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Molecular differentiation of schizoaffective disorder from schizophrenia using *BDNF* haplotypes

Todd Lencz, Robert H. Lipsky, Pamela DeRosse, Katherine E. Burdick, John M. Kane and Anil K. Malhotra

Background
Allelic variation in the gene encoding brain-derived neurotrophic factor (*BDNF*) has been associated with affective disorders, but generally not schizophrenia. Brain-derived neurotrophic factor variants may help clarify the status of schizoaffective disorder.

Aims
To test the hypothesis that *BDNF* haplotypes are associated with psychiatric illness marked by a prominent affective component.

Method
Frequencies of a 5-marker *BDNF* haplotype were examined in 600 White participants across four diagnostic categories and healthy controls.

Results
Individuals with schizoaffective disorder and other affective disorders were significantly more likely to carry two copies of the most common *BDNF* haplotype (containing the valine allele of the Val66Met polymorphism) compared with healthy volunteers. Moreover, when compared with people with schizophrenia, individuals with schizoaffective disorder were significantly more likely to carry two copies of the common haplotype.

Conclusions
To our knowledge, this is the first candidate gene study to demonstrate association with schizoaffective disorder but not schizophrenia. Variation in the *BDNF* gene may be associated with the clinical phenotype of affective dysregulation across several DSM–IV diagnostic categories.

Declaration of interest
None.

Since its introduction as a diagnostic entity,[1] schizoaffective disorder has held an uncertain role in psychiatric nosology. Although Kraepelin himself had acknowledged the presence of such intermediate cases,[2] the so-called 'Kraepelinian dichotomy' (dementia praecox *v.* manic–depressive illness) has guided both clinical reasoning and pathophysiological research for a century. Consequently, clinicians and researchers often consider schizoaffective disorder to be a subtype of schizophrenia or bipolar disorder, each of which is seen as a discrete nosological entity.[3] It is possible, however, that careful comparison of schizoaffective disorder with the other 'major' diagnostic categories may yield insights into the underlying nature of these disorders. Data from family studies[4] and population genetics[5] provide strong evidence that schizoaffective disorder shares a familial relationship with both schizophrenia and bipolar disorder. Moreover, molecular genetic studies are increasingly finding polymorphic sequence variants that increase susceptibility to mental illness across traditional diagnostic boundaries.[6–8] Although it has been suggested that molecular genetics will introduce new nosological conceptualisations by undermining simple categorical constructs,[9] a genetic association approach has not yet been utilised to refine our understanding of schizoaffective disorder.

The present study was designed to examine genetic variation in the gene encoding brain-derived neurotrophic factor (*BDNF*) in people diagnosed with schizoaffective disorder, in comparison with people diagnosed with schizophrenia, bipolar disorder and unipolar depression, as well as healthy volunteers. Brain-derived neurotrophic factor was selected because it is highly expressed in critical brain regions such as the hippocampus, amygdala and striatum, where it is involved in key processes that may be implicated in psychopathology; such functions include associative learning and memory, fear conditioning and social defeat stress.[10–12] In addition, the association of several psychiatric diagnoses with polymorphisms located within *BDNF*, especially the Val66Met amino acid substitution, has been examined in multiple studies. Several family studies have reported overtransmission of the Val66Met valine allele in bipolar disorder,[13–16] and a few studies have also demonstrated an association of other *BDNF* polymorphisms with major depression.[17,18] By contrast, association studies of *BDNF* in schizophrenia have been largely negative, although one case–control study demonstrated a significant over-representation of the valine66 allele in people with schizophrenia or schizoaffective disorder.[19] Based on these data, *BDNF* variation has been hypothesised to be related to the affective components of psychiatric illness.[3,20] The present study was designed to test the hypothesis that frequency of common variants within the *BDNF* gene would be associated with affective illnesses, including schizoaffective disorder (as well as bipolar disorder and major depressive disorder), but not schizophrenia.

