De Novo CNVs in Bipolar Disorder: Recurrent Themes or New Directions?

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In this issue of *Neuron*, Malhotra and colleagues report an enrichment of de novo copy number variants in bipolar disorder and schizophrenia when compared with those of controls. The study highlights the importance of a genetic model involving rare and disruptive variants to further our understanding of complex neuropsychiatric traits.

Identification of novel, rare variants occurring exclusively among affected probands has contributed to the discovery of several copy number variants (CNVs) associated with intellectual disability (Cooper et al., 2011; Kaminsky et al., 2011), schizophrenia (Xu et al., 2008), and autism (Sanders et al., 2011). These findings have led to screens for large CNVs in a variety of other neuropsychiatric conditions, with less clear results regarding the overall contribution of CNVs. In this issue of *Neuron*, Malhotra and colleagues (Malhotra et al., 2011) have extended the paradigm, reporting an enrichment of de novo CNVs in individuals with bipolar disorder and schizophrenia when compared with controls.

Bipolar disorder is associated with episodic mood disturbances, including extreme elation or mania to severe depression with high lifetime risks of suicide. Although there is a high degree of heritability, familial aggregation, and a lifetime prevalence as high as 4% (Kessler et al., 2005), the complex genetics of bipolar disorder has been a tough nut to crack for a number of reasons. Genome-wide association studies based on common genetic variants have yielded relatively few candidate genes that have withstood replication. Previous screens for CNVs and CNV burden among bipolar patients have given conflicting results with CNV enrichments observed in some studies but not others. Finally, family-based studies have given inconsistent results with respect to segregation of specific diagnoses (Owen et al., 2007). The heterogeneity of clinical presentations coupled with our limited understanding of the pathogenesis and considerable overlap with symptoms of schizophrenia have called into question the traditional "Kraepelinian" dichotomous classification of bipolar disorder and schizophrenia (Owen et al., 2007). Indeed, one of the largest population-based surveys of schizophrenia and bipolar disorder found significant evidence of comorbidity within families—most of which (63%) was explained by additive genetic effects (Lichtenstein et al., 2009).

Based on the hypothesis that sporadic, disruptive mutations are an important risk factor for bipolar disorder and schizophrenia, Malhotra's strategy for bipolar disorder was to search for de novo CNVs enriching for cases with an earlier age of onset—a tried and true approach taken directly from the human genetics playbook. The authors found about five times the rate of de novo CNVs in individuals with bipolar disorder (8/185, 4.3%) and schizophrenia (8/177, 4.5%) compared with that of controls (4/426, 0.9%). As predicted, the rate was slightly higher (6/107, 5.6%) for patients with an earlier age of onset of symptoms (<18 years), intimating a neurodevelopmental basis for at least a subset of the disease. Similar to previous observations from other neurodevelopmental disorders, a significant enrichment was also observed for larger (>500 kbp) inherited duplications for familial cases of bipolar disorder, but this trend was not observed for deletions.

The bipolar-disorder-associated CNVs identified by Malhotra and colleagues may be considered in two different contexts: individual CNVs corresponding to specific loci and collectively as an estimate of overall CNV burden (Figure 1). With respect to the former, two of the ten de novo CNVs observed among the bipolar patients correspond to genomic hotspots—regions bracketed by segmental duplications (Sharp et al., 2006). Because of their predisposition to recurrent mutations as a result of nonallelic homologous recombination, de novo events within these regions occur frequently enough such that they can be assessed for their exclusivity to bipolar disorder compared with other disorders. Although none of these specific CNVs could be replicated in a larger collection of bipolar disorder patients (2,777 bipolar cases versus 3,508 controls), two hotspot de novo CNVs (the 16p11.2 duplication and 3q29 deletion) are well known and have been previously associated with intellectual disability/multiple congenital anomalies (ID/MCA), autism, and schizophrenia (Cooper et al., 2011; McCarthy et al., 2009; Mulle et al., 2010). Similarly, an inherited hotspot variant included the 1q21.1 duplication previously associated with autism and ID/MCA (Cooper et al., 2011; Kaminsky et al., 2011). With the exception of the 9p24 duplication also reported in schizophrenia individuals (Xu et al., 2008), several nonhotspot CNVs are singleton events and, therefore, warrant further investigation. While potentially important to our understanding of the genetics of psychosis, there is little evidence that the most likely pathogenic

