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Dissecting a Genomic Role of BDNF in Schizophrenia and Psychosis

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Brain-derived neurotrophic factor (BDNF) is a neurotrophin that plays a primary role in the development, patterning and plasticity of the central nervous system. After 2 decades of investigation, a definitive role for BDNF in psychiatric illness remains unresolved. This is particularly the case for clinically heterogeneous and genetically complex disorders such as schizophrenia. Early evidence for a role of BDNF in schizophrenia emerged from postmortem studies in which expression of BDNF mRNA (~23%) and protein (~40%) was decreased in the dorsolateral prefrontal cortex of schizophrenia patients.[1] More recent studies that have examined the effect of *BDNF* gene variants on clinical indices, antipsychotic response, brain morphology, cognition, and circulating BDNF concentrations have provided further evidence of a complex role of this neurotrophin in schizophrenia.[2] However, this pool of evidence has been variable and implies that if a role for BDNF in schizophrenia exists, it is unlikely to follow a simple genetic model—a result echoed by large consortia studies that have failed to provide evidence that BDNF is a major locus of risk for the disorder.[3]

In the study by Zhang et al[4] published in the current issue of the *Journal*, 4 *BDNF* gene variants were screened for risk as well as for an effect on cognitive domains often reported to be disrupted in schizophrenia. Despite not meeting sample size guidelines for genetic association studies, as the authors themselves concede, this report still boasts one of the largest sample sizes utilized in a single study of defined *BDNF* gene variants in the recent schizophrenia literature (cases, n = 844; controls, n = 1,043; total N = 1,887). Of interest is the result that the *BDNF* rs10835210 variant—located approximately 16 kb from the widely studied and functional Val66Met polymorphism—was associated with schizophrenia, which replicates a recent report.[5] The other principal result to emerge from the study by Zhang et al[4] was a series of *BDNF* haplotypes that ostensibly regulate specific cognitive domains among schizophrenia patients. This study thus adds incremental evidence for a role of BDNF in risk of schizophrenia and the cognitive symptoms of the disorder that are heterogeneously present between cases.

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While the results of Zhang et al[4] add important clinical data to the existing schizophrenia literature, there remain several conceptual issues to be resolved if a definitive role for BDNF in schizophrenia is to be determined. Sampling factors aside,[6] important experimental considerations to be addressed in the wider literature include (1) determining *BDNF* gene variant functionality and (2) screening for biological and environmental determinants that may shape or unmask BDNF-dependent phenotypes.

Reverting to the first point, despite there being many single nucleotide polymorphisms (SNPs) reported in the human *BDNF* gene to date (see dbSNP), only 2 variants have reported functionality in vivo. Specifically, these functional variants are the coding rs6265 (Val66Met) and intronic rs12291063 polymorphisms. The rs6265 variant has been shown to disrupt the activity-dependent release of BDNF[7] and alter the putative interaction of the cleaved BDNF prodomain with the SorCS2 receptor,[8] making it a widely studied gene variant in the psychiatric literature.[6] On the other hand, the rs12291063 variant has been recently shown to alter ventromedial hypothalamic *BDNF* expression, binding and transactivation of the transcriptional regulator hnRNPD0B, and risk of obesity.[9] Given the strong linkage disequilibrium of many *BDNF* gene variants with one another, and specifically the Val66Met polymorphism, most schizophrenia studies often include other gene variants as tag SNPs and have generally not taken a mechanistic approach in dissecting how other *BDNF* variants may exert independent effects even when false discovery thresholds have been exceeded. While most other common *BDNF* gene variants are not located in the protein coding exon of the *BDNF* gene, the functionality of the intronic rs12291063 variant highlights that it should not be assumed that noncoding variants are unimportant for regulatory mechanisms governing *BDNF* gene expression or activity. In this respect, where evidence of functionality in the clinical literature is promising, a bottom-up design should be employed to better understand the genomic mechanisms that govern BDNF functionality and a potential role in psychiatric illness. This is especially true for other SNPs located in the BDNF protein coding region, alternatively spliced exons (that serve to direct subcellular trafficking of BDNF), or those located in other genomic structures (including introns, such as the rs10835210 variant), where an effect on gene expression, mRNA translation, stability, trafficking, or protein activity may be differentially altered to produce a subtle phenotype.