Methods

Participants

A total of 381 individuals were recruited from the in-patient and out-patient clinical services of the Zucker Hillside Hospital, a division of the North Shore–Long Island Jewish Health System. The Structured Clinical Interview for DSM–IV Axis I disorders (SCID, version 2.0)[21] was administered by trained raters. All participants were screened, recruited and assessed by the same ratings team at a single site, the Zucker Hillside Hospital. On average, participants had spent 13.52 years (s.d.=8.91) in treatment at our institution (in-patient and out-patient), therefore allowing us to capture the majority of their illness course with our own medical records. All available family members (over age 18) were also interviewed to enhance diagnostic validity. Thus, the diagnostic process included the SCID, detailed medical record

review, interviews with family members, consultation with the clinical treatment team and formulation of a detailed two to three page case summary of each participant that was discussed in a diagnostic consensus conference led by the project principal investigator (A.K.M.).

We have also operationalised DSM–IV Criterion C for schizoaffective disorder, which differentiates it from schizophrenia.[22] Criterion C requires that mood symptoms meeting criteria for a mood episode 'must be present for a substantial portion of the entire period of illness' for a diagnosis of schizoaffective disorder to be made. Our operationalised criteria took 'a substantial portion' to be greater than 20% of duration of illness. Following these procedures, all but three individuals (0.8%) were assigned a consensus diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder or unipolar major depressive disorder. The consensus diagnosis and demographic information for these 378 individuals are presented in Table 1.

Healthy controls (n=222) were recruited by use of local newspaper advertisements, flyers and community internet resources and underwent initial telephone screening to assess eligibility criteria. Participants who met eligibility criteria were administered the non-patient SCID (SCID–NP) to rule out the presence of an Axis I psychiatric disorder; a urine toxicology screen for drug use and an assessment of the participant's family history of psychiatric disorders were also performed.[23] Exclusion criteria included (current or past) Axis I psychiatric disorder, psychotropic drug treatment, substance misuse, a first-degree family member with an Axis I psychiatric disorder and the inability to provide written informed consent. All participants were White by self-report and drawn from a single geographic location (surrounding Glen Oaks, New York, USA). After complete description of the study, written informed consent was obtained from all participants. As shown in Table 1, the groups significantly differed in age ($F_{4,558}$=15.5, P<0.001). By design, somewhat older individuals were selectively recruited for the healthy control group so that they might be outside the window of maximal risk for onset of schizophrenia, schizoaffective disorder and bipolar disorder. As is typical in schizophrenia studies, males were over-represented among those with schizophrenia compared with the other groups (χ^2=49.6, d.f.=1, P<0.001).

Genotyping

Genotyping was performed by 5′-exonuclease assay with allele-specific flourescence detection probes. As shown in online Fig. DS1, five single nucleotide polymorphisms (SNPs) encompassing the single protein-coding exon of *BDNF* were genotyped (listed in order of chromosomal position): rs4923463, rs6265 (the Val66Met polymorphism), rs11030104, rs2049045 and rs7103411. Single nucleotide polymorphisms were selected on the basis of three considerations:

(a) availability of reliable TaqMan assays at the time of initiation of the study, which was prior to the completion of the HapMap;

(b) coverage on both sides (3′ and 5′) of the single protein-coding exon; and

(c) minor allele frequency of at least 10% in White populations, to permit adequate power.

Genotyping reactions (5 µl) were performed in 384-well plates containing 10 ng of genomic DNA, 0.5 µmol of primers, 0.2 µmol of probes, and 2.5 µl of Master Mix (Applied Biosystems Inc.). The reaction thermal cycle programme consisted of 50°C for 2 min, 95°C for 10 min, followed by 40 cycles of 95°C for 15 s, 59°C or 60°C for 1 min. End-point amplification genotypes were determined using an Applied Biosystems 7900 Sequence Detector with Sequence Detection System 2.0 software. Genotyping accuracy was verified by regenotyping at least 10% of the DNA samples, randomly selected. Genotyping accuracy was >99% and genotyping completion was >99%. All SNPs were in Hardy–Weinberg equilibrium in controls (all P>0.30).

