BRIEF RESEARCH COMMUNICATION

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Suggestive Linkage at 9p22 in Bipolar Disorder Weighted by Alcohol Abuse

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Bipolar disorder (BP) is a highly heritable disorder, however attempts to map genetic risk factors are challenging. One possible reason for these difficulties is the genetic heterogeneity of BP. Hence, focusing on clinically homogeneous families to create a genetically more homogeneous sample may increase the power of finding a specific variant. Alcohol abuse (AA) and alcohol dependence (AD) are familial in BP families, and these families may carry a specific risk variant for BP. We tested this hypothesis by performing a genome-wide linkage scan in 638 pedigrees (1,835 individuals) from the National Institute of Mental Health Genetics Initiative for BP, weighting the evidence for linkage according to the family's frequency of AA or AD. Using AA weighting, we identified a linkage region on 9p22.2 with an NPL score of 3.23. The region had previously been identified in a meta-analysis of linkage in bipolar disorder. We used permutation analysis to assess if weighting by AA increased the linkage signal more than expected by chance and observed a significant *P*-value ($P = 0.048$). Therefore, the genetic risk factor for BP on 9p22.2 has an increased effect in families with high levels of AA. In summary, we present an example of using covariates such as AA and AD to define subtypes of BP, demonstrate how using such subtypes can improve the power of a linkage scan, and demonstrate statistical approaches to validate the suggested interaction.

Key words: bipolar disorder; genetics; alcoholism; mood disorder; linkage analysis

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Bipolar disorders (BP) are recurrent, episodic disorders of mood characterized by manic or hypomanic and depressive episodes affecting 1–2% of the population [Merikangas et al., 2007]. BP has concordance rates of 67% in monozygotic twins and 20% in dizygotic twins and first-degree relatives [Bertelsen et al., 1977] and an estimated heritability of 59–87% [Smoller and Finn, 2003]. Linkage studies in BP have had promising, but mixed, results. Three recent meta-analyses of BP linkage studies show evidence for linkage in six different areas: chromosome 9p and 10q [Segurado et al., 2003], 13q and 22q [Badner and Gershon, 2002], and 6q and 8q [McQueen et al., 2005]. One possible reason for disparate findings in different studies is clinical heterogeneity in the diagnosis of BP [Kelsoe, 2003]. If such clinical heterogeneity is the effect of multiple underlying risk alleles, families will segregate different risk alleles and thus provide conflicting information. Under this model, concentrating the analysis on families that carry a specific variant will increase the power of these studies substantially. One approach to identify such a subset of families is to study linkage in a more clinically homogeneous sample. Recent linkage studies of BP have used this approach with age of onset [Faraone et al., 2004; Lin et al., 2005; Zandi et al., 2007], comorbid anxiety [Zandi et al., 2007], comorbid panic disorder [MacKinnon et al., 1998; Cheng et al., 2006], psychosis [Potash et al., 2003; Cheng et al., 2006; Zandi et al., 2007], and suicidal behavior [Cheng et al., 2006; Willour et al., 2007].

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Here we explore BP in comorbidity with alcohol abuse (AA) or alcohol dependence (AD). AA is defined as continued drinking despite social, legal or interpersonal problems; AD includes physiological tolerance or withdrawal [APA, 2000]. We differentiate between AA and AD because the categories describe different patterns of use: AA can occur when an individual uses alcohol in a manner that seriously interferes with their lives. It may be intermittent, for example in a binge-drinking fashion only during manias or represent a persistent maladaptive pattern of over use, for example, frequent but predictable heavy use with notable personal consequences. Alcohol dependence, on the other hand, describes a level of chronic use that results in physiological consequences (e.g., tolerance) with overwhelming psychological cravings and a repertoire of behaviors centered around using alcohol. Furthermore AA and AD diagnoses describe distinct long-term behavioral patterns; in prospective studies only 3.5% of AA subjects develop AD within 5 years, comparable to 2.5% incidence of AD in subjects with no alcohol-related diagnosis [Schuckit et al., 2001]. Thus, AA is not simply a "first step" to AD, but a different pattern of drinking that persists over time.

