A genetic analysis of the validity of the Hypomanic Personality Scale


Objectives: Studies of mania risk have increasingly relied on measures of subsyndromal tendencies to experience manic symptoms. The measures of mania risk employed in those studies have been shown to predict manic onset, to show familial associations, and to demonstrate expected correlations with psychosocial variables related to bipolar disorder. However, little work has been conducted to validate such measures against biologically relevant indices, or to consider whether early adversity, which has been shown to be highly elevated among those with bipolar disorder, is related to higher scores on mania risk measures. This study tested whether a well-used, self-report measure of vulnerability to mania is associated with several candidate genes that have previously been linked with bipolar disorder or with early adversity. Interactions of genes with early adversity in the prediction of mania vulnerability were also tested.

Methods: Undergraduate students from the University of Miami (Coral Gables, FL, USA) (N = 305) completed the Hypomanic Personality Scale and the Risky Families Scale, and provided blood for genotyping.

Results: Findings indicated that the Hypomanic Personality Scale was related to a number of dopamine-relevant polymorphisms and with early adversity. A polymorphism of ANKK1 appeared to specifically increase mania risk in the context of early adversity.

Conclusions: These results provide additional support for the validity of the Hypomanic Personality Scale.

Several different measures have been developed to assess risk for mania, including the General Behavior Inventory (GBI) (1), the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego (2), and the Hypomanic Personality Scale (HPS) (3). Each of these measures assesses tendencies towards subsyndromal manic symptoms as well as personality traits thought to be related to bipolar disorder (BD), such as positive affectivity. Substantial evidence has accrued that the HPS and the GBI prospectively predict the onset of diagnoses of BD. For example, over a 13-year follow-up period, 73% of persons at high risk for mania as defined by the HPS developed diagnosable symptoms of bipolar spectrum disorder (4). Moreover, a substantial body of research indicates that many of the psychosocial variables that predict the course of mania within BD are also robustly correlated with these measures of mania risk (5–7). These measures of risk provide an opportunity to study basic risk factors without the confounding influence of the lifestyle, health, and medication changes that emerge as bipolar symptoms reach a diagnosable level.

Surprisingly, researchers have not determined whether genetic or early adversity correlates of mania risk measures parallel those that have been documented as relevant to bipolar diagnoses. The goal of the study reported here was to consider whether one commonly used, well-validated measure of mania, the HPS, demonstrates an association with genetic polymorphisms related to BD.
and with early adversity. HPS scores have been found to show familial associations (8) but, to the best of our knowledge, researchers have not examined polymorphisms relevant to this or other mania risk scales. We focus here specifically on genes relevant to the function of dopamine and serotonin, as well as brain-derived neurotrophic factor (BDNF).

We begin with evidence regarding serotonin. Imaging studies suggest diminished serotonin transmission among persons diagnosed with BD in key regions of the brain (9). Euthymic persons diagnosed with BD have been found to display a blunted response to agents that increase the availability of serotonin (10). First-degree relatives of those with BD show elevated mood reactions and more of a decline in neurocognitive tasks after acute tryptophan depletions, a procedure that temporarily depletes serotonin levels, compared to matched controls (11, 12). Taken together, the evidence implicates serotonin dysfunction in the etiology of BD.

Of the multiple genes related to serotonin function, the serotonin transporter region has been studied relatively extensively within BD. Meta-analyses of the more than 20 studies of the serotonin transporter region (5-HTTLPR) in BD have yielded positive but small effects [e.g. (13, 14)]. Beyond the serotonin transporter, meta-analyses indicate that polymorphisms of the tryptophan hydroxylase 1 (TPH1), tryptophan hydroxylase 2 (TPH2), and serotonin 1A receptor genes are significantly associated with BD (15–17). Here, then, we considered a set of genetic polymorphisms relevant to serotonin function.