Statistical analysis

Haplotype block structure was determined using Haploview version 3.32.[24] Haplotype blocks were defined in accordance with Gabriel method[25] using default settings for all criteria. Using this method, a single haplotype block was identified with a very tight linkage disequilibrium structure (Fig. 1). A common haplotype (AGAGT), containing the valine-coding allele for rs6265, had a 74% frequency in the overall sample. The complementary haplotype (GAGCC) was the only other common haplotype (18% frequency), with several rare haplotypes also detected. PHASE 2.1.1[26] was then used to determine phase of alleles and assign haplotypes for each participant individually. Seven participants' samples (three with schizophrenia, two healthy controls, one with schizoaffective disorder and one with bipolar disorder) could not be phased with greater than 95% confidence and were excluded from subsequent analyses.

To reduce the number of multiple comparisons, analyses were conducted in a hierarchical fashion. Primary analyses were conducted comparing number of copies (zero, one or two) of

Table 1 Demographics of the five participant groups (total n=600)

	n (% male)	Mean age (s.d.)
Schizophrenia	211 (73.9)	38.3 (10.3)
Schizoaffective disorder	61 (52.5)	38.6 (12.2)
Bipolar I	77 (53.2)	36.6 (11.8)
Major depressive disorder	29 (44.8)	42.4 (9.4)
Healthy controls	222 (41.0)	47.6 (18.6)

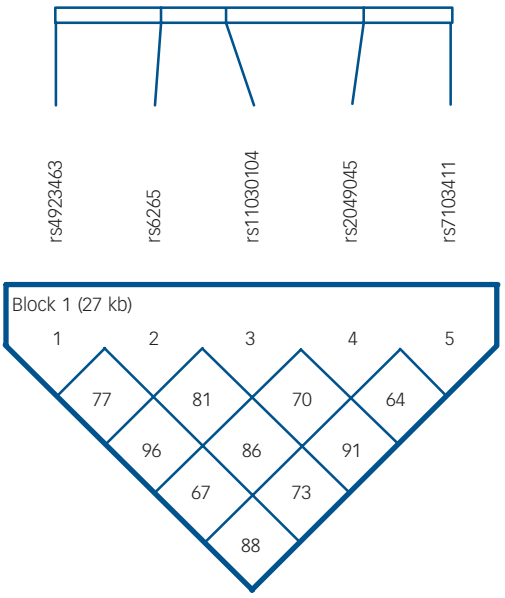

Fig. 1 Linkage disequilibrium plot of the five single nucleotide polymorphisms (SNPs) genotyped in the present study; inter-SNP r^2 is displayed for each pair. D′ is at or near unity for all pairs of SNPs.

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the AGAGT haplotype, across members of each of the diagnostic groups. Pearson chi-squared tests permuted 500 000 times were used to empirically determine *P*-values. Groups were first examined individually (full matrix), and then certain groups were combined (e.g. all individuals with a major affective component to disorder) in order to test the hypothesis described above. Subsequent to significant effects of haplotype for a given comparison, individual genotypic effects of each constituent SNP were examined.

Results

As groups differed in ratio of males to females, gender effects on number of copies of the common haplotype were examined first. No differences in common haplotype frequency were observed between males and females either in the total sample (χ^2=1.42, d.f.=2, *P*=0.49) or in any of the diagnostic subsamples (all $P > 0.43$).

