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Letter to the Editor

What have official classifications ever done for psychiatric genomics? Implications for DSM-V schizophrenia

In their comprehensive review Gill *et al*. (2010) convincingly argue for the contribution of genomics to the understanding of psychoses. It is of note that the authors have centred their discussion around psychosis and not used official nomenclature in the title. Indeed, deconstructing complex phenomena like schizophrenia (Allardyce *et al*. 2007) increases the rigour of genomic research, e.g. clearly defined symptom dimensions or non-clinical correlates yield higher effect sizes for susceptibility loci or allelic variants.

However, official communication and funding of science dictate uniform language, and findings from novel integrative research (van Os & Rutten, 2009) are attuned to the definitions of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Much of the discussion on the methodology of genome-wide association studies (GWAS) focuses on power calculations (Psychiatric GWAS Consortium Coordinating Committee, 2009), with the implication that reliability and validity, prerequisites for sound methodology, are taken for granted.

A question that precedes the one addressed in the article is, thus: 'Do current official psychiatric classifications facilitate research as much as they did at the time they were rebuilt for this purpose?' At a time when rapid progress in genomic research coincides with the development process of DSM-V (APA, 2009), the answer warrants a reconsideration of the epistemological assumptions in DSM-III, apparently maintained in the upcoming edition.

In order to accelerate replicable research, DSM-III prioritized reliability over validity and emphasized standard clinical assessment (Kendler, 2009). Inherent to the major paradigm change reflected in the atheoretical perspective of DSM-III, however, was the assumption that many of its definitions would eventually fit the disease model, as missing biological information was acquired. Widespread clinical use of DSM definitions and adoption of a strictly medical model in psychiatry solidified this view, so that the polythetic constructs of DSM have been regarded as diseases, and the Manual as a natural classification. Today, given the small effects of individual genetic variants on the distal phenotype of schizophrenia and evidence of 'shared' susceptibility loci or genes with other disorders (Carroll & Owen, 2009), it is time to re-emphasize that this construct may not be a natural entity. Part of the challenge in the design, funding and interpretation of research comes from using one nosological system for both research and clinical purposes, and DSM is too influential to overlook this problem.

Level of agreement on the categorical diagnosis is another consideration, since genomic research necessitates multisite collaboration. Structured clinical interviews largely rely on patients' accounts and barely emphasize the experienced clinical reasoning critical for proper assessment of mild intellectual deficits, psychosis or impaired functioning in a developmental perspective. These stigmata have been overemphasized as characteristic for 'chronic psychosis', and their overlap with antipsychotic side-effects further decreases the likelihood of questioning an established diagnosis in future assessments, even when other neurodevelopmental or early-onset conditions (e.g. velocardiofacial syndrome or severe anxiety disorders) are properly recognized as 'comorbid' disorders. Overdiagnosis could be reduced, if DSM-V criteria relevant to differential diagnosis address individual symptoms rather than the global picture.

Declaration of Interest

During the previous 12 months the author has received lecture fees and advisory panel payments from AstraZeneca and Janssen Cilag, and a travel grant from Eli Lilly.

Declaration of Interest

None.

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The authors reply

Dr Atbasoglu's letter is thoughtful and interesting and we agree with the general theme. DSM-III and DSM-IV diagnoses of major mental disorders such as schizophrenia are certainly reliable but have more limited value with respect to validity, particularly construct validity. However, we would argue that they have served the genomics research as well as might be expected. Other phenotypic constructs, including symptom dimensions, cognitive function, evoked potentials and neuroimaging measures have not been studied sufficiently in classical or molecular genetic studies to say definitively that they 'yield higher effect sizes for allelic variants'.

We believe the nosological problem is even more difficult than Dr Atbasoglu suggests. The 'natural entity' he refers to in his letter could be considered as a given mutation of moderate penetrance. From recent studies, apparently similar mutations appear, in different individuals, to result in not only a clinical diagnosis of schizophrenia, but also of autism spectrum disorder, epilepsy, learning disability and a variety of other neurodevelopmental conditions (Mefford *et al*. 2008; International Schizophrenia Consortium, 2008). Indeed, such phenotypic diversity (between schizophrenia, bipolar affective disorder and recurrent unipolar depression) resulting from the same mutation was previously suggested by the Scottish family with the t(1;11) translocation disrupting DISC1 (Blackwood *et al*. 2007).

Furthermore, very few DNA variants of small effect size have yet been individually identified, and the rare mutation findings to date, generally in the form of copy number variation, could well point to an extreme heterogeneity model accounting for a sizable component of the heritability of DSM-III or DSM-IV schizophrenia where individual mutations have relatively large penetrance values for schizophrenia and other variable phenotypes.

To tease out the diagnostic constructs for DSM-V and beyond, the field will need to await the completion of current and planned GWAS studies on categorical DSM diagnoses and on cognitive and other measures of phenotype. Further to that information, large-scale genomic sequencing studies of unselected cases (perhaps that simply come to the attention of mental health services), may be required where it will be possible to determine the range and frequency of rare mutations and follow them as they segregate, or not, through extended pedigrees.

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