In addition to serotonin, evidence for dopamine dysfunction in BD has accrued across imaging and pharmacological paradigms (18). Several studies have shown that mania can be triggered by administration of stimulants, which increase dopamine activity (19), as well as by dopamine precursors, such as L-dopa (20). Consistent with the idea of a super-sensitivity of dopamine receptors, several researchers have used sensitization paradigms to understand mania. Extensive animal research has documented that, with repeated administration of amphetamines, dopamine receptors in the nucleus accumbens become more sensitive (21). In human studies of sensitization, one of the chief measures of sensitization effects is the Young Mania Rating Scale (22), which is the most commonly used measure of symptom severity within the literature on BD. Intriguingly, during first episodes, people with mania demonstrate a profile of responses to repeated administration of amphetamines suggesting that they have already undergone sensitization of dopamine receptors (22). Positron emission tomography studies also indicate higher availability of D1 receptors in the prefrontal cortex and of striatal dopamine transporter (DAT) among persons with BD (23, 24). Beyond the human studies, researchers have used mice with several different manipulations of the DAT as animal models of mania (25, 26).

Given this evidence for a role of dopamine in the genesis of manic symptoms, several researchers have examined the role of dopamine-relevant genes in BD. Multiple studies support associations of BD with the dopamine transporter variable number tandem repeat (VNTR) (SLC6A3) (27), with the A1 polymorphism of the dopamine D2 receptor gene (DRD2) ANKK1 (28) and with the dopamine D4 receptor gene 48-base-pair-repeat (DRD4.2) polymorphism (29). The A1 allele of ANKK1 has also been found to be more common among those with bipolar II disorder as compared to controls (30). No consistent findings have emerged for polymorphisms in the D1 and D3 receptor genes (29, 31). Catechol-O-methyltransferase (COMT) is involved in the degradation of catecholamines, including dopamine. The Met allele of COMT has been related to greater risk for BD (32).

Finally, considerable research has focused on BDNF in BD. Strong functional relationships between BDNF and dopamine have been noted. For example, spikes of dopamine appear to enhance levels of BDNF, playing a critical role in memory consolidation processes within the hippocampus (33). BDNF and dopamine also appear to interact within the nucleus accumbens (34). BDNF has been implicated in stressor-related cell death in key neural regions such as the hippocampus and prefrontal cortex, regions implicated in mood disorders (35). Across several family studies, BD was characterized by high levels of the Val 66 allele of Val66Met (rs6265) (36–38), a finding that has been replicated with a case–control design (39). Others have found links of BD with other BDNF single nucleotide polymorphisms (40). Nonetheless, in one meta-analysis of 13 studies on BD, no consistent effect emerged for BDNF with BD (41). LIN7 is the first gene downstream of BDNF. Although it has not been examined in BD, the presence of the A allele has been related to risk of attention-deficit hyperactivity disorder, a condition that is highly comorbid with BD (42).

In examining the effects of these genes, it is important to note that gene × gene interactions have been documented, with particular evidence that polymorphisms in COMT and BDNF can modulate the influence of other dopaminergically
relevant genes (43, 44). Within the current study, then, we tested whether gene × gene interactions were related to mania risk scores.

Beyond the effects of genes, a growing body of research supports gene × environment interactions in psychopathology. Most relevant here, childhood adversity appears to amplify the effects of polymorphisms of the serotonin transporter (45) and BDNF genes (46, 47) on emotion dysregulation, as well as on related biological correlates, such as increased salivary cortisol and abnormal hippocampal, amygdala, and prefrontal cortex volumes (48). Although such gene × environment interactions have received less focus in BD (49), rates of early adversity have been shown to be highly elevated among persons diagnosed with BD and to be associated with worse outcomes across a range of studies (50). Early adversity has also been found to moderate the influence of dopaminergic genes on dopamine function (51). Here, then, we consider two novel questions of whether early adversity is related to mania risk and whether early adversity amplifies the links of genes with mania risk.

In sum, BD has been related to genetic polymorphisms related to serotonin, dopamine, and BDNF. In this study, we evaluated whether the HPS, a commonly used and well-validated measure of mania risk, shows parallel associations with this set of genetic polymorphisms. To do so, students were genotyped on a set of polymorphisms relevant to dopamine, serotonin, and BDNF dysfunction and completed the HPS and the Risky Families Scale.

Methods

The methods were approved before data collection by the University of Miami Institutional Review Board (Coral Gables, FL, USA). Undergraduate students read a general description of the project on a departmental website; interested persons signed up for group sessions (approximately 20 per session). All gave informed consent (N = 305; 196 female), then completed the HPS and Risky Families Scale (along with other self-reports not relevant to this article), and had blood drawn for genotyping.

