cost of applying either adapted or culturally developed measures, however, is that it confounds the process of making direct international comparisons of prevalence rates and mental health need. Hence, the real challenge facing world psychiatry is how to combine the strengths of psychiatric epidemiology[3] with improvements in culturally valid assessment.[4,5] Showing consistent patterns of comorbidity and risk-factor profiles across countries can only partially address this issue.

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BDNF Val66Met polymorphism and the affective component

I read the paper by Lencz *et al*[1] with concern for the future of psychosis genetics. The authors claim that their candidate gene study of *BDNF* is 'the first to demonstrate association with schizoaffective disorder but not schizophrenia' and therefore that '*BDNF* variation is associated with psychiatric disorders with a primary affective component'. To reach this conclusion they argue on the basis of a sample size of 596 individuals against two meta-analyses and two cohort studies with sample sizes between 6 and 26 times larger (Table 1). Each of these studies examined the Val66Met polymorphism (the subject of Lencz *et al*'s report) and reached the conclusion that *BDNF* genotype does not exert an influence on the development of affective illness whether or not associated with psychosis.

A literature survey indicates that between 2004 and 2009 these authors between them published 25 papers relating to associations of 19 genes with aspects of psychiatric disease. Concerning one gene (*FEZ1*) they drew negative conclusions, but concerning each of the other 18 they claim a relationship was established. Such a rate of gene discovery would be a remarkable achievement. My review of the linkage literature,[4] as represented by the four largest (each >300 sibpairs) studies, suggests that none of Lencz *et al*'s candidate genes were replicated in these systematic searches, and the association study of Sanders *et al*[5] that investigated six of them (*DISC1*, *DAOA*, *HTTLPR*, *DTNBP1*, *COMT*, *DRD2*) in 1870 individuals with schizophrenia or schizoaffective disorder and 2002 controls concluded these genes were unrelated to psychosis.

When large numbers of variables are examined, simultaneously alluring relationships can often be discerned that evaporate in the wider context of large and systematic studies. It appears that by ignoring this context Lencz *et al* are operating an algorithm for generating positive associations in selected data-sets.

1 Lencz T, Lipsky RH, DeRosse P, Burdick KE, Kane JM, Malhotra AK. Molecular differentiation of schizoaffective disorder from schizophrenia using *BDNF* haplotypes. *Br J Psychiatry* 2009; **194**: 313–8.

2 Kanazawa T, Glatt SJ, Kia-Keating B, Yoneda H, Tsuang MT. Meta-analysis reveals no association of the Val66Met polymorphism of brain-derived neurotrophic factor with either schizophrenia or bipolar disorder. *Psychiatric Genet* 2007; **17**: 165–70.

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4 Crow TJ. How and why genetic linkage has not solved the problem of psychosis: review and hypothesis. *Am J Psychiatry* 2007; **164**: 13–21.

5 Sanders AR, Duan J, Levinson DF, Shi J, He D, Hou C, et al. No significant association of 14 candidate genes with schizophrenia in a large European ancestry sample: implications for psychiatric genetics. *Am J Psychiatry* 2008; **165**: 497–506.

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Authors' reply: Dr Crow is concerned that the publication of our recent study on *BDNF* endangers the field of psychiatric genetics. We would suggest that this concern may be overstated for the following reasons.

First, Dr Crow claims that the two meta-analyses and two cohort studies invalidate our results. We find this conclusion to be puzzling, given that none of these studies assessed the phenotype of schizoaffective disorder. Notably, the cohort studies relied on a single self-report item as the primary assessment of

Table 1 Main findings of two recent studies of the Val66Met variation in *BDNF* in relation to psychiatric diagnosis compared with Lencz *et al*[1]

	Controls, *n*	Schizophrenia, *n*	Schizoaffective disorder, *n*	Bipolar disorder, *n*	Depression, *n*	*P*
Kanazawa *et al*[2]						
Meta-analysis	4035	2955				0.944
Meta-analysis	6347			3143		0.161
Chen *et al*[3]						
BWHHS	2367				553	0.360
ALSPAC	6242				596	0.834
Meta-analysis	11 040				3879	0.537
Lencz *et al*[1]						
HC *v.* Sz	222	211				NS
HC *v.* (SzAf+Bip+MDD)	222		61	77	29	0.015
Sz *v.* (SzAf+Bip+MDD)		211	61	77	29	0.008

ALSPAC, Avon Longitudinal Study of Parents and Children; BWHHS, British Women's Heart and Health Study; HC, healthy controls; MDD, major depressive disorder; NS, not significant; Sz, schizophrenia; SzAf, schizoaffective disorder.

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psychopathology. We addressed limitations of the meta-analyses in our original paper. We suggest that careful and comprehensive examination of the diverse phenotypes associated with neuropsychiatric illness may be a more fruitful approach.

Second, Dr Crow cites his own review of the linkage literature to suggest that most of the candidate genes reported by our group, and many others, are not supported by linkage studies and thus should be discounted. This reasoning is based on a flawed understanding of the role of linkage in complex disorders and is inconsistent with a large body of recent empirical evidence in complex genetics. In other complex disorders, a majority of susceptibility loci that have been unambiguously replicated in association studies fall outside of previously identified areas of even suggestive linkage (e.g. Barrett *et al*[1]). Therefore, an argument utilising non-significant linkage data to invalidate a subsequent candidate gene association is erroneous.

