Biological Psychiatry: Celebrating 50 Years

Commentary

Clinically Defined Subtypes of Bipolar Disorder Are Reflected in Genomic Architecture

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Neuropsychiatric disorders are currently defined by behavioral criteria, and the broader experience of patients who meet the same diagnostic criteria can vary widely. This range of symptom severity and comorbid traits among patients with a single diagnosis has led to the conceptualization of several neuropsychiatric conditions as "spectrums"—for example, autism or bipolar spectrum disorders. The diversity of patient experiences is mirrored at the genetic level, where risk-associated DNA sequence variants are spread across numerous genes in a polygenic pattern. Given this heterogeneity, there is interest across psychiatry in both defining subtypes of patients within diagnoses and characterizing symptom dimensions across diagnoses in order to facilitate the study and successful treatment of patients with similar traits. In this issue of *Biological Psychiatry*, Charney *et al.* (1) present new work from the International Cohort Collection for Bipolar Disorder (ICCBD) on the contribution of rare copy number variants (CNVs) in different bipolar disorder (BD) subtypes and across the symptom dimension of psychosis.

BD is a mood disorder characterized by episodes of mania and/or depression. Several BD subtypes have been recognized based on differing patterns of mania, depression, and psychosis: bipolar I disorder (BD I) (full manic episode), bipolar II disorder (BD II) (cyclical depression and hypomania), and schizoaffective disorder, bipolar subtype (SAB) (psychosis and mania) (2). Family studies demonstrate a role for genetics in BD risk (3–5), and advances in genomic technology and widespread collaboration across the field of human genetics have successfully identified genetic variants associated with disease risk. In large sample collections that include sufficient phenotype information, we are also able to address the question of whether phenotypically defined disorder subtypes show different genetic risk profiles. Such differences would lend biological support to the distinctions between behaviorally defined subtypes and could potentially suggest different treatment strategies.

Multiple lines of evidence have supported the possibility of etiologically distinct BD subtypes. Early on, studies of recurrence rates for BD subtypes and affective disorders within family members with BD and schizoaffective disorder probands showed patterns consistent with the existence of distinct genetic risk factors separating BD from major depressive disorder and BD I, BD II, and SAB from each other (3,4). Genomic analysis of common variants in the ICCBD further supported these patterns, demonstrating greater single nucleotide polymorphism–based heritability for BD I than BD II and greater overlap with common variant schizophrenia (SCZ) risk for SAB than BD (6). In their current work from the ICCBD, Charney *et al.* (1) have expanded and leveraged this data set to explore the contribution of rare CNVs to BD subtypes.

CNVs are deletions or duplications of large segments of chromosomes, and these variants can be detected by evaluating raw probe intensity data and allele frequency patterns from genotyping microarrays. As predicted by the laws of natural selection, variants that are tolerated at high frequencies in a population tend to have individually small effects on fitness, while individual rare variants are more likely to have large effects—for example, by deleting one copy of a gene with a critical role in development or by disrupting the transcription of multiple genes. Analyses of rare CNVs in neuropsychiatric disorders have shown a trifecta of effects: a greater incidence of CNVs, larger CNVs, and a greater number of genes affected by rare CNVs in cases compared with controls (7).

Rare, large CNVs have been consistently implicated in risk for SCZ, autism spectrum disorder, and developmental delay (8,9). However, studies of large BD samples (~2600 cases, 8800 controls) have not consistently detected a significantly increased burden of rare CNVs in BD (10), suggesting that the contribution of rare CNVs to BD risk is minimal. Alternatively, it is also possible that rare CNVs contribute differently to specific BD subtypes, and that these signals are overwhelmed by the heterogeneity in broad case-control comparisons. Now, with genotype data from more than 6300 BD cases, the purpose of this latest work by Charney *et al.* (1) is twofold: to test again for rare CNV burden relative to controls—now in the largest sample of BD cases to date—and to assess rare CNV burden separately within BD subtypes.

