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Letter to the Editor

Will whole genome association studies sink psychosis research? A response to Collier, Sullivan and O'Donovan *et al.*

I thank Collier, Sullivan, and O'Donovan *et al*. for commenting on my review (Crow, 2008) in this issue of the Journal.

We are agreed that the genetic component to schizophrenia is substantial and presently unknown. Each of the commentators believes that the variation is in the DNA sequence, and that there is no alternative to linkage and linkage disequilibrium as the method of identifying it. Schizophrenia is a 'complex' disease and multiple genes of small effect are to be expected.

While I previously entertained the first two of the above premises, comparison of the results of systematic genome scans convinces me that another hypothesis – that the variation is exclusively epigenetic, and relates to that part of the human genome that harbours the most recent change in hominid evolution (Crow, 2004, 2007) – is a viable alternative.

I agree with several of the points made by Sullivan (2008) (but see below), and appreciate the charm but do not share the confidence of Collier (2008) in his 'hundred flowers should bloom' approach. Unless the pea-sensitive Princess assay is calibrated false positives are sure to multiply! To my surprise I am in most disagreement with O'Donovan *et al*. (2008), although I respect their technical expertise and rely upon their findings for conclusions which in significant respects differ from their own.

They write that in their view 'for some of the genes, *DTNBP1, NRG1, G72* and *DISC1*, the genetic findings are strong'. The original papers proposing these as candidate genes are:

(1) Straub *et al*. (1995) in 265 pedigrees found a maximum lod score, assuming locus heterogeneity of 3.51 in region 6p24-22. Non-parametric analysis 'yielded suggestive, but substantially weaker, findings'. No peak was observed on chromosome 8p
(2) Stefansson *et al*. (2003) in 33 families found a multipoint lod score of 3.06 on chromosome 8p. No peak was observed on chromosome 6p.
(3) Chumakov *et al*. (2002) selected papers in the diverse literature with 'suggestive to significant' linkage on chromosome 13, and did an association study of this region on 213 schizophrenia patients and 241 normal individuals with 20 markers and found four markers to deviate from expectation at the 0.05 level.
(4) Millar *et al*. (2005) found in a single large family that psychiatric disturbance of various types was linked to a translocation involving chromosomes 1 and 11.

Subsequent to these papers genome scans with sample sizes in excess of 300 sibling pairs became available for comparison (Crow, 2007):

(1) there are no significant peaks on chromosome 6p (dysbindin);
(2) one genome scan showed a modest peak on chromosome 8p, but the authors established that it was not at the site of neuregulin;
(3) there are no peaks on chromosome 13 (G72);
(4) there are no peaks on chromosome 1q (DISC1).

Thus with sample sizes from 3 to 30 times greater than the original studies, there is no evidence of linkage to the loci of the putative predisposing genes. The only conclusion one can draw is that the original findings were unreplicable in larger samples. 'The results are valid,' Collier writes. But if they are not reliable they cannot be valid!

If O'Donovan *et al*. became convinced (even though linkage was the source of the original evidence) that linkage was no longer an appropriate technique ('deeply unfashionable' according to Collier), and that linkage disequilibrium studies would be the final arbiter, then the confidence they have in their conclusions should have been shattered by the findings of Sanders *et al*. (2008). In a population of 1870 controls and 2002 patients a mean of 45 markers across each of these genes revealed no evidence of linkage disequilibrium.

Sullivan writes that 'it is highly disappointing that neither association (*DTNBP1* and *NRG1* with schizophrenia) has been compellingly proven or disproved'. It is very hard to see what could constitute more cogent empirical disproof than failure to replicate the original linkages in more than 900 sibling pairs combined with absence of linkage disequilibrium as demonstrated by Sanders *et al*.

Dysbindin, neuregulin, G72 and DISC1 should not be regarded as having anything to do with schizophrenia, and this conclusion should have been reached at the point where it became clear that the original linkages were not replicable in larger samples. These genes along with platelet MAO and the pink

spot should be consigned to the defumigated archive dedicated to red herrings (Anon, 1966) in the search for the cause of psychosis.

