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Editorial

Would Kraepelin reconsider the distinction between schizophrenia and bipolar disorder if he had access to recent molecular genetics evidence?

Emil Kraepelin divided psychotic disorders into two distinct categories, dementia praecox and manic-depressive illness (1). This dichotomous classification has been maintained in the ICD and recently updated in DSM diagnostic systems, but there is clearly overlapping phenotypes between the diagnoses of schizophrenia and bipolar disorder as well as schizoaffective disorders (2). Further, several authors have argued for the continuum model, with prototypic bipolar disorder in one end and prototypic schizophrenia in the other (3). These models are all based on descriptive symptomatology and not on underlying mechanisms (4). Epidemiological studies have shown that schizophrenia and bipolar disorder run in families (5), and provided support for shared genetic risk factors. Twin studies have estimated heritability rates to be ~80% for both disorders (6,7). With the recent progress in technology in the genetics field, it has been proposed that molecular genetics may help inform the nosology of severe mental disorders.

The microarray genotyping technology has provided a boost to psychiatric genetics. This has enabled genotyping of unprecedented large samples (6,8), and facilitated by the international Psychiatric Genomics Consortium (PGC; https://pgc.unc.edu/index.php), a series of recent large genome-wide association studies (GWAS) has been conducted. These have identified several new common risk variants [single nucleotide polymorphisms (SNPs)] associated with psychotic disorders (9,10). A recent PGC cross-disorder mega-analysis ($n = 33\,332$ cases, $n = 27\,888$ controls) investigating schizophrenia, bipolar disorder, major depressive disorder, autism spectrum disorders and attention-deficit hyperactivity disorder identified common risk variants (SNPs) for all five disorders (11). Among these disorders, the strongest overlap in genetic risk was observed between schizophrenia and bipolar disorder. In addition to common variants (SNPs), rare structural variants called copy number variants (CNVs) have been found associated with schizophrenia (12). Interestingly, CNVs seem not to be associated with bipolar disorder to the same degree (13). Thus, there is evidence for shared as well as disease-specific genetic risk for schizophrenia and bipolar disorder. This supports the hypothesis of partial genetic overlap between the two disorders, which was the rationale for the study by Gu et al. (14) In this issue of the journal. Gu et al. performed a meta-analysis of eight studies with schizophrenia ($n = 2953$ cases, $n = 3153$ controls) and six studies of bipolar disorder ($n = 923$ cases, $n = 928$ controls), focusing on the 1354C/T genetic polymorphism of 5-hydroxytryptamine receptor 2A. In their samples with both Caucasian and Asian ethnicity, they did not find any association with this gene marker for neither schizophrenia nor bipolar disorder. This negative finding is in line with the concept of overlapping genetic risk factors in these disorders.

However, the single SNP approach is not able to capture much of the heritability of these disorders. Recently, new evidence for a polygenic architecture of bipolar disorder and schizophrenia was presented. The first evidence for a polygenic overlap in psychotic disorders came from a combined GWAS (6), where the cumulative risk from the entire genome is extracted from one GWAS dataset to predict risk in an independent sample (6). As schizophrenia and bipolar disorder share common genetic risk, we have applied new statistical methods to leverage the pleiotropy between the two disorders to improve gene discovery, that is, use information on risk variants identified in one disorder to improve detection of risk variants in the other (15). Based on these Bayesian methods, it is also possible to estimate the

total number of SNPs associated with these disorders. These analyses suggest that there are ~12 000 SNPs associated with both schizophrenia and bipolar disorders. Further, these new statistical methods for analysing GWAS results of polygenic complex disorders can also be used to identify potential common biological pathways, as illustrated with schizophrenia and cardiovascular disease risk factors (16).

The advance in our understanding of the underlying genetic architecture of bipolar disorder and schizophrenia may have a large potential for generating new knowledge about the pathophysiology of these major neuropsychiatric disorders – which may eventually also lead to better diagnostic systems as well as new drug development.

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