The mean age of the sample analyzed was 18.65 years [standard deviation (SD) = 1.692 years, range: 17–33 years]; the sample self-identified as follows: 52% (n = 159) Caucasian, 21.2% (n = 65) Hispanic, 5.6% (n = 17) African American, 3.9% (n = 12) Caribbean, 6.8% (n = 21) Asian, and 10.4% other or unspecified.

The HPS

The HPS (3) was developed to identify people at risk for mania or hypomania (bipolar spectrum disorders). It contains 48 true/false self-report items (e.g., ‘There have often been times when I had such an excess of energy that I felt little need to sleep at night’, and ‘I often feel excited and happy for no apparent reason’). In previous research, more than 78% of undergraduates with high HPS scores (two or more SDs above the mean) met diagnostic criteria for bipolar spectrum disorders (3). Over a 10-year period, high scorers were found to have a ninefold higher prevalence of hypomanic episodes compared to low scorers (4). Eckblad and Chapman (3) reported that the HPS correlates well with other screening instruments for mania and is uncorrelated with a Social Desirability Scale. The measure has high reliability (15-week test–retest reliability = 0.81; alpha = 0.87). In this sample, internal consistency was high (alpha = 0.86). The distribution approximated normalcy (skew = 0.25, kurtosis = −0.31), with a mean score of 18.898 (SD = 8.031). In the sample of 305, only 11 persons met or exceeded the value of 35, the cutoff for elevated scores [two SDs above the mean of the validation study (3)].

Childhood adversity

Childhood adversity was measured using the self-report Risky Families Scale (52). This 13-item measure was adapted from an earlier scale designed to assess the relation of family stress to mental and physical health outcomes in adulthood (53). Respondents are asked to rate 13 aspects of their early family environment on five-point scales ranging from 1 (not at all) to 5 (very often or very much). Items assess the extent to which the respondent had felt loved and cared for (reversed); was insulted, put down, sworn at, or made to feel threatened; was shown physical affection (reversed); was pushed, grabbed, shoved, or slapped; was verbally abused; was physically abused; observed quarreling or shouting between parents; observed violence or aggression between family members; lived with a substance abuser; lived in a well-organized, well-managed household (reversed); and the extent to which family members knew what the child was doing (reversed). Item responses are averaged to yield scores ranging from 1 to 5 (mean = 1.840, SD = 0.587) with higher values representing a more adverse early family environment. The measure has been validated against ratings from clinical interviews (52). Scores on this scale have also been found to interact with the 5-HTTLPR
polymorphism to predict current depression symptoms (54, 55). Internal consistency was adequate in this sample (alpha = 0.86).

Polymorphisms

Genotyping was performed at the laboratories of the Hussman Institute of Human Genomics, University of Miami Miller School of Medicine. Single nucleotide polymorphism genotyping was conducted using Taqman allelic discrimination assays from Applied Biosystems (ABI, Grand Island, NY, USA). Genomic DNA (3 ng), which was extracted from whole blood according to established protocols, was used in the amplification reaction. Cycling was performed on GeneAmp PCR Systems 9700 thermocyclers from ABI, with conditions recommended by ABI. End-point fluorescence was measured on the ABI 7900 HT system from ABI. Genotype discrimination of results was then conducted using ABI’s 7900 HT Sequence Detection Systems version 2.3 analysis software. To ensure genotyping accuracy, 32 quality control samples per 384 plates that matched within and across plates were included. Sample call rates across all polymorphisms discussed here were 99.7%.

Genotyping was performed for the GrA (valin-ermethionine) variation at position 758 of the BDNF coding sequence (rs6265); for the single nucleotide polymorphism located in exon 8 of the ANKK1 gene; and for the Met to Val substitution at codon 158 of the COMT gene, all using Taqman allelic discrimination. Custom analyses, conforming to established protocols, were used for DRD4 and 5-HTTLPR. BDNF frequencies were Val/Val 68%, Val/Met 26%, and Met/Met 6%. ANKK1 frequencies were GG 61.3%, AG 34.1%, and AA 4.6%. COMT frequencies were Met/Met 19%, Val/Met 52%, and Val/Val 29%. DRD4 frequencies were short/short 66.6%, short/long 29.1%, and long/long 4.3%. 5-HTTLPR frequencies were LL 33.3%, SL 47.1%, and SS 19.5%. LIN-7C frequencies were AA 26.8%, AT 47.0%, and TT 26.2%. Serotonin receptor 1B6 (HTR1B6) frequencies were CC 55.6%, CG 39.8%, and GG 6.6%. Serotonin receptor 1B13 (HTR1B13) frequencies were AA 7.9%, TA 40.0%, and TT 52.1%. TPH1 frequencies were CC 37.2%, AC 47.0%, and AA 15.8%. TPH2 frequencies were GG 56.4%, GT 36.7%, and TT 6.9%. All polymorphisms in the sample were in Hardy–Weinberg equilibrium.