None of the commentators considers the implications of my Table 2 – that a substantial literature has grown up around the 'candidate genes' that makes claims concerning the relationship between DNA sequence variation and aspects of psychosis that cannot be justified by any linkage or association finding. Even supposing the genetic findings to be replicable, the sizes of phenotypic effect claimed in relatively small samples are implausible. In particular, the claim that correlates of DNA sequence variation can be readily detected by imaging procedures has led to grossly inflated expectations of research in the field. It illustrates the influence of some of the logical and sociological factors contributing to false-positive conclusions to which Ioannidis (2005) has drawn attention. Unless this literature is critically evaluated psychosis research will evaporate in a cloud of unsubstantiated positive claims.

Concerning the polygenes that elude identification by a version of Zeno's paradox – they are not found so they must be more numerous and of smaller effect than previously thought – I reiterate the following uniformities of psychosis that the genetic predisposition has to account for:

(1) range and sex dependence of age of onset;
(2) selectivity of symptoms to higher CNS functions, including particularly language;
(3) constancy of structural change, e.g. ventricular enlargement across populations.

These three facts require explanation in terms of species-specific sex-dependent variation that relates to brain development. An obvious candidate is cerebral asymmetry (Crow, 2004), the genetic basis of which is obscure, but which is associated with a sex difference and has recently been confirmed in the BBC internet survey as a major determinant of the elements of verbal and spatial ability (Peters *et al*. 2006). One can add to this list:

(4) discordance for presence and form of psychosis in monozygotic twins, triplets and quadruplets;
(5) the paternal age effect;

as phenomena that raise difficulties for a simple sequence difference hypothesis, and are at least consistent with an epigenetic influence.

I draw two conclusions:

(1) From genetic linkage and association studies, incautiously interpreted, a body of literature has mushroomed that cannot be relied upon.
(2) The belief that genome-wide association studies are bound to succeed can be questioned.

The scope for positive interpretation of whole genome association findings whatever these may be is illustrated by three of the eight points of Sullivan's penultimate paragraph: 'the GWAS dice are rolling,' he writes, 'and dice are famously disinterested in the cogitations of punters', but his points 3, 4 and 6 raise a doubt about whether the punters in the GWAS strategy as he describes it are really as without influence on the dice as he claims. His point 3 as I read it says 'and if the results are negative we are going to re-sample and re-analyse until this is not the case'. Point 4 states that 'if necessary we will redefine the phenotype' and point 6 'environmental variables (unspecified) will be factored into the analysis'. Note well that when the whole world collection of psychotic samples is the arbiter no other sample is available to which appeal can be made concerning the edicts of the consortium.

On this basis, I fear that Mongolian variant schizoaffective disorder linked to the C > T SNP in intron 5 of schizogene 17β has an assured future! The next step in this scenario is for some cowboy imager to report that by adjusting the focus of his 7T MRI scanner, he can discern that, contrary to perceived wisdom, the C > T transition in the SNP in intron 5 is not neutral but can be used (in expert hands) to define a new 'endophenotype'. As illustrated in my Table 2, the enterprise is off to a galloping start. With the anticipated yield of GWAS it may well be unstoppable.

Thus while I do support O'Donovan *et al*.'s appeal for genetic research in psychosis, I have the premonition that the large sums of institutional and charitable money currently deployed to whole genome association studies as now conceived may well serve to amplify the escalating confusion in psychosis genetics. For more modest expenditure the alternatives outlined in my second paragraph could be investigated – and may be eliminated.

'False facts are highly injurious to the progress of science,' Darwin wrote 'because they often long endure; but false views, if supported by some evidence, do little harm, as everyone takes salutary pleasure in proving their falseness; and when this is done, one path towards error is closed and the road to truth is often at the same time opened.'

Declaration of Interest

None.

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