Frequencies of two, one or zero copies of the common AGAGT haplotype across the five diagnostic groups are displayed in Fig. 1. The frequency of individuals possessing two copies of the AGAGT haplotype was 54% across the entire sample; frequency of one-copy carriers was 41%, and only 5% of the total sample carried zero copies of AGAGT. As shown in Fig. 2, these frequencies differed across diagnostic groups. Slightly fewer than half of the healthy controls carried two copies of the common haplotype (48.6%) and slightly more than half of the individuals with schizophrenia (53.4%) were two-copy carriers (χ^2=0.96, *P*=0.33). By contrast, at least 60% of people in each of the three affective groups (schizoaffective 60.0%; bipolar 61.8%; and major depressive disorder 69.0%) carried two copies of the common haplotype. Similarly, frequency of one-copy carriers can be seen to decline across the three affective groups relative to the non-affective groups (i.e. healthy controls and people with schizophrenia).

Statistical examination of these comparisons, designed to test the hypothesis that dosage of the *BDNF* common haplotype differs in individuals with an affective diagnosis (including schizoaffective disorder) relative to individuals who do not have an affective illness, are displayed in Table 2. First, the full matrix (five groups compared across three levels, with eight degrees of freedom) reveals a statistically significant difference across the entire sample (first row of Table 2). The second and third rows of Table 2 demonstrate that comparisons remain statistically significant when the affective illness groups are combined. The next two rows demonstrate that the combined affective group significantly differs from the healthy controls and the schizophrenia group, respectively. Finally, the last row of Table 2 reflects a specific comparison of people with schizoaffective disorder with people with schizophrenia, again demonstrating a significant difference. Because gender differences across groups were noted, all comparisons in Table 2 were re-analysed using multinomial logistic regression with haplotype and gender as predictors. For all comparisons, effects of gender were negligible, and all haplotype effects in Table 2 remained statistically significant in the regression analyses.

As demonstrated in the final column of Table 2, only one SNP (rs7103411) was consistently associated with diagnostic status in a manner parallel to the common haplotype. This was the strongest tag SNP for the haplotype, insofar as it had the highest minor allele frequency and was therefore most informative for identification of uncommon haplotypes. However, we also note that for each comparison, *P*-values were slightly lower (i.e. stronger) for the full haplotype, indicating that additional individuals with rare haplotypes were not fully captured by rs7103411. Specifically, four participants who were homozygous for the common allele at rs7103411 were carriers of rare haplotypes and three of these were healthy controls (the remaining one had bipolar disorder). Thus, use of the haplotypes results in a slightly more effective differentiation of cases and controls, resulting in an additional 1.4% reduction in common haplotype frequency in controls. By contrast, the Val66Met SNP (rs6265) examined in isolation was only significant in the comparison of healthy controls *v.* all individuals with schizoaffective or major affective disorder.

Discussion

Results of the present study support the hypothesis that *BDNF* variation is associated with psychiatric disorders with a primary affective component. This association cuts across several traditional DSM–IV diagnostic categories, consistent with the oft-repeated complaint that the current categorical structure of the DSM system does not effectively describe the underlying biology of the disorders.[27] Further, the present study provides

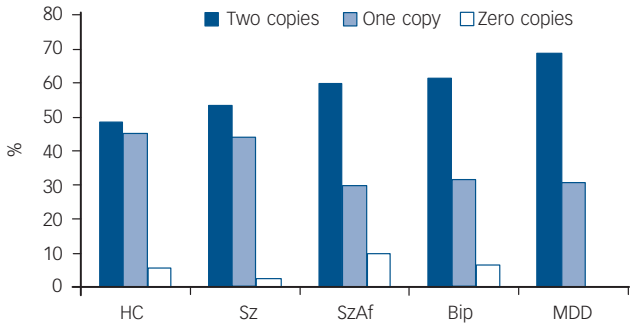

Fig. 2 Frequency of two, one and zero copies of the common AGAGT haplotype for members of the five diagnostic groups.

HC, healthy control; Sz, schizophrenia; SzAf, schizoaffective disorder; Bip, bipolar disorder; MDD, major depressive disorder.

Table 2 Statistical tests of haplotype frequencies (two, one, or zero copies of the common haplotype) across groups.

