *et al* (1990) conceded the correctness of our argument and in a reanalysis found that the evidence for increased sex concordance in affected schizophrenic pairs was much weaker than they had claimed. In the recent study, markers linked to sex are used and these will produce artefactual evidence in favour of linkage when there is an excess of affected sibling pairs who are concordant for sex. The fact that MIC2 is unlinked to schizophrenia in female meioses further supports the notion that the positive results reported with this marker are simply an artefact of the increased sex concordance.

The paper is also deficient because it gives no account of the penetrance functions or gene frequencies used for the linkage analyses. Nor do the authors clarify what they mean by "other major psychiatric disorders". The authors also fail to discuss the statistical interpretation of their findings. We are concerned that readers might gain the impression that the cited lod score of 2.44 provides noteworthy evidence of linkage: one would not normally regard a lod score of less than 3.00 as providing any worthwhile evidence for localisation of a disease locus. Multiple testing is carried out with three different markers and two transmission models. In addition, recombination fractions are allowed to vary independently for male and female meioses.

This means that it is likely for lod scores as high as 2.44 to occur entirely by chance, even without the effects of the sex-concordance bias. Lastly, we must

draw attention to the negative studies (Barr *et al*, 1991; Ishida, 1993; Wang *et al*, 1993; Curtis *et al*, 1993) reported for pseudoautosomal linkage in schizophrenia which Crow *et al* did not cite.

References appear below

D. CURTIS
G. KALSI
H. M. D. GURLING
Molecular Psychiatry Laboratory
Department of Psychiatry
University College London Medical School
London W1P 6DB

AUTHORS' REPLY: In responding to Curtis *et al* we make three points.

First, we note that they misrepresent out paper:

(a) by stating that we did not refer to the paper on linkage by Wang *et al* when this paper is cited in the Discussion (p. 163)

(b) by implying that we failed to refer to two abstracts (Curtis *et al*, Ishida *et al*) which in fact were presented and published after our paper was accepted (these studies are apparently in agreement with our conclusion that the evidence does not support a locus within the pseudoautosomal region; Curtis *et al*'s last sentence leaves us in doubt whether they have understood that, as stated in our summary and Discussion, this is a major conclusion of our study)

(c) by suggesting that the diagnostic criteria we have used are not specified when these are stated (p. 160).

Second, we respond to what we take to be Curtis *et al*'s main point, that the positive lod score can be accounted for by allele sharing on the Y chromosome at MIC2. We are in agreement with this and state (p. 162) that "it is likely that the lod score of 2.44 is accounted for by linkage on the Y chromosome, i.e. to sex".

Could this finding be due, as Curtis *et al* suggest, to multiple testing or to a predominance of affected males? We investigated how likely it would be that the lod scores we observed had arisen by chance (assuming an autosomal gene for schizophrenia) with our sample and method of analysis. We simulated a marker (MIC2) that was unlinked to the phenotype (schizophrenia) but linked to the boundary of the pseudoautosomal region (sex locus). The linkage between MIC2 (using information from the p19b-TaqI probe[1]) and the sex locus (in males $r=0.05$, in females $r=0.02$) was as expected for the pseudoautosomal region and as estimated from our data.

The simulated pedigrees were then analysed with ISIM (using the ILINK algorithm) and maximum lod scores were calculated over a range of male and female recombination fractions. As in our paper, we used a lifetime penetrance of 0.5, penetrance for phenocopies of 0.005, and a gene frequency of 0.0052. The overall maximum of $Z=0.5$ occurred at a recombination fraction of 0.15 in males and approximately 0.5 in females. This suggests that the maximum lod scores found in the analysis should be corrected by 0.5. Using data for the p19b-TaqI probe for MIC2 alone (as in the simulation) we find a maximum lod score (Z) of 2.95, giving 2.45 after correction. These calculations suggest that our lod score of 2.4 cannot be accounted for by "artefactual evidence in favour of linkage when there is an excess of affected sibling pairs who are concordant for sex".

In addition, the sample was selected for schizophrenia and not for sex. More of our probands are males than females[2] (135:51) – probably because our sample is weighted towards early onset. Whether Curtis *et al* are justified in describing this as an 'excess' is at the heart of the matter. The issue, as we see it, is whether the well known sex differences in schizophrenia (e.g. with respect to age of onset) are extrinsic to the disease process or whether they reflect directly on its genetic origin. We refer interested readers to our original paper (Crow *et al*, 1989) and to the subsequent discussion (Curtis & Gurling, 1990; Crow *et al*, 1990), of which we do not altogether share Curtis *et al*'s interpretation.

Third, we agree with Curtis *et al* that a lod score of 2.44 is no more than suggestive evidence of linkage. Like all such findings it requires further investigation, by ourselves (e.g. DeLisi *et al*, 1994) and others. The point is justly made by the group that reported a lod score of 6.49 to a locus on the long arm of chromosome 5 (Sherrington *et al*, 1988), a finding unsupported by subsequent studies.

BARR, C. L., KENNEDY, J. L. & PAKSTIS, J. (1991) Progress in genome scan for linkage in schizophrenia. *Psychiatric Genetics*, **2**, 66.

COLLINGE, J. S., DELISI, L. E. & BOCCIO, A. (1991) Evidence for a pseuoautosomal locus for schizophrenia using the method of affected sib pairs. *British Journal of Psychiatry*, **158**, 624–629.

1. The SLINK program was used for the simulations. Only the TaqI information was used because it was difficult to simulate all three probes together in this program.

2. Out of a total of 85 families studied there were 38 MM, 8 FF and 28 MF pairs. In addition there were 1 FFM, 3 MMF, 4 MMM, 1 FFMM, 1 MMMM, and 1 MMMMMM sets of ill siblings.