AA is comorbid with any BP at a rate of 39.1%; AD at a rate of 23.2% [Merikangas et al., 2007], these rates are twice as high as those in the general population [Hasin et al., 2007]. In a prospective cohort study, risk of AA was increased by pre-existing manic symptoms (OR 2.4 (95% CI 1.2–4.8)), and by a pre-existing diagnosis of BPII (OR 9.1 (95% CI 27–31.2)). The risk of AD was also increased by pre-existing manic symptoms (OR 4.4 (95% CI 1.6–12.7)), and by pre-existing BPII (OR 21.1 (95% CI 6.6–67.5)) [Merikangas et al., 2008]. Clinically, comorbidity of AA/AD with BP is detrimental to the patient in more ways than the added burden of disease. AA/AD is correlated with higher rates of suicidality [Potash et al., 2000; Baldassano, 2006] and increased number of hospitalizations [Cassidy et al., 2001], a less favorable response to lithium [Goldberg et al., 1999] and rapid-cycling [McKowen et al., 2005].

The genetic predisposition to alcoholism has been hypothesized to constitute part of the genetic predisposition to bipolar disorder and vice versa [Winokur et al., 1996, 1998], and this genetic overlap explains the greater propensity for developing both BP and AA/AD. Heritability estimates of AA/AD based on twin studies have been as high as 50–60% [Prescott, 2001]. Furthermore, we and others found AA/AD to be familial in bipolar disorder, indicating that the increased comorbidity may be related to heritable causes [Winokur et al., 1996; Schulze et al., 2006; Nurnberger et al., 2007; Potash et al., 2007; Saunders et al., 2008]. Evidence of heritability for AA/AD and BP, combined with studies of familiality suggest nonlinear interaction of AA/AD and genetic risk variants for BP. In this model such risk variants will be more common in families with large number of members with AA/AD. Thus, we expect stronger signals for linkage in families with high levels of AA or AD. We tested this hypothesis by weighting the evidence for linkage in each family according to the family's frequency of AA or AD. We consider AA and AD separately because they describe differing, enduring patterns of drinking behavior that may have different genetic bases. In addition to directly considering the resulting linkage signal we also test whether our weighting scheme significantly improves the evidence for linkage.

We obtained phenotype and genotype data on 711 pedigrees (5,364 individuals) from the National Institute of Mental Health Genetics Initiative for BP. This sample was collected over 15 years at 10 sites across the country. Methods for collection of this sample have been described elsewhere [Dick et al., 2003; McInnis et al., 2003]. Diagnostic assessment was done using the Diagnostic Interview for Genetic Studies [Nurnberger et al., 1994], and psychiatric diagnoses including mood and substance use disorder diagnoses were assigned using a best-estimate process [Leckman et al., 1982]. Within that sample, four disorders were of interest: BPI (N = 956), schizoaffective disorder-bipolar type (SAB) (N = 72), BPII (N = 128), and major depressive disorder-recurrent (MDDR) (N = 148). We classified subjects into three affectation status models. Model 1 included 635 families with subjects affected by SAB or BPI, model 2 included 637 families affected by SAB, BPI, or BPII, and model 3 included 638 families affected by SAB, BPI, BPII, or MDDR.

Information on alcohol use was collected for 1,835 of these persons; 64% of this subsample were female, and the mean age of interview was 43. The mean age of onset of BP was significantly reduced in both the AA ($P = 0.006$, t-test) and AD ($P = 7.2 \times 10^{-6}$, t-test) groups. AD in BP families was associated with a smaller likelihood of being currently married ($P = 1.6 \times 10^{-5}$, χ^2-test, 1 df), lower mean number of school years ($P = 3.0 \times 10^{-7}$, χ^2-test, 1 df), lower mean number of children ($P = 0.009$, χ^2-test, 1 df), and more episodes of illness ($P = 0.015$, χ^2-test, 1 df).

Individuals were typed for 391 microsatellite markers with an average spacing of 9 cM and average heterozygosity of 0.76 from a modification of the Cooperative Human Linkage Center version 9 [Dick et al., 2003; McInnis et al., 2003]. We used GENEHUNTER-PLUS (GHP) [Kruglyak et al., 1996] to perform multipoint non-parametric linkage analyses using the allele-sharing model (ASM) [Kong and Cox, 1997] analysis found in the GHP package calculating an NPL-score for each locus.