In the ICCBD sample, Charney *et al.* (1) identified CNVs >100 kb in size and <1% frequency. They then tested for burden differences between cases and controls, separately for all BD cases and for the BD I, BD II, and SAB subtypes, as well as for differences between subtypes relative to each other. Charney *et al.* (1) also tested multiple combinations of variant type (all CNVs, deletions, and duplications), size (>100 kb and >500 kb), and frequency (<1% and singletons, which only occurred once in the data set), for a total of 252 tested hypotheses. To address the variable reported links between rare CNVs and BD, Charney *et al.* (1) tested 27 nominally significant BD CNV associations reported in the literature, as well as three sets of disorder-associated, specific CNV loci, for a total of 276 tests. Critically, results from all tests are appropriately corrected for multiple testing.

Much like earlier work in smaller samples, Charney *et al.* (1) do not observe differences in CNV burden between the full set of BD cases and controls that reach a corrected significance threshold (Figure 1A). Furthermore, only 2 of the 27 previously

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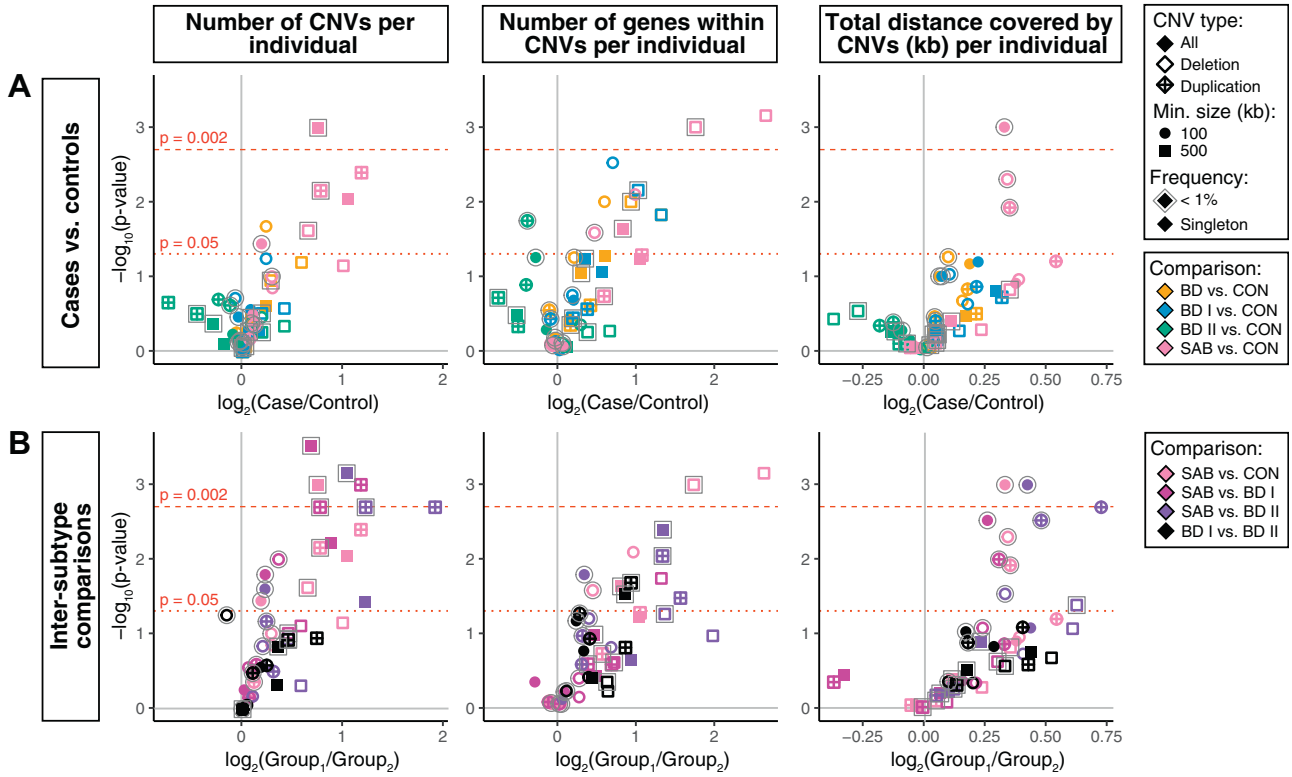