Third, Dr Crow notes the productivity of our lab over the past several years as a source of concern for him. In so doing he mischaracterises our papers. First, he is simply incorrect in stating that only one paper reports strictly negative results (see Fubke *et al*[2] and Hodgkinson *et al*[3]). Moreover, many of our papers report complex relationships that are not so simplistically reduced to 'positive' *v.* 'negative'. More importantly, Dr Crow fails to mention that most of our papers are not simply analyses of association to schizophrenia diagnosis, but instead examine alternative phenotypes. For example, our study of *DRD2* assessed the relationship between a functional promoter region polymorphism and clinical response to olanzapine and risperidone in the context of a randomised controlled clinical trial in first-episode schizophrenia.[4] Therefore, it is not surprising that our *DRD2* results were not 'replicated' in either linkage studies or the association study of Sanders *et al*,[5] as these papers were restricted to mere association to diagnosis.

Although Dr Crow is entitled to his opinions, the field of psychiatric genetics may be better served by more constructive discussion leading towards a better understanding of the complexities of these devastating disorders.

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2 Funke BH, Lencz T, Finn CT, DeRosse P, Poznik GD, Plocik AM, et al. Analysis of TBX1 variation in patients with psychotic and affective disorders. *Mol Med* 2007; **13**: 407–14.

3 Hodgkinson CA, Goldman D, Ducci F, DeRosse P, Caycedo DA, Newman ER, et al. The FEZ1 gene shows no association to schizophrenia in Caucasian or African American populations. *Neuropsychopharmacology* 2007; **32**: 190–6.

4 Lencz T, Robinson DG, Xu K, Ekholm J, Sevy S, Gunduz-Bruce H, et al. DRD2 promoter region variation as a predictor of sustained response to antipsychotic medication in first-episode schizophrenia patients. *Am J Psychiatry* 2006; **163**: 529–31.

5 Sanders AR, Duan J, Levinson DF, Shi J, He D, Hou C, et al. No significant association of 14 candidate genes with schizophrenia in a large European ancestry sample: implications for psychiatric genetics. *Am J Psychiatry* 2008; **165**: 497–506.

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Outcome of group psychoeducation for stabilised bipolar disorders

The article by Colom *et al*[1] further enhanced our understanding about the role of psychoeducation in the management of bipolar disorders. The study draws its strengths from the fact that it included an active control group and individuals with bipolar disorder and Axis II comorbidity, follow-up rates were excellent and the authors assessed the outcome in the form of the number and type of recurrences, time to recurrence, time spent ill and number of hospitalisations at 5 years. However, some of the issues require further clarification.

When one looks at the article reporting 2-year follow-up of the same cohort,[2] the authors report that individuals with Axis I comorbidity were excluded, but at 5-year follow-up the authors report that only those with severe Axis I diagnosis were excluded. Further, the authors do not define 'severe'. Individuals with bipolar disorder can have a high rate of comorbidity, hence clarification of this fact is very important from the perspective of generalisability of the study findings. In addition, Colom *et al* do not provide details of status and/or type of Axis I/II comorbidities and whether the drop-out rate and the number of completers made any difference with regard to clinical and demographic features.

Another important aspect is the way the authors defined recurrence based on rating scale scores. This type of definition in the true sense does not include the subsyndromal symptoms and can influence almost all the outcome measures such as time spent ill, time to recurrence and the number of recurrences, especially when the cohort is being followed up at a frequency of every 2 weeks. Similarly, although the study included the number and duration of hospitalisations as an outcome measure, the authors have not discussed the criteria for hospitalisation.

Another important aspect which needs clarification is the analysis of data. In many places Colom *et al* have used parametric tests to compare the numerical variables, although the standard deviation is more than the mean. Similarly, mean values are given for the number of recurrences without standard deviations, and comparison statistics are given as *F*-values. In Table 2,[1] again the authors compare the mean values using Fisher *F* statistics and demonstrate that there was a significant difference in the number of days spent in each episode for all types of episodes. However, when one looks at the data, it is difficult to understand this contention. In the same table when one adds the mean number of days spent in each episode for the control group, the data regarding each episode and the total duration do tally, but the same is not the case for the psychoeducation group.

1 Colom F, Vieta E, Sánchez-Moreno J, Palomino-Otiniano R, Reinares M, Goikolea JM, et al. Group psychoeducation for stabilised bipolar disorders: 5-year outcome of a randomised clinical trial. *Br J Psychiatry* 2009; **194**: 260–5.

2 Colom F, Vieta E, Martinez-Aran A, Reinares M, Goikolea JM, Benabarre A, et al. A randomized trial on the efficacy of group psychoeducation in the prophylaxis of recurrences in bipolar patients whose disease is in remission. *Arch Gen Psychiatry* 2003; **60**: 402–7.

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Authors' reply: We would like to provide some clarifications in response to Gaur & Grover's queries.

First, only those patients with 'severe' Axis I comorbidity diagnoses were excluded. This means that patients were excluded if