Correspondence

EDITED BY KIRIAKOS XENITIDIS and COLIN CAMPBELL

Is *DISC1* really a gene predisposing to psychosis?

In their editorial on chromosomal abnormalities and psychosis Muir *et al* (2006) concluded that *DISC1* 'is an important modulator of risk for schizophrenia and severe affective disorder in people without cytogenetic abnormalities and may also influence cognition and brain structure in the general population'. They base their conclusions on work that originated in the finding of a rearrangement between chromosomes 1 and 11 in a single large family with polymorphic psychiatric syndromes (Millar *et al*, 2001). The two genes (*DISC1* and *DISC2*) that they are concerned with were identified at the breakpoint and by linkage analysis were postulated to be relevant to psychiatric disease within that family.

Muir *et al* argue that these findings are relevant to schizophrenia in general. However, the evidence is less compelling than they suggest. Figure 1 presents the findings of the three largest linkage studies to date in relation to the location of *DISC1* on chromosome 1 (the location of another 'candidate gene' *RGS4* is also shown). Each study included over 300 sibling pairs with schizophrenia or schizoaffective disorder and each included markers spaced at 10 cM intervals across the genome. The Lod (log of the odds) score is a measure of linkage – transmission of a disease state with particular genetic markers within families – and values above 3 are generally taken as significant evidence for linkage. In these three studies there is no evidence of linkage at the *DISC1* locus or elsewhere on chromosome 1. The two claims of linkage made in Table 1 of Muir *et al*'s editorial relate to *post hoc* subdivision of one of these populations by diagnosis and to a finding in a separate smaller Finnish study. Given the ubiquity of psychosis across populations, and the relative uniformity of incidence of the core syndrome, and in the face of lack of evidence of linkage in populations of over 1000 sibling pairs (Crow, 2007), it is difficult to see that *DISC1* can have an 'important role in the development of psychosis' as Muir *et al* argue. The evidence has been overinterpreted.

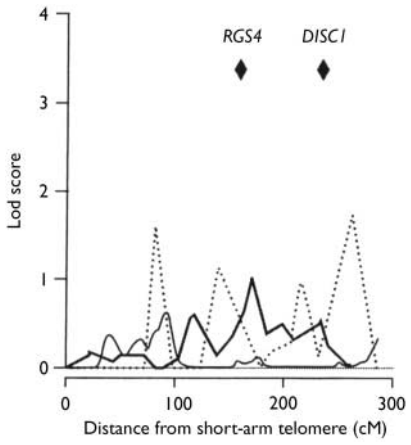

Fig. 1 Linkage studies of *DISC1* in sibling pairs with schizophrenia or schizoaffective disorder. —, DeLisi *et al*, 2002 (382 sibling pairs); ...., Williams *et al*, 2003 (353 sibling pairs); —, Suarez *et al*, 2006 (409 sibling pairs).

Crow, T. J. (2007) How and why genetic linkage has not solved the problem of psychosis: review and hypothesis. *American Journal of Psychiatry*, **164**, 13–21.

DeLisi, L. E., Shaw, S., Crow, T. J., *et al* (2002) A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*, **159**, 803–812.

Millar, J. K., Christie, S., Anderson, S., *et al* (2001) Genomic structure and location within a linkage hotspot of Disrupted In Schizophrenia 1, a gene disrupted by a translocation segregating with schizophrenia. *Molecular Psychiatry*, **6**, 173–178.

Muir, W. J., Pickard, B. S. & Blackwood, D. H. R. (2006) Chromosomal abnormalities and pscyhosis. *British Journal of Psychiatry*, **188**, 501–503.

Suarez, B. K., Duan, J. B., Sanders, A. R., *et al* (2006) Genomewide linkage scan of 409 European-ancestry and African American families with schizophrenia: suggestive evidence of linkage at 8p23.3-p21.2 and 11p13.1-q14.1 in the combined sample. *American Journal of Human Genetics*, **78**, 315–333.

Williams, N. M., Norton, N., Williams, H., *et al* (2003) A systematic genomewide linkage study in 353 sib pairs with schizophrenia. *American Journal of Human Genetics*, **73**, 1355–1367.

T. J. Crow SANE Prince of Wales Centre, Warneford Hospital, Oxford OX3 7JX, UK. Email: tim.crow@psych.ox.ac.uk

doi: 10.1192/bjp.190.3.270

Authors' reply: Professor Crow takes issue with our view that *DISC1* is important to schizophrenia in general and is not restricted to the initial family in which disruption of this gene was reported. His argument is based on a selected set of sib-pair studies whose results do not support linkage anywhere on chromosome 1. This finding was unsurprising in view of the lack of power of such studies in the presence of genetic heterogeneity in schizophrenia susceptibility, which was not mentioned by Professor Crow. We and a large number of other workers in the field consider that such locus heterogeneity is highly likely and have shown that the sib-pair strategy has limited power to detect a locus that contributes less than 20% of the variance (Macgregor *et al*, 2002). Where heterogeneity is expected then linkage analysis, especially of extended multiplex pedigrees, and gene candidacy identified though the investigation of psychosis-associated karyotype anomalies are appropriate research strategies. Where there is *a priori* evidence from cytogenetic and linkage studies (such as the Finnish studies mentioned in the editorial) then the case–control association approach provides a useful resource to delineate potential population haplotype distortions that may indicate underlying functional mutations.

We would therefore disagree strongly with Crow in his statement that we have 'overinterpreted' the importance of *DISC1* and commend an excellent review of schizophrenia neurobiology which emphasises heterogeneity (Ross *et al*, 2006). Although our theoretical framework differs from that of Bleuler (1950), we feel that the recent genetics and neurological discoveries are in agreement with his position that there is indeed a 'group of schizophrenias'.

Bleuler, E. (1950) *Dementia Praecox or the Group of Schizophrenias* (trans. J. Zinkin). International Universities Press.