Letter to the Editor

Response to Amar J. Klar: The Chromosome 1;11 Translocation Provides the Best Evidence Supporting Genetic Etiology for Schizophrenia and Bipolar Affective Disorders

J. Kirsty Millar,[*,1] **Pippa A. Thomson,**[*] **Naomi R. Wray,**[*] **Walter J. Muir,**[*,†] **Douglas H. R. Blackwood**[*,†] **and David J. Porteous**[*]

[*]*Medical Genetics Section, Department of Medical Sciences, The University of Edinburgh, Molecular Medicine Centre, Edinburgh, EH4 2XU United Kingdom and* [†]*Department of Psychiatry, Royal Edinburgh Hospital, Edinburgh, EH10 5HF United Kingdom*

MANY common disorders, including schizophrenia and bipolar affective disorder, are highly heritable, yet do not exhibit simple inheritance patterns. Individual risk is usually attributed to the coalescence of multiple, independent, and additive risk factors (modifiers), both genetic and environmental, or to the effect of one of a number of genes of major effect and variable penetrance, with secondary genetic modifiers and environmental factors determining the degree of penetrance. Nowhere is the debate more lively and contentious than in psychiatric genetics (WEISS and TERWILLIGER 2000), but in truth there is a dearth of substantiated, empirical data. For example, the reported number of positive linkage and association studies far exceeds the number of replications. This in part reflects the statistical challenge of replication and the complexities of diagnostic criteria and boundaries. Attempts to rationalize observations through a novel mechanistic proposal are therefore to be welcomed and merit careful discussion. Klar recently proposed one such novel mechanistic interpretation of data published by us on a large multigeneration Scottish family with a high loading of major psychiatric illness (KLAR 2002). However, several points of information not considered by Klar allow us to conclude that his model is not supported by the available data.

In this family, a balanced (1;11)(q42;q14) translocation cosegregates with major psychiatric illness with a maximum LOD score of 7.1 (ST. CLAIR *et al.* 1990; BLACKWOOD *et al.* 2001). The odds for the translocation being linked to the psychiatric disorders in this family are therefore extremely high. Not all translocation carri-

ers are affected, however, and the probable mode of disease inheritance is dominant with reduced penetrance. That is to say inheritance of the translocation confers a genetic predisposition to develop psychiatric illness rather than a certainty of becoming ill. One possible reason for this is the presence of modifiers with either a protective or a disease-enhancing influence. Similar rates of penetrance have been observed in Hirschsprung disease (aganglionic megacolon), and a recent report demonstrates that the genetic interplay of three different loci, one of major effect, can explain the inheritance pattern of this disorder (GABRIEL *et al.* 2002). Given that genetic interplay between one major and two minor genetic risk factors is sufficient to explain the incomplete penetrance of Hirschsprung disease mutations, it is not unreasonable to propose a similar mechanism for the 1;11 translocation and major psychiatric illness.

In his recent Note to GENETICS (KLAR 2002), A. J. S. Klar favors an alternative theory to explain the observed reduced penetrance in translocation carriers. On the basis of mating-type switching in *Schizosaccharomyces pombe*, Klar proposes a theory of random chromosome strand segregation that predicts 50% of translocation carriers will be unaffected, while the other 50% will suffer from a major psychiatric illness. In fact, generations II–V of the family segregating this translocation indicate that 62% (18 of 29) of translocation carriers are affected by schizophrenia, bipolar affective disorder, or major depression (note that only 29 translocation carriers have been subject to full clinical assessment, although a total of 37 translocation carriers have been identified; BLACKWOOD *et al.* 2001). Moreover, at the time of ascertainment, many of the translocation carriers in generation V were at, or below, the average age of onset. It is therefore more appropriate to consider only generations II–IV where an adult life history is available and where 70% (16/23) of translocation carri-

[1]*Corresponding author:* Medical Genetics Section, Department of Medical Sciences, The University of Edinburgh, Molecular Medicine Centre, Western General Hospital, Crewe Road, Edinburgh EH4 2XU, UK. E-mail: kirsty.millar@ed.ac.uk

ers are affected. If the two-sided binomial test is used on the translocation carriers in generations II–IV to examine Klar's hypothesis that 50% of carriers are affected, a *P* value of 0.093 is generated. This suggests evidence for rejection of his hypothesis, given that the number of translocation carriers is small for such a statistical test.