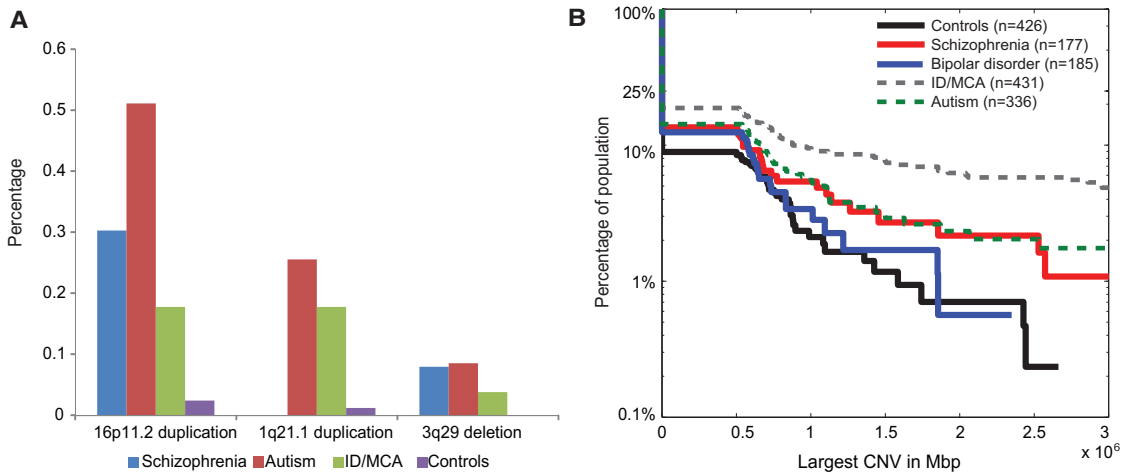

Figure 1. Shared CNVs and Comparison of Large CNV Burden in Neuropsychiatric Disorders

(A) The histogram shows the frequency (in percentage) of known disease-associated hotspot CNVs (de novo and inherited) discovered in the bipolar cohort. The frequency of each CNV was obtained from published studies (Cooper et al., 2011; McCarthy et al., 2009; Mulle et al., 2010; Sanders et al., 2011).

(B) The population frequency of the largest, rare CNVs is shown for schizophrenia, bipolar disorder, and controls (Malhotra et al., 2011), along with autism and ID/MCA (Girirajan et al., 2011). The data from Malhotra and colleagues (Malhotra et al., 2011) was downsampled and size selected (>500 kbp) to allow cross-platform array comparisons.

events reported in this study are specific to bipolar disorder.

An assessment of total, rare CNV burden and comparison with those with autism and ID phenotypes (Girirajan et al., 2011) suggest some interesting trends as well as potential insights into disease. It is noteworthy, for example, that de novo bipolar CNVs tend to be smaller (median size 137 kbp) than de novo schizophrenia CNVs (415 kbp). The ability to detect smaller CNVs stems, in part, from the authors' use of a higher-density microarray (2.1 million probes), allowing them to detect CNVs >10 kbp in size. There is an excess of both de novo and inherited duplications as opposed to deletions in bipolar patients when compared with schizophrenia patients. Finally, the overall rare CNV burden is more modest for bipolar disorder, with both schizophrenia and autism showing an increase in the number of larger CNVs. All of these lines of evidence suggest CNVs with more subtle and less severe effects among bipolar patients as opposed to those with ID, autism, and schizophrenia. Caution, however, must be employed because much larger sample sizes are required to replicate these findings.