Comparison	*n*	χ^2	d.f.	*P*	Significant SNPs[a]
5 group: HC *v.* Sz *v.* SzAf *v.* Bip *v.* MDD	593	17.5	8	0.026	rs7103411
4 group: HC *v.* Sz *v.* SzAf *v.* (Bip+MDD)	593	15.5	6	0.017	rs7103411
3 group: HC *v.* Sz *v.* (SzAf+Bip+MDD)	593	13.2	4	0.010	rs4923463, rs7103411
2 group: HC *v.* (SzAf+Bip+MDD)	385	8.5	2	0.015	all
2 group: Sz *v.* (SzAf+Bip+MDD)	373	9.5	2	0.008	rs7103411
2 group: Sz *v.* SzAf	268	9.2	2	0.009	rs4923463, rs7103411

HC, healthy control; Sz, schizophrenia; SzAf, schizoaffective disorder; Bip, bipolar disorder; MDD, major depressive disorder.
a. Final column indicates individual single nucleotide polymorphisms (SNPs) that demonstrated nominally significant (*P*=0.05) genotypic effects for the given comparison.

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explicit support for the model proposed by Craddock *et al*,[3] in which schizophrenia, schizoaffective disorder and bipolar disorder are seen as partially overlapping constructs against a background of genetic susceptibility to more specific traits such as psychosis or mood disturbance. Future studies incorporating dimensionalised ratings of psychopathology across multiple dimensions would be helpful in elaborating this model more fully.

Importantly, schizoaffective disorder haplotype frequencies were found to be similar to other affective disorders, and dissimilar from schizophrenia and healthy controls in the present study. To our knowledge, this is the first molecular genetic study to report such a distinction. In our prior study of *DISC1*,[28] allelic heterogeneity was observed such that people with schizophrenia, schizoaffective disorder and bipolar disorder all significantly differed from controls, but at different SNP loci within the gene. Similarly, a recent linkage study of schizoaffective disorder (also the first of its kind), demonstrated a risk locus near *DISC1*.[29] In that study, no evidence of linkage was found on chromosome 11p near *BDNF*. That negative result is not inconsistent with the present study, insofar as the linkage study examined pedigrees derived roughly equally from studies of probands with schizophrenia and probands with bipolar disorder. Thus, the linkage study was designed to identify risk genes common to both disorders, such as *DISC1*. Another suggestive locus reported in the schizoaffective linkage study was at chromosome 22q11, and we have previously reported that a single *COMT* haplotype increases risk for all disorders in our sample.[6] At the same time, other genetic variants predisposing to psychotic illness may be shared between schizophrenia and schizoaffective disorder, but not pure affective disorders.[3]

In the present study, the haplotype more commonly observed in people with affective diagnoses contained the valine allele at Val66Met. Thus, results are consistent with several prior studies identifying an over-transmission of the Val66Met valine allele to individuals with bipolar disorder,[13–16] and no effect of this polymorphism on risk for schizophrenia *per se*.[30] Notably, one study demonstrating an over-representation of the valine allele in a schizophrenia sample included an unspecified proportion of individuals with schizoaffective disorder.[19] Another identified a very rare *BDNF* haplotype that was associated with a depression subphenotype within a schizophrenia cohort.[18]

The present study also extends prior genetic association findings on *BDNF* in primary affective disorder by demonstrating association with bipolar and unipolar affective disorders in a general population case–control sample. Most prior case–control association studies of *BDNF* Val66Met in bipolar disorder have been negative[31] (except for one),[32] although two studies have reported association with the rapid cycling subtype.[16,33] Although a few prior studies have reported increased Val66 in childhood-onset and geriatric-onset major depressive disorder,[17,34,35] to our knowledge, no studies have demonstrated association of Val66Met with major depression in a general White population.