Likewise, reverting to the second point—that a greater emphasis on identifying, screening and stratifying analyses for BDNF interaction factors is required in schizophrenia

research—is particularly important given a consistently inconsistent role of *BDNF* gene variants in schizophrenia.[6] While environmental factors such as early life stress, trauma, and drug abuse are known risk factors for a variety of psychiatric disorders, these factors have been poorly interfaced with biological measurements of BDNF within the clinical schizophrenia literature. There have been several notable studies that have found evidence that environmental factors may shape or unmask an effect of *BDNF* variants in schizophrenia, such as that cannabis use may decrease age at onset of psychosis among females depending on *BDNF* Val66Met genotype.[10] However, the majority of studies examining a genomic role of BDNF in schizophrenia have failed to investigate these types of complex gene-environment interactions despite the fact that a number of environment-related factors that interact with, or depend on, BDNF are already known (eg, exercise, as reported in mice,[11] healthy humans,[12] and recently in schizophrenia patients[13]). A range of biological factors are also believed to putatively act via or interact with BDNF, but have not been widely investigated within the schizophrenia literature.

One understudied interaction theme is the role of hormones in schizophrenia, and the possibility that they may act at least partially via BDNF. While stress hormones have been examined in schizophrenia, and are known to down-regulate the expression of BDNF[14] and induce hippocampal atrophy,[15] few studies have examined a modulatory effect of *BDNF* genotype in patient susceptibility to stress. To emphasize the importance of this point, we recently reported that in humanized BDNF (hBDNF) transgenic mice carrying the Val66Met polymorphism, a chronic stress paradigm administered during late adolescence produced a long-lasting effect to "rescue" the hippocampus-dependent memory phenotype of adult $hBDNF^{Met/Met}$ mice.[16] Given the strong basic science that has established an interaction of glucocorticoid stress hormones with BDNF, further investigation of stress sensitivity, early life stress, or trauma as covariates in schizophrenia research on BDNF may thus be a promising line of further research. Likewise, given the earlier onset of schizophrenia among men as well as a peak in schizophrenia cases among menopausal-aged women,[17] it is likely that estrogenic hormones are also involved in the pathophysiology of schizophrenia.[18] Indeed, schizophrenia symptomatology fluctuates over the menstrual cycle,[19] and several recent reports have provided evidence that estradiol[20] and the selective estrogen receptor modulator raloxifene[21] may be viable adjunctive treatments for aspects of schizophrenia symptomatology. As the *BDNF* gene contains a putative estrogen response element,[22] enabling transcriptional control of BDNF by estrogens within the brain, it is conceivable that estrogens may partially exert their protective effects via BDNF.[23] Further research on this topic may thus be useful in determining the relative contribution of BDNF in the sex differences observed in schizophrenia, and the viability of emerging sex-steroid hormone adjunctive treatments.

Ultimately, the investigation of *BDNF* variant functionality as well as complex gene-environment interactions in schizophrenia is likely to lead back to a bottom-up design using transgenic rodent lines for validation purposes, and was the same approach applied to the Val66Met variant to determine cellular,[24,25] mouse,[7] and human[26] phenotype translation. The high degree of BDNF gene conservation between species enables the development of analogous BDNF variant knock-in rodent models, especially coding variants, with likely conserved outputs. In the case of schizophrenia, few studies have examined psychosis endophenotypes using genetically modified rodent models of BDNF. That said, a variety of paradigms are available to model aspects of the positive-symptom class of schizophrenia in rodents,[27] such as drug-induced hyperlocomotor activity and prepulse inhibition, that have already been used to highlight the effect of BDNF availability in vivo as well as through interaction with chronic corticosterone,[28] cannabinoid,[29] and methamphetamine[30,31] treatments. The tools required to dissect the effect of *BDNF* variants on psychosis endophenotypes using rodents are thus available and awaiting application to guide clinical research.[32]

In closing, a role for BDNF in schizophrenia seems likely; however, a genomic effect remains contentious. While *BDNF* gene variants are not likely to be major risk factors for schizophrenia in isolation, based on a lack of effect in large consortia studies, this does not rule out the possibility that *BDNF* variants may modify clinical aspects of the disorder by modulating BDNF availability or function. Not to be overlooked, the generation of BDNF transgenic mice provides an important tool to assay psychosis-related endophenotypes in an environmentally controlled system that can be manipulated at will, providing not just a tool but also an opportunity for clinicians and scientists working on schizophrenia to collaborate by validating population genetic findings in genetically-modified rodents. In this respect, further investigation is required to determine the functional effects of commonly occurring *BDNF* gene variants, such as the rs10835210 variant reported to be associated with schizophrenia by Zhang et al,[4] as well as whether *BDNF* phenotypes are gated by biological or environmental factors if a definitive role of BDNF in schizophrenia is to be determined.

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