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COMMENTARY

Schizophrenia: complex genetics, not fairy tales

A commentary on 'The emperors of the schizophrenia polygene have no clothes' by Crow (2008)

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In essence Crow's argument (Crow, 2008) has three components: first, findings in schizophrenia genetics are inconsistent and must therefore be wrong; second, this means that genetic variation cannot underlie susceptibility to the disorder; third, schizophrenia must therefore be caused by an epigenetic imprint. The first of these is debatable, the second flies in the face of a large body of evidence from genetic epidemiology and the recent successful identification of genes of small effect (polygenes) in other common diseases, and the third unnecessarily invokes, on the basis of no positive evidence, an unusual mechanism, thus violating the principles of parsimony of which Crow has reminded us repeatedly over the years.

We have reviewed the evidence in regard to specific genes for schizophrenia with appropriate caveats elsewhere (Owen *et al*. 2005; Craddock *et al*. 2006). In our view, for some of the genes, *DTNBP1, NRG1, G72* and *DISC1*, the genetic findings are strong while for others it is less so. Moreover, data *consistent* with the involvement of a number of the more strongly implicated genes has additionally come from studies of extended and intermediate phenotypes, principally neurocognitive and neuroimaging, and from analyses of gene expression, animal models and other aspects of neurobiology (Law *et al*. 2006; Hall *et al*. 2006; Bray *et al*. 2005; Porteous *et al*. 2006; Ishizuka *et al*. 2006). However, in spite of the impressive weight of this evidence, genes can only be considered unambiguously implicated as causal on the strength of the genetic evidence. In no case does the strength and consistency (same alleles or haplotypes across studies) of the genetic evidence approach that for genes now known to be involved in other complex disorders (see below). Therefore, notwithstanding the strong support from non-genetic disciplines and the large number of positive genetic findings, the above genes cannot yet be viewed as schizophrenia susceptibility genes with *absolute* confidence. This of course does not imply that these and other findings are false positives, simply that a degree of uncertainty remains.

Crow's interpretation of the genetic evidence is based upon the entirely unsubstantiated belief that individual risk alleles make a large and homogeneous influence on disease risk at a population level. In fact he has until recently been consistently arguing that all of schizophrenia is accounted for by one gene (Crow, 1995), this despite evidence that has, for a very long time, excluded that possibility (Risch, 1990). Most informed genetic researchers, regardless of whether they study schizophrenia, bipolar disorder, type II diabetes or cancer, are now aware that the population effect sizes of individual risk genes and alleles are in general small and unlikely to result in consistent patterns of genetic linkage or association with the sample sizes that have been deployed so far in psychiatry (Wellcome Trust Case Control Consortium, 2007). To put things in context, in the recent large study of type 2 diabetes involving an effective sample size of about 64 000 subjects (Zeggini *et al*. 2008), the median effect size or odds ratio for risk loci was 1.1. Crow may rail against small gene effects as if this is some kind of refuge for scoundrels; however, identification of polymorphisms conferring small effect sizes is precisely the pattern that is emerging from studies of non-psychiatric complex diseases. Furthermore, robust demonstration of even small genetic effect sizes pinpoints the proteins involved in illness and thus makes a major contribution to informing understanding of pathophysiology.

Faced with what is known from studies of non-psychiatric disorders, there can be no logical connection between Crow's starting position that no risk genes have yet been proven for schizophrenia to his claim that this means that there are none to find. It is also important to point out that, while the involvement of epigenetic imprinting is a fashionable hypothesis, and one we do not deny might make a contribution, there is as yet very little evidence for a widespread

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involvement of this phenomenon in the transgenerational transmission of mammalian phenotypes. This contrasts markedly with polygenic inheritance which is found repeatedly across the plant and animal kingdoms. This is not to claim that polygenic inheritance accounts for all the genetic effects in schizophrenia. There is increasing evidence that rare alleles with larger effects including structural chromosomal abnormalities may also play a role in a proportion of cases (Kirov *et al*. 2008; Walsh *et al*. 2008), and of course other mechanisms including epigenetics may be involved. The great fictional detective Sherlock Holmes, who was famed for his deployment of logical argument, said when you have excluded the impossible, whatever remains, however improbable, must be the truth. So far, no reasonable commentator could claim that the most probable has come even close to being excluded.

Recent work in human genetics using genome wide association studies in large enough samples has resulted in the identification of robust associations in a number of common diseases, for example, coronary artery disease, atrial fibrillation, asthma, Crohn's disease, rheumatoid arthritis, type 1 and type 2 diabetes, obesity, prostate cancer, breast cancer and coeliac disease (Wellcome Trust Case Control Consortium, 2007; Petretto *et al*. 2007; McCarthy *et al*. 2008). We do not have to spell out to readers of *Psychological Medicine* the challenges psychiatric researchers face in assembling samples of equivalent size and power. Arguably the greatest challenge in psychiatric genetics, however, will be how best to deal with the phenotype (Angst, 2007). Despite having 21st-century molecular genetic research tools, we are still using what are essentially modified 19th-century descriptive diagnostic categories (Craddock *et al*. 2007). Crow himself has argued for alternative approaches to the psychosis phenotype (Crow, 1987, 1995) and there is increasing evidence from classical and molecular genetic studies (Craddock & Owen, 2007) and other fields of research (Murray *et al*. 2004) that challenge the traditional dichotomous diagnostic approach for psychosis (Craddock & Owen, 2005). The genetic overlap between disorders suggests that it is likely to be fruitful to explore the relationship between specific genetic findings and specific symptom profiles and dimensions between as well as within diagnostic groupings (Owen *et al*. 2007). Moreover, it is important to appreciate that, because diagnostic categories are not anchored to an underlying pathophysiology, even quite subtle differences in ascertainment and diagnosis could alter the constellation of alleles conferring risk within different samples with damaging consequences for consistency and replication (Craddock *et al*. 2007). It follows that if psychiatric genetics is to harness fully the power of molecular genetic (and indeed other) research approaches we must pay close attention to how we define the phenotype, and expect a high degree of 'co-morbidity' and heterogeneity.

Psychiatry now has available new and powerful research tools capable of delineating the biological systems involved in illness. We would have hoped that influential psychiatrists like Crow would be campaigning vigorously for the resources needed to translate the potential of genetics into benefits for patients, rather than prematurely discarding approaches that are at last transforming our understanding of common human disorders.

Declaration of Interest

None.

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