very dense (and expensive) screening tools. To the extent that rare alleles are important to schizophrenia, study designs based on a naive 'common disease–common allele' model will yield variable and non-replicable results (King *et al*, 2006).

Characteristic patterns of age at onset, gender differences and brain changes associated with schizophrenia are fully compatible with causal influences of rare severe-effect events, either genetic or epigenetic. Each such event alters the expression, timing or function of one of a very large number of genes. The products of these genes converge in common pathways. Aberrations of a pathway by any of multiple mechanisms may lead to clinically similar disorders.

Crow's proposition that schizophrenia arises from the disruption of uniquely human genetic elements is very appealing. This premise, however, need not narrow the search for causes, genetic, epigenetic or environmental. Human speciation likely occurred primarily as a result of regulatory changes in genes, rather than common polymorphisms leading to changes in gene sequence (King & Wilson, 1975). The extraordinary number of repeated elements in the human genome gave rise to a vast number of new genes and regulatory mechanisms. Their architecture also created an increased risk for copying errors. Thus, one cost of the genomic complexity that enabled human brain development may be a *de novo* error rate that results in the maintenance of schizophrenia in the population.

Autism has recently been shown to be associated with a significantly increased frequency of rare *de novo* mutations (Sebat *et al*, 2007). These results presage the identification of many more rare mutations associated with other neurodevelopmental illnesses, as advances in technology enable the detection of ever-smaller genomic lesions. The ultimate resolution of this debate lies in gene discovery, for which we encourage the application of study designs most likely to be fruitful.

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Anticipation and the genetics of psychosis

A theoretical model should explain all of the observed facts. Both the model of schizophrenia which proposes many genes of small effect (McClellan *et al*, 2007) and that which proposes few gene mutations of large effect (Craddock *et al*, 2007) explain many of the observed facts. In particular, the model of many genes of small effect explains the observed spectrum of mental illness, from bipolar disorder, through schizoaffective disorder to schizophrenia.

We have both observed schizophrenia occurring in particular families. One of us (M.A.) has studied a number of South-Asian families with multiple members with schizophrenia. In some of these families, patients of a second generation developed the illness at a much younger age than their parents and their illness was more severe. Thus far we have assumed that these observations were related to the concentration of many genes of small effect within these families.

One of us (M.B.-P.) has also observed the same effect, known as anticipation, in a group of families in Slovenia. Thirty-six parent–offspring pairs with schizophrenia were studied. First hospital admission was used as a proxy for disease onset. In the offspring group, mean age at onset was identified as 23.5 years whereas this was 39.6 years in the parent group. There was a higher mean total number of days of hospitalisation in the first 5 years of treatment in the offspring group (223 *v.* 161), and a higher mean number of hospitalisations over the same period in the offspring (7.27 *v.* 7.51) (both results statistically significant). These two measures were used as a proxy for increased intensity of illness. The offspring had a higher level of education but demonstrated fewer working years and had fewer children (Blinc, 2002).

What arises is the question of whether the 'many genes of small effect' or the 'few genes of large effect' model is best suited to explaining this observation of anticipation of schizophrenia.

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Attention-deficit hyperactivity disorder and mood disorders in adults

Asherson *et al* (2007) raise some important issues regarding adult attention-deficit hyperactivity disorder (ADHD). They state that some symptoms of bipolar disorder are similar to those of ADHD but the distinction is not difficult. However, although ADHD and classic euphoric mania (bipolar I) may be distinct, differentiation of ADHD and bipolar disorder may be difficult, especially in bipolar II, bipolar-spectrum disorder and episodes of mixed symptomatology. At times, it may be almost impossible to discriminate solely by symptoms. Irritability, excessive activity, impulsive behaviour, poor judgement and denial of problems are characteristic of both ADHD and bipolar disorder, thus making diagnosis difficult. The two also clearly occur together in some individuals: the reported overall lifetime prevalence of comorbid ADHD in people with bipolar disorder is 9.5% (Nierenberg *et al*, 2005); comorbidity with unipolar disorder is also frequent.

Asherson *et al* state that ADHD is a persistent trait whereas bipolar disorder is episodic. However, inter-episodic symptoms are common in bipolar disorder and the course of both bi- and unipolar disorder is frequently chronic; for example, up to 13% of people with bipolar disorder report continuous cycling without a well phase