A number of "endophenotypes" or trait markers of risk have been proposed for psychiatric illness. Endophenotypes are measurable biological phenomena that represent a trait marker for the inheritance of a given genotype. Endophenotypes are usually consistently displayed as a result of the genotype and can be useful in defining carrier status of individuals who do not present with a psychiatric disorder. One such endophenotype is the P300 scalp-recorded averaged evoked brain potential occurring some 300 msec after a sensory stimulus presented randomly against a background of regular sensory stimuli. The latency and amplitude of the P300 event-related potential are thought to reflect the speed and efficiency of information processing, and prolonged latency and reduced amplitude are characteristic of subjects with schizophrenia and their close relatives (BLACKWOOD *et al.* 1991; SHAM *et al.* 1994). P300 latency and amplitude have been measured in 12 translocation carriers, in 10 of their unaffected, nontranslocation-carrying relatives, and in population controls (BLACKWOOD *et al.* 2001). A group of 12 translocation carriers showed significantly prolonged latency and reduced amplitude compared to 10 relatives who do not carry the translocation. These P300 abnormalities were not restricted to the 9 subjects with psychiatric symptoms but were observed also in 3 unaffected subjects with the translocation. Of the 12 translocation carriers the longest P300 latency was recorded from an individual from generation IV with no psychiatric symptoms, and a second carrier from generation V with no symptoms recorded the third longest latency. These two individuals also had P300 amplitudes less than two standard deviations from the control mean (BLACKWOOD *et al.* 2001). Klar's theory predicts that translocation carriers will be either affected or completely normal. In fact the P300 data point toward changes in central information processing in all translocation carriers, including those who are clinically unaffected. When the P300 data are taken into account, the numbers of affected translocation carriers are even less consistent with Klar's hypothesis than when only clinical symptoms are considered. For example, if abnormal P300 response is included as a measure of "caseness," then 74% (17/23) translocation carriers from generations II–IV are classed as affected. This remains consistent with a model of dominant inheritance of illness with reduced penetrance, depending on the actions of modifying factors.

Moreover, as Klar himself points out, individuals inheriting the translocation present with a range of psychiatric illnesses (BLACKWOOD *et al.* 2001). There are cases

of schizophrenia ($n = 7$), recurrent major depression ($n = 10$), and bipolar affective disorder ($n = 1$), all of which should therefore be considered manifestations of the same inherited risk of major psychiatric illness. This again argues strongly for the actions of modifiers (genetic, epigenetic, or environmental). Such variability in disease presentation is paralleled, for example, by families segregating neurofibromatosis where clinical phenotypes arising from the same genetic lesion differ substantially between individuals (CAREY and VISKOCHIL 1999). In these patients the actions of modifying factors are also thought to be involved. Therefore, such a disease mechanism whereby a gene of major effect acts against a background of modifiers may be relatively common. Thus, if modifiers modulate disease presentation at the level of clinical phenotype, it is reasonable to propose that they also modulate disease at the level of clinical penetrance.

On chromosome 1, the translocation directly disrupts two overlapping brain-expressed genes, *DISC1* and *DISC2* (MILLAR *et al.* 2000), a fact that Klar's theory does not take into account. Because they are both disrupted, we consider that *DISC1* and/or *DISC2* are likely to be involved in causing the susceptibility to major psychiatric illness in translocation carriers. Klar adds a *Note in proof* referring to our preliminary report of genetic polymorphisms at the *DISC1/DISC2* locus (DEVON *et al.* 2001), which he claims "eliminated the possibility of the translocation creating a disease-causing mutation, as the translocation junction region shows no association with the disorder in many other affected families without the translocation." This conclusion is unfounded since disruption of the *DISC* genes in the translocation family does not necessarily imply that association between the region and the disease should be found in nontranslocation families in all populations. Furthermore, the density of markers reported in our study was inadequate to eliminate *DISC1/DISC2* as a susceptibility locus. This is because in the absence of linkage disequilibrium across the entire gene the existence of a mutation not in linkage disequilibrium with the markers used cannot be ruled out. Several independent studies on other populations do point toward the presence of a susceptibility locus within the region of chromosome 1 containing *DISC1* and *DISC2* in affected individuals lacking the $(1;11)(q42;q14)$ translocation (reviewed in BLACKWOOD *et al.* 2001). Of particular note is a report of a LOD score of 3.21 for schizophrenia in the population of Finland, generated by a marker located within an intron of *DISC1* (EKELUND *et al.* 2001). The significance of this finding is not altered by the recently reported meta-analysis that failed to identify a schizophrenia locus of major effect on chromosome 1q (LEVINSON *et al.* 2002) since such studies are highly population dependent. Consequently, we believe that the disruption of *DISC1* and *DISC2* by the translocation, together with independent support for the presence of a susceptibility locus