Figure 1. Rare copy number variant (CNV) burden in bipolar disorder (BD) cases, controls (CON), and subtypes. The relative burden of rare CNVs in BD cases vs. controls and between subtypes is shown in volcano plots with the $\log_2$-transformed burden ratio on the x-axis and $-\log_{10}$ (*p* value) from a two-sided permutation test on the y-axis; plotted data are adapted from Table 2 in Charney *et al.* (1). Rare CNV burden is tested using three measures: the number of rare CNVs per individual (left), the number of genes within rare CNVs per individual (center), and the total distance covered by rare CNVs in kilobases (kb) per individual (right). **(A)** Comparison of all BD cases and each of the bipolar I disorder (BD I), bipolar II disorder (BD II), and schizoaffective disorder, bipolar subtype (SAB) subtypes vs. controls. **(B)** Comparison of the SAB subtype vs. controls, BD I, and BD II, and the comparison of BD I vs. BD II cases. Nominal significance ($p \leq .05$) and significance after correcting for 276 tests ($p \leq .002$) are indicated by the red dotted and dashed lines, respectively.

reported BD rare CNV burden differences achieved even nominal significance ($p \leq .05$) in the ICCBD sample, perhaps demonstrating a winner's curse for the originally reported patterns. Comparisons by BD subtype, however, were more revealing: SAB cases showed greater rare CNV burden than controls (Figure 1A), BD I, and BD II cases (Figure 1B) for all three measures of burden. This pattern was most striking for CNVs ≥500 kb and <1% frequency, where SAB showed significantly greater CNV incidence compared with controls, BD I, and BD II. In fact, of all 252 tests run in the main analysis, only comparisons of SAB cases met the corrected significance threshold ($p < .002$) (Figure 1). Differences between BD I and BD II were less apparent; though rare CNV burden appears to be proportionately greater in BD I than BD II, these differences are small in magnitude and are not statistically significant (Figure 1B).

These results show that rare CNV burden differs across BD subtypes, with the greatest and most consistent burden in SAB cases. Psychosis is a symptom required for a SAB diagnosis, though it can also be a comorbid feature of BD I, most commonly occurring during manic episodes. This raises the question, then, of whether rare CNVs contribute specifically to the symptom of psychosis independently from other diagnostic criteria for SAB. To test this, Charney *et al.* (1) compared the burden of rare (<1%) CNVs ≥500 kb in SAB cases and in BD I cases with and without a history of psychosis. This analysis showed that CNV burden was significantly greater in SAB compared with either subset of BD I cases but not different between BD I cases with and without psychosis. Like rare CNVs, polygenic risk scores based on common variants associated with SCZ were also greater in SAB than BD I cases with or without psychosis, but in contrast to rare CNVs, SCZ polygenic risk was significantly greater in BD I cases with psychosis than without. Together, these results show that both rare and common variants distinguish SAB from other BD subtypes, independently from psychosis, and further indicate that common variants may contribute to psychosis risk across diagnostic boundaries.

With the addition of this work to the literature, we now see that clinically defined subtypes of BD are reflected consistently in epidemiology (3,4), common genetic variants (6), and rare, large genetic variants (1). This contrasts with autism spectrum disorder, for example, in which clinical subdivisions were not supported by contemporary analyses and were removed in the DSM-5 (2). Looking forward, a gap in BD genetic architecture that remains to be explored is the role for rare single nucleotide and small insertion-deletion ("indel") variants. Particularly in coding sequences, these small variants have the potential to

be as disruptive as a large CNV. However, rare single nucleotide variants and indels cannot be discovered from existing genotyping array data and will require the collection of high-throughput exome or genome sequencing data from case and control samples.

Still, the classes of variation tested thus far in the ICCBD both in previous work (6) and by Charney *et al.* (1) strongly suggest that the distinctions between BD subtypes, as originally defined by clinical presentation, have a basis in biology. With an eye toward developing effective and targeted treatment strategies for neuropsychiatric conditions, it is encouraging to see that the top-down categorization of BD by symptom profiles aligns with different profiles of genetic risk variants. Given this, subtype-stratified association testing may prove to be an effective strategy for future gene discovery work in BD. Similar patterns of distinct genetic architecture between subtypes, but shared genetic risk along symptom dimensions, may also be evident in other neuropsychiatric disorders. As the results from the ICCBD suggest, further etiological dissection of clinically distinct disorder subtypes and of symptoms that span multiple categorical diagnoses will likely be facilitated by similarly large-scale efforts to combine genotyping with consistent, dimensional phenotype information.

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Article Information

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