It is perhaps counterintuitive that the more common haplotype was associated with increased risk for illness in the present study. One potential explanation of our findings is that the common haplotype may carry deleterious variants, not directly genotyped in our study, which are individually rare but have accumulated in the population over time.[36] However, it is also notable that the genetics literature to date carries numerous examples of common alleles associated with disease. Approximately one-third of all significant illness-based genomewide association results have been with the common allele.[37] In psychiatry, a recent study demonstrated that the most common haplotype of the *PPP1R1B* (DARPP-32) gene is associated with increased risk for schizophrenia;[38] intriguingly, this common risk haplotype was associated with enhanced brain function. Similarly, the *BDNF* Val66 allele is associated with larger hippocampal volumes[39] but may lead to heightened risk for affective illness. It is important to note that these associations are by no means deterministic, and pleiotropy is likely to provide multiple positive and negative effects of a given polymorphism across a population. For example, a promoter region variant (the minor allele at rs4950928) in *CHI3L1* has been associated with increased risk for schizophrenia[40] but decreased risk for asthma.[41]

Limitations

As described above, our primary findings represent novel extensions of the *BDNF* association literature. However, it is important to emphasise that the genetic association occurs at the group level, and is not diagnostic for any individual case. Additionally, it should be noted that the sample sizes of the individual affective disorders groups were relatively modest for genetic association studies, and larger samples will be needed to confirm our results. Nonetheless, sample size for the primary, full-group comparisons was robust (total n approaching 600), yielding statistically significant results. In this context, it is notable that significant differences were obtained in sub-comparisons with smaller numbers (Table 2), but not in the largest two-group comparison (schizophrenia group *v.* controls, total $n > 400$). This contrast suggests that Type I error is not a likely explanation of our results, and that significant results for the affective disorders group were less likely to be a result of an atypical healthy control sample. Although our results are consistent with prior theory and literature as described above, lack of additional replication samples means that the possibility of false-positive findings cannot be excluded. In designing replication studies, it is important to acknowledge the trade-off between large multisite studies (with increased ascertainment, diagnostic and environmental heterogeneity) *v.* the ascertainment of smaller yet potentially more reliably ascertained cohorts of participants (patients and controls).[42]

Population stratification is a potential confound in any case–control study. In our recent genomewide association study of a case–control cohort collected at our institution,[43] we tested for stratification using 210 ancestry informative markers selected for maximal informativeness (minor allele frequencies > 0.50 between ethnic groups) and did not observe any deviation from that predicted by chance, suggesting that undetected substructure is not present in our geographically homogeneous population. Moreover, none of the participants ascertained at the Zucker Hillside Hospital deviated from a single population as assessed by the structure program (http://pritch.bsd.uchicago.edu/software.html). We also note that, although undetected substructure in US White populations is a theoretical concern, empirical data collected to date suggests that self-identified race/ethnicity (SIRE) is sufficient with which to match study groups from the US population. Tang and colleagues[44] examined this question in 3636 people assessed with SIRE information, genotyped with 326 microsatellite markers and analysed with the structure program. These investigators reported 'a nearly perfect correspondence between genetic cluster and SIRE for major ethnic groups living in the United States' (p. 273), and suggested that the critical information needed to avoid confounding is SIRE, not necessarily additional genetic marker information.

Mechanism

It is worth noting that the risk haplotype in the present study contains the Val66Met valine allele. Therefore, results of the present study and others listed above could be described as

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demonstrating that the Met allele (or haplotypes that carry it) may be protective against affective disorders. The Val66Met substitution is a logical candidate for a causative variant, in one or more ways. First, this polymorphism may diminish the dendritic localisation and secretory activity of *BDNF*, thereby altering the amount of mature protein available for activation of the TrkB pathway.[12] Second, it may affect the level and extracellular processing of proBDNF that acts through $p75^{NTR}$, downregulating synaptic plasticity through long-term depression via a bidirectional pathway.[45] Diminished synaptic strength among certain circuits, in particular excitatory glutamatergic networks, may contribute to a protective mechanism against development of affective disorders.