Because of the relatively low frequency of persons homozygous for rare alleles, HTR1B6, HTR1B13, TPH2, ANKK1, DRD2 C deletion, DRD4, and BDNF were collapsed into two levels for analyses (0, 1), with those who were either homozygous or heterozygous for the rare variant considered as one level. 5-HTTLPR, TPH1, COMT, and LIN-7C were examined with three levels (0, 1, 2). Generally, the rare allele was coded as a higher score, with the exception of BDNF, LIN-7C, and COMT, where the more common allele is associated with risk.

Data analytic strategy

In this analysis we began with a set of multilocus genetic composites, followed by tests of individual genes. One multilocus composite score reflected the mean of dopamine-relevant polymorphisms (56), a second composite score reflected the mean of serotonergic relevant polymorphisms, and a third reflected the mean of BDNF and LIN7. The dopamine composite summarized COMT, DRD4, DRD2 C deletion, and ANKK1 (mean = 0.525, SD = 0.266, range: 0–1.25). The serotonergic composite included HTTLPR, TPH1, TPH2, HTR1B6, and HTR1B13 (mean = 0.613, SD = 0.278, range: 0–1.40). The mean of the BDNF/LIN-7C composite was 0.652 (SD = 0.383, range: 0–1.5). Correlations among the composite scores were quite small, |r| < 0.05. Genetic scores were z-transformed before conducting analyses. Interaction terms were created by multiplying centered Risk by the relevant genetic variable. All analyses were completed using SPSS version 21 (IBM, Armonk, NY, USA), with an alpha level of 0.05.

Results

Hierarchical regression analysis was used to examine the effects of the genes on HPS scores. Gender and ethnicity (minority or not) were entered using forced entry in the first block, family risk was entered using forced entry in the second block, the serotonin, dopamine, and BDNF/LIN-7C composite scores were entered using forced entry in the third block, interactions of the three genetic scores with each other were tested in the fourth block using forward selection, and interactions of the three genetic scores with Risky Families scores were tested in the fifth block using forward selection.

Control variables (gender and ethnicity) entered in the first block accounted for 0.8% of the variance [F-change (2,302) = 1.197, p = 0.30]. Risky Families score entered in the second block accounted for 7% of the variance [F-change (1,301) = 22.314, p < 0.001], and genetic variables entered in block 3 accounted for an additional
4.4% of the variance [F-change (3,298) = 5.001, p < 0.002]. As shown in Table 1, there was no direct effect of gender or ethnicity on HPS scores. The Risky Families score was significantly related to HPS scores. The serotonergic composite was not significantly related to HPS scores, but the dopaminergic composite score and the BDNF/LIN-7C composite scores were both related to HPS. None of the interaction terms, either among genetic composites or of genetic composites with Risky Families scores, were significant. The overall model was significant [R^2 = 0.121, F (6,298) = 6.817, p < 0.001].

Supplemental analyses tested whether the effects of the three genetic composite scores interacted with gender or ethnicity. No interaction terms with gender or ethnicity were significant (all t < 1.5, all p > 0.14).

Separate regression analyses were also conducted (controlling for gender, ethnicity, and Risky Families scores) to examine individual effects of specific dopamine-relevant and BDNF-LIN-7C polymorphisms (see Table 2). DRD4, DRD2 C Deletion, and BDNF were not significantly related to HPS scores. There were, however, significant effects of LIN-7C (such that the A allele was related to higher HPS scores than the T allele) and COMT (such that the Met allele was related to higher HPS scores than the Val allele). Although ANKK1 was not significantly related to HPS scores as a main effect, the interaction of ANKK1 and Risky Families scores contributed significant variance. The form of the interaction (Fig. 1) indicated that the effect of early adversity on the HPS scores of A carriers was quite substantial [beta = 0.39, t (299) = 4.720, p < 0.001]. The effect of adversity on those homozygous for the G allele was also significant [beta = 0.16, t(299) = 2.042, p < 0.05], but significantly smaller.

