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.

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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.