in the region of *DISC1* and *DISC2,* provides compelling evidence that the translocation alters the risk of disease by affecting expression of *DISC1* and/or *DISC2* rather than by some other mechanism.

The *DISC1/DISC2* locus is not the only example of a potential susceptibility locus for psychiatric illness; genome scans have generated significant LOD scores in other areas of the genome also. These include LOD scores of 6.5 (1q21-22), 4.4 (2q35), 3.9 (6pter-22), 7.7 (6q25), 3.6 (8p22), 4.1 (13q32), and 4.0 (18q12; Wang *et al.* 1995; Blouin *et al.* 1998; Brzustowicz *et al.* 2000; Gurling *et al.* 2001; Lindholm *et al.* 2001; Maziade *et al.* 2001; Paunio *et al.* 2001). This gives an indication of the degree of genetic heterogeneity that is likely to underlie major psychiatric disorders. Klar suggests that identification, in other psychiatric patients, of translocations with different breakpoints on chromosome 1 or 11 will disprove any involvement in disease of gene lesions at the 1;11 translocation breakpoints. In contrast, we assert that the evidence of considerable genetic heterogeneity in psychiatric illness suggests that identification of additional chromosomal rearrangements will pinpoint additional candidate genes. Furthermore gene disruption by chromosomal translocations is a well-established disease mechanism, with examples including neurofibromatosis (Carey and Viskochil 1999), lissencephaly (Gleeson *et al.* 1998), and speech/language disorder (Lai *et al.* 2001), as well as numerous cases of leukemia.

In summary, Klar has presented an interesting and novel theory to explain the molecular mechanism underlying psychiatric illnesses. However, upon close examination of the predictions arising from his model, we find that the data are inconsistent with his hypothesis in the (1;11)(q42.1;q14) translocation family. Consequently we believe that it is right and proper to continue study of *DISC1* and the translocation breakpoint region in relation to psychiatric illness. Nevertheless, we await with interest any evidence in favor of this proposed novel disease mechanism in psychiatric patients unrelated to the translocation family and, indeed, in patients suffering from other disorders where brain laterality may be affected.

LITERATURE CITED

Blackwood, D. H. R., D. M. St. Clair, W. J. Muir and J. Duffy, 1991 Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. Arch. Gen. Psych. **48:** 899–909.

Blackwood, D. H. R., A. Fordyce, M. T. Walker, D. M. St. Clair, D. J. Porteous *et al.*, 2001 Schizophrenia and affective disorders—cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 finding in a family. Am. J. Hum. Genet. **69:** 428–433.

Blouin, J. L., B. A. Dombroski, S. K. Nath, V. K. Lasseter, P. S. Wolyniec *et al.*, 1998 Schizophrenia susceptibility loci on chromosomes 13q32 and 8p21. Nat. Genet. **20:** 70–73.

Brzustowicz, L. M., K. A. Hodgkinson, E. W. Chow, W. G. Honer and A. S. Bassett, 2000 Location of a major susceptibility locus for familial schizophrenia on chromosome 1q21-q22. Science **288:** 678–682.

Carey, J. C., and D. H. Viskochil, 1999 Neurofibromatosis type 1: a model condition for the study of the molecular basis of variable expressivity in human disorders. Am. J. Med. Genet. **89:** 7–13.