Although this mechanism is clearly speculative in terms of the pathophysiology of affective disorders, recent animal studies support this possibility. For example, *BDNF* and its receptor have been found in terminals critical to associative learning within the amygala,[46] and changes in *BDNF* expression in the amygdala have been linked specifically to the acquisition of fear-conditioned responses.[10] Similarly, *BDNF* knockdown in the nucleus accumbens abolishes the learned avoidance response to aggression (social defeat stress);[11] chronic, but not acute, administration of antidepressants had the same effect. Future studies in humans can extend these observations by examining the relationship of *BDNF* variation with neuroanatomic and functional measures of the amygdala and basal ganglia.

This line of research holds promise to enhance our understanding not only of the mechanisms underlying affective disorders, but also their treatment.[20] Several recent studies have demonstrated that treatment with antidepressants or mood stabilisers upregulates *BDNF* expression.[47] Moreover, *BDNF* polymorphisms may also affect response to both mood stabilisers and antidepressants.[48]

Finally, although results of the present study are consistent with prior data concerning the functional effects of the Val66Met polymorphism, it should be noted that the haplotype contained several markers that have not been previously examined. Whereas all five markers, including Val66Met, significantly differentiated healthy controls from the combined sample of people with affective illnesses (fourth row of Table 2), only rs7103411 consistently differentiated the diagnostic groups as effectively as the entire haplotype. It is possible that the conflicting results of prior studies examining only Val66Met reflect effects of different haplotypic backgrounds.

It should be noted that our survey of genetic variation at the *BDNF* locus was not exhaustive: the Phase II HapMap indicates that additional haplotypes exist within the region examined in the present study, and potential splicing variants in the 5′ region of the gene were not examined in the present study. It also cannot be ruled out that prior associations of Val66Met to affective disorders reflect linkage disequilibrium with a distal variant.

Nevertheless, results of the present study suggest that negative conclusions of recent meta-analyses[31,49] of *BDNF* Val66Met may be premature; notably, these meta-analytic reports combined studies across multiple ethnicities with very different baseline allele frequencies and excluded several positive reports from family-based samples. Moreover, the combined sample sizes in the psychiatric genetics literature may be inadequate at this point to reach definitive conclusions. A prominent recent example from the diabetes literature illustrates a seeming paradox in the relationship between sample size and detection of genetic associations. Specifically, the association of the *PPARG* Pro12Ala polymorphism with type 2 diabetes was initially identified in a sample of 91 people.[50] Although several subsequent studies with hundreds or even thousands of participants failed to replicate the association, the most recent analysis of tens of thousands of participants has definitively confirmed the association.[51] Thus, further research on *BDNF* as a promising candidate for affective psychopathology is warranted, especially in samples that may be informative for future nosological refinements.

Todd Lencz, PhD, Center for Translational Psychiatry, Feinstein Institute for Medical Research and Division of Psychiatry Research, The Zucker Hillside Hospital, New York; **Robert H. Lipsky**, PhD, Laboratory of Neurogenetics, National Institute on Alcohol Abuse and Alcoholism, Bethesda; **Pamela DeRosse**, PhD, Division of Psychiatry Research, The Zucker Hillside Hospital; **Katherine E. Burdick**, PhD, Center for Translational Psychiatry, Feinstein Institute for Medical Research and Division of Psychiatry Research, The Zucker Hillside Hospital, New York; **John M. Kane**, MD, Center for Translational Psychiatry, Feinstein Institute for Medical Research and Department of Psychiatry, The Zucker Hillside Hospital; **Anil K. Malhotra,** MD, Center for Translational Psychiatry, Feinstein Institute for Medical Research and Division of Psychiatry Research, The Zucker Hillside Hospital, New York, USA.

Correspondence: Todd Lencz, The Zucker Hillside Hospital, Psychiatry Research, 75–59 263rd Street, Glen Oaks, New York 11004, USA. Email: lencz@lij.edu

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