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) perseverate 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 anteroposterior 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.

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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