

## Correspondence

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### Genetic hypotheses for schizophrenia

In their ‘common disease – rare alleles’ hypothesis McClellan *et al* (2007) come close to formulating an untestable theory. Although they refer to currently fashionable ‘candidate genes’ – e.g. dysbindin, neuregulin and *DISC1* – it appears that they do not regard these as established. I agree that there is no consistency in the findings across even the largest genome scans conducted to date (sample sizes exceeding 300 and totally over 1000 sib-pairs; Crow, 2007) but disagree profoundly about the alternative.

We know that in schizophrenia: (a) incidences are more uniform across populations as one moves to the core syndrome, e.g. nuclear symptoms (Jablensky *et al*, 1992); (b) structural brain changes (e.g. ventricular enlargement) are consistent across populations (Chua *et al*, 2003) and uniform across patients relative to controls (Vita *et al*, 2000); (c) age at onset has a specific distribution throughout the reproductive phase of life; (d) there are gender differences (earlier onset and worse outcome in males); (e) the core syndrome comprises symptoms that are language related (i.e. specific to *Homo sapiens*). None of these findings would be expected if schizophrenia were a result of random mutations in a large number of genes such as McClellan *et al* postulate, nor would one expect variation in the form of illness within families as is generally observed.

While McClellan *et al*'s hypothesis promises a search for elusive rare alleles that will never reach a conclusion, Craddock *et al* (2007) persevere in their claim that ‘Several genes have been implicated repeatedly as conferring risk for schizophrenia or bipolar disorder’. Comparison of the largest and most systematic linkage studies, including those of Craddock *et al* themselves, shows that these claims cannot be sustained (Crow, 2007).

Alternative hypotheses to the ‘rare alleles of major effect’ and the ‘polygenes of small effect’ deserve consideration. One such hypothesis (Crow, 2007) is that the variation arises in relation to characteristics that are specifically human, i.e. recent in evolution, and that it is ‘epigenetic’ in form, i.e. involves a modification of the sequence (methylation of DNA) or the associated chromosomal structure (methylation, phosphorylation or acetylation of histones) rather than a change in the DNA sequence itself. We do know that the risk for first-degree relatives is approximately 10%, whereas that for second-degree relatives is very little increased compared with the population as a whole. Although this is often held to be consistent with polygenic influence, it is also compatible with an ‘imprint’ that is applied and reapplied in meiosis (i.e. with a short time course between generations). The solution proposed is that the variation arises in relation to the change (speciation event) that defined the species, and that this is associated with the cerebral torque – the bias from right frontal to left occipital across the antero-posterior axis that is characteristic of the human brain. In contrast to McClellan *et al*'s rare alleles and Craddock *et al*'s polygenes of small effect, this hypothesis is specific and refutable – a gene has been identified that duplicated at 6 million years from the X to the Y chromosome to give rise to the ProtocadherinX/Y gene pair. This pair has been subject to accelerated evolution since the duplication event (Williams *et al*, 2006) and is in an unusual situation with respect to epigenetic modulation. This variation can be assessed and the hypothesis thereby tested.

**Chua, S. E., Lam, I. W. S., Tai, K. S., et al (2003)** Brain morphological abnormality in schizophrenia is independent of country of origin. *Acta Psychiatrica Scandinavica*, **108**, 269–275.

**Craddock, N., O'Donovan, M. C. & Owen, M. J. (2007)** Phenotypic and genetic complexity of psychosis. Invited commentary on . . . Schizophrenia: a common

disease caused by multiple rare alleles. *British Journal of Psychiatry*, **190**, 200–203.

**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.

**Jablensky, A., Sartorius, N., Ernberg, G., et al (1992)** Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychological Medicine Monograph Supplement*, **20**, 1–97.

**McClellan, J. M., Susser, E. & King, M.-C. (2007)** Schizophrenia: a common disease caused by multiple rare alleles. *British Journal of Psychiatry*, **190**, 194–199.

**Vita, A., Dieci, M., Silenzi, C., et al (2000)** Cerebral ventricular enlargement as a generalized feature of schizophrenia: a distribution analysis on 502 subjects. *Schizophrenia Research*, **44**, 25–34.

**Williams, N. A., Close, J., Giouzei, M., et al (2006)** Accelerated evolution of ProtocadherinIX/Y: a candidate gene-pair for cerebral asymmetry and language. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, **141**, 623–633.

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**Authors' reply:** We are delighted that our article has stimulated discussion about strategies for gene discovery in schizophrenia. We agree that schizophrenia, like other complex traits, will be influenced by a large number of genetic and epigenetic events with a spectrum of effects. Both rare alleles of large effect and common alleles of modest effect are likely to be discovered (Craddock *et al*, 2007). Rare severe-effect alleles are fully compatible with familial patterns of schizophrenia because many (perhaps most) such alleles have arisen *de novo* in the present or recent generations. *De novo* mutations play havoc with predictions of conventional recurrence risk models. For example, *de novo* meiotic mutations (in the parental germline) increase disease concordance among monozygotic but not dizygotic twins. In contrast, *de novo* mitotic mutations or epigenetic events (in early embryogenesis) reduce concordance among both monozygotic and dizygotic twins.

Genetic association studies are not the most straightforward path to gene discovery for schizophrenia. Individually rare alleles cannot be identified by comparing frequencies of common alleles among unrelated patients with controls, even with enormous numbers of well-diagnosed patients, properly matched controls and

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.

**Craddock, N., O'Donovan, M. C. & Owen, M. J. (2007)** Phenotypic and genetic complexity of psychosis. Invited commentary on . . . Schizophrenia: a common disease caused by multiple rare alleles. *British Journal of Psychiatry*, **190**, 200–203.

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**Sebat, J., Lakshmi, B., Malhotra, D., *et al* (2007)** Strong association of *de novo* copy number mutations with autism. *Science*, **316**, 445–449.

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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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**Craddock, N., O'Donovan, M. C. & Owen, M. J. (2007)** Phenotypic and genetic complexity of psychosis. Invited commentary on . . . Schizophrenia: a common disease caused by multiple rare alleles. *British Journal of Psychiatry*, **190**, 200–203.

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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