To weight for each pedigree by family levels of AA, we counted the number of individuals with AA in a family regardless of affection status and divided this count by the total number of family members with information known regarding alcohol abuse or dependence. We generated weights for family levels of AD analogously. Under this weighting scheme, 510 families based on AA and 355 families based on AD had a weight of zero (Fig. 1) and were thus ignored in the linkage analysis.

Using these weights, we recalculated NPL-scores for each family and each locus in the genome. Note that families with a weight of zero do not contribute to the evidence for linkage. To assess the significance of the observed increase in NPL score, we performed permutation studies. In each replication, we randomly reassigned the AA weights to the 711 families. Using the randomized weight file we repeated the ASM analysis and recorded the maximum NPL score. The process was repeated 1,000 times providing an empirical distribution. Comparing this empirical distribution with NPL scores generated using the original AA weighting, we generated P-values for these observations. We analogously generated P-values for NPL-scores based on AD weights.

Using AA weighting and affection status model 1, we observed a maximum NPL score of 3.23, with a corresponding LOD of 2.77. This linkage peak was located on chromosome 9p22.2, at 38.45 cM

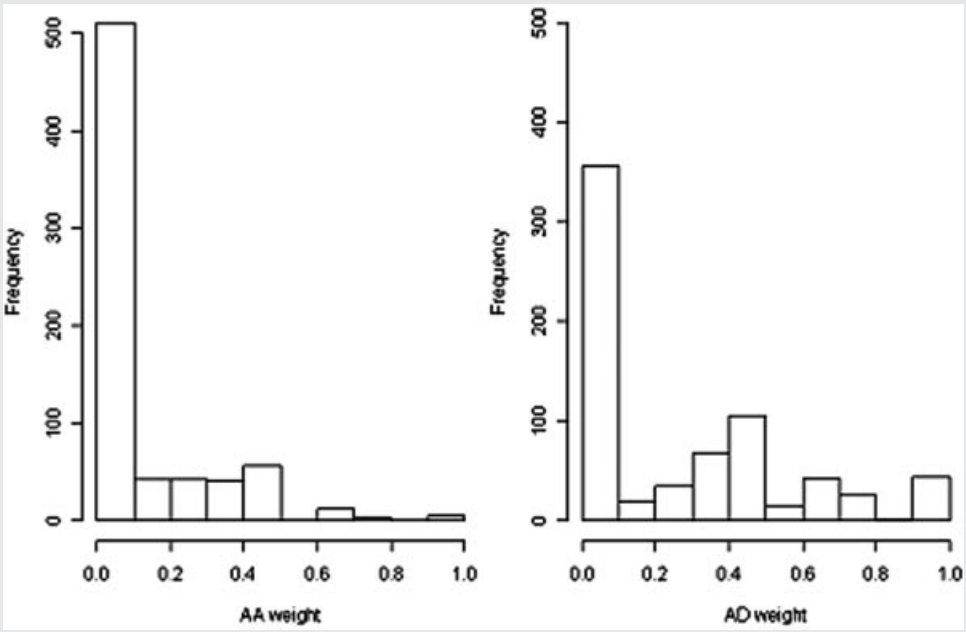

FIG. 1. Number of families with each alcohol abuse (left) or alcohol dependence (right) weight. Weights are a proportion calculated by the number of family members with AA or AD divided by the total number of family members.

marker D9S925 (Fig. 2). This NPL score is a substantive improvement over the NPL-score generated using uniform weights (1.74). Nevertheless, the LOD score does not meet genome-wide significance standard of 3.3; however it is higher than the threshold of 1.9 for suggestive linkage [Lander and Kruglyak, 1995]. Permutation analysis indicated that the improved signal for linkage at 9p22.2 is higher than expected by chance ($P = 0.048$) and thus likely a result of our weighting scheme. The second strongest signal generated using weighting by AA was located on chromosome 3p14 at 77.12 cM, marker D3S4542. The NPL of 2.94 and LOD of 2.53 observed at this locus were above the threshold for suggestive linkage as well. Weighting on AD, we did not observe any regions