Discussion

The findings provide substantial support for the hypothesis that mania risk is related to early adversity and to genetic polymorphisms that influence dopamine function. More specifically, mania risk was associated with a composite of dopamine-relevant genes, and with specific polymorphisms of ANKK1 and COMT. Hence, findings parallel those of the literature concerning diagnosed BD in pointing toward the importance of dopamine-relevant genes, and particularly to the Met allele of COMT and the A allele of ANKK1 (28, 30, 32). The findings also extend work showing a link of the A allele of LIN-7C to attention-deficit hyperactivity disorder (42), by suggesting that this polymorphism may also be relevant to mania risk. As little previous research has examined the role of LIN-7C in disorders, current findings add to an early literature suggesting that this polymorphism may have promise for understanding psychiatric problems. Findings indicated that genes and early adversity may jointly intensify the risk of higher mania scores, as the effects of early adversity were more pronounced among A carriers of ANKK1 than among those who were homozygous for the G allele.

Unlike the previous literature on diagnoses of BD, our findings did not suggest a role of polymorphisms relevant to serotonin or BDNF as relevant to mania risk. This may reflect the nature of the content of the HPS scale, which tends to emphasize positive affectivity, social dominance, and tendencies toward hypomanic symptoms, rather than emotion dysregulation and lability. Previous research has suggested that serotonergic function and BDNF may both be relevant for cognitive and effortful control over emotion (57, 58). Other mania risk scales, such as the GBI, which provide more coverage of this type of content, might

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BDNF = brain-derived neurotrophic factor; SE = standard error.

*p < 0.01.
Current findings are consistent with the idea that manic tendencies, as measured using scales such as the HPS, are heritable. This idea is also consistent with a series of findings that unaffected family members of those with BD are characterized by diagnoses of cyclothymia and hyperthymia, and also obtain high scores on measures of heightened positive affectivity and mood lability (59–61). Similarly, HPS scores have been shown to demonstrate a familial association (8). The present findings extend this work, however, in that previous family studies could not disentangle whether such trait-like elevations were related to environmental or genetic influences. The present findings also extend a growing body of research documenting high rates of childhood abuse and early adversity among those diagnosed with BD (50). This set of findings is highly consistent with research showing that early adversity is associated with compromised development of the prefrontal cortex and with difficulties with emotion regulation (45–48). The present findings, however, extend this work by demonstrating that early adversity is correlated with a measure of mania risk.

Although the findings provide promising evidence for the validity of the HPS and, more broadly, for research paradigms focused on subsyndromal symptoms and affective traits, the findings must be interpreted cautiously. Our study was small for genetic analyses, limiting our ability to consider potentially important effects of gender and ethnicity. The sample size also had limited statistical power for examining polymorphisms, such as the serotonin transporter polymorphism, that have been found to have quite small effects in BD (15). We are also limited to a focus on a relatively small set of polymorphisms. Extensive previous research has considered the role of other polymorphisms in BD, such as those of the DISC-1 (62) and ANK3 genes (63). A focal goal, then, will be to examine how mania risk inventories relate to a broader set of polymorphisms in larger samples. Another broad-level goal will be the identification of factors, both biological and psychological, that protect those at high risk from developing diagnosable forms of the disorder, as many of those with high scores on the HPS will not convert into bipolar disorder. Such work would build on several recent examples suggesting that biological and psychological parameters may help predict the conversion from at-risk to diagnosed status (64, 65). Highly validated scales for measuring risk may help these ongoing research goals. As a first study of how early adversity and genetic polymorphisms correlate with the HPS, the current findings provide support for ongoing work on the parallels between mania risk scales and diagnoses of BD.

### Table 2. Individual effects for dopamine-related genes, brain-derived neurotrophic factor (BDNF), and LIN-7C, controlling for gender, ethnic minority status, and Risky Families scores (N = 305)

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<sup>a</sup>p < 0.05.

**Fig. 1.** Mania risk [Hypomanic Personality Scale (HPS)] as a function of ankyrin repeat and kinase domain containing 1 (ANKK1) status and Risky Families score.

display stronger associations with these polymorphisms.
Acknowledgements
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Disclosures
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References


Genetic polymorphisms related to the HPS