Devon, R. S., S. Anderson, P. W. Teague, P. Burgess, T. M. J. Kipari *et al.*, 2001 Identification of polymorphisms within Disrupted in Schizophrenia 1 and Disrupted in Schizophrenia 2, and an investigation of their association with schizophrenia and bipolar affective disorder. Psychiatr. Genet. **11:** 71–78.

Ekelund, J., L. Hovatta, A. Parker, T. Paunio, T. Varilo *et al.*, 2001 Chromosome 1 loci in Finnish schizophrenia families. Hum. Mol. Genet. **10:** 1611–1617.

Gabriel, S. B., R. Salomon, A. Pelet, M. Angrist, J. Amiel *et al.*, 2002 Segregation at three loci explains familial and population risk in Hirschsprung disease. Nat. Genet. **31:** 89–93.

Gleeson, J. G., K. M. Allen, J. W. Fox, E. D. Lamperti, S. Berkovic *et al.*, 1998 Doublecortin, a brain-specific gene mutated in human X-linked lissencephaly and double cortex syndrome, encodes a putative signalling protein. Cell **92:** 63–72.

Gurling, H. M., G. Kalsi, J. Brynjolfson, T. Sigmundsson, R. Sherrington *et al.*, 2001 Genomewide genetic linkage analysis confirms the presence of susceptibility loci for schizophrenia, on chromosomes 1q32.2, 5q33.2, and 8p21-22 and provides support for linkage to schizophrenia, on chromosomes 11q23.3-24 and 20q12.1-11.23. Am. J. Hum. Genet. **68:** 661–673.

Klar, A. J. S., 2002 The chromosome 1;11 translocation provides the best evidence supporting genetic etiology for schizophrenia and bipolar affective disorders. Genetics **160:** 1745–1747.

Lai, C. S., S. E. Fisher, J. A. Hurst, F. Vargha-Khadem and A. P. Monaco, 2001 A forkhead-domain gene is mutated in a severe speech and language disorder. Nature **413:** 519–523.

Levinson, D. F., P. A. Holmans, C. Laurent, B. Riley, A. E. Pulver *et al.*, 2002 No major schizophrenia locus detected on chromosome 1q in a large multicenter sample. Science **296:** 739–741.

Lindholm, E., B. Ekholm, S. Shaw, P. Jalonen, G. Johansson *et al.*, 2001 A schizophrenia-susceptibility locus at 6q25, in one of the world's largest reported pedigrees. Am. J. Hum. Genet. **69:** 96–105.

Maziade, M., M. A. Roy, E. Rouillard, L. Bissonnette, J. P. Fournier *et al.*, 2001 A search for specific and common susceptibility loci for schizophrenia and bipolar disorder: a linkage study in 13 target chromosomes. Mol. Psychiatry **6:** 684–693.

Millar, J. K., J. C. Wilson-Annan, S. Anderson, S. Christie, M. S. Taylor *et al.*, 2000 Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum. Mol. Genet. **22:** 1415–1423.

Paunio, T., J. Ekelund, T. Varilo, A. Parker, I. Hovatta *et al.*, 2001 Genome-wide scan in a nationwide study sample of schizophrenia families in Finland reveals susceptibility loci on chromosomes 2q and 5q. Hum. Mol. Genet. **10:** 3037–3048.

Sham, P. C., N. E. Morton, W. J. Muir, M. Walker, A. Collins *et al.*, 1994 Segregation analysis of complex phenotypes: an application to schizophrenia and auditory P300 latency. Psychiatr. Genet. **4:** 29–38.

St. Clair, D., D. Blackwood, W. Muir, A. Carothers, M. Walker *et al.*, 1990 Association within a family of a balanced autosomal translocation with major mental illness. Lancet **336:** 13–16.

Wang, S., C. E. Sun, C. A. Walczak, J. S. Ziegle, B. R. Kipps *et al.*, 1995 Evidence for a susceptibility locus for schizophrenia on chromosome 6pter-p22. Nat. Genet. **10:** 41–46.

Weiss, K. M., and J. D. Terwilliger, 2000 How many diseases does it take to map a gene with SNPs? Nat. Genet. **26:** 151–157.