How do we reconcile the lack of CNV specificity and the modest CNV burden with the significant increase in de novo CNVs among bipolar cases? Increased CNV size and burden have been shown to be associated with ID in individuals with autism (Girirajan et al., 2011) and there is a general trend that the larger the CNV event, the greater the number of genes affected and the more severe the outcome (Cooper et al., 2011; Girirajan et al., 2011). The burden of large (>500 kbp) CNVs is highest among cases of ID/MCA (Girirajan et al., 2011) and decreases for autism, schizophrenia, and bipolar disorder (Malhotra et al., 2011; Sanders et al., 2011) (Figure 1B). Some conditions, such as dyslexia, show no evidence of increased rates or burden of CNVs. It follows that for "less severe" adult phenotypes, such as bipolar disorder, de novo CNVs might be smaller in size, affecting fewer genes and/or manifesting as an excess of duplications. It is well known that certain CNVs are much more variable in their outcome, having been associated with a diverse range of phenotypes, and that the transition to ID among pediatric cases associates with a significant excess of additional CNVs, so-called second "hits" (Girirajan et al., 2011). It is, therefore, conceivable that a subset of bipolar disorder and schizophrenia are part of a spectrum of neurodevelopmental disease where the effects of both de novo and inherited, rare, gene-disruptive and gene-imbalance events are additive. Depending on the underlying genes and their downstream interactions, as the total number of events increases, different thresholds are passed, resulting in outcomes ranging from bipolar disorder to schizophrenia to autism to ID. Comorbidity of these traits within families is the natural extension of this model (Lichtenstein et al., 2009; Woodberry et al., 2008). If these trends continue, there is reason to hope that smaller, disruptive CNVs, as well as de novo point mutations, may unveil a larger fraction of the genetic etiology of neuropsychiatric disease, as has been suggested by preliminary exome sequencing studies of autism and schizophrenia (O'Roak et al., 2011; Xu et al., 2011).

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Observations on Clustered Synaptic Plasticity and Highly Structured Input Patterns

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In this issue of *Neuron*, Makino and Malinow and Kleindienst et al. present evidence of a behaviorally induced form of synaptic plasticity that would encourage the development of fine-scale structured input patterns and the binding of features within single neurons.

Input processing and storage within dendrites is at the heart of neuronal computation. Yet our understanding of the fundamental operations performed by neurons is incomplete and continues to evolve. Neurons possess numerous mechanisms that allow them to uniquely respond to and store distinct synaptic input patterns, and these capabilities could be used to produce behaviorally related network ensemble activity. Thus the exact level of structure present in normal-experience-induced input patterns remains an important but unresolved issue for which there is both insufficient and conflicting data. While there is strong evidence of topographically organized inputs onto the dendrites of neurons in several species, such organization has not yet been observed in mammalian brain regions (reviewed in DeBello, 2008; Branco and Häusser, 2010). Two papers in this issue of *Neuron* are relevant in that they provide evidence related to the type of synaptic plasticity that could lead to the development of highly structured input patterns in mammalian neurons.

Makino and Malinow (2011) present evidence that LTP-like synaptic plasticity induced by sensory experience occurs in a clustered spatial pattern in pyramidal neurons of the barrel cortex. The authors used fluorescently tagged AMPA receptors to monitor activity-dependent AMPA receptor trafficking in mice with intact whiskers and found that GluR1 subunits were enriched in groups of neighboring spines that were located in an ~10 μm region of a dendritic branch. GluR2 subunits did not show this same enrichment pattern. The tagged GluR1 subunits present in spines show a relatively low mobility, suggesting that the enrichment is due to synaptic incorporation of additional receptors, as would be expected for an LTP-type process. Thus, it appears that a clustered form of synaptic potentiation is produced by normal neuronal activity patterns. This result is contrasted with that produced by a second experimental condition where sensory deprivation (induced by whisker trimming) was instead associated with a spine enrichment of GluR2 subunits (but not GluR1) that displayed no significant spatial correlation between nearby spines. These data suggest that the homeostatic type of plasticity thought to be induced by whisker trimming produces a more global synaptic enrichment. A final experiment was performed in mice with intact whiskers, but with neocortical neurons expressing a mutated form of AMPA receptors that lack the appropriate phosphorylation site required for synaptic incorporation (GluRAA). In this case, no evidence of clustered synaptic plasticity was observed.

Previous in vitro work has shown that neurons possess mechanisms that could act to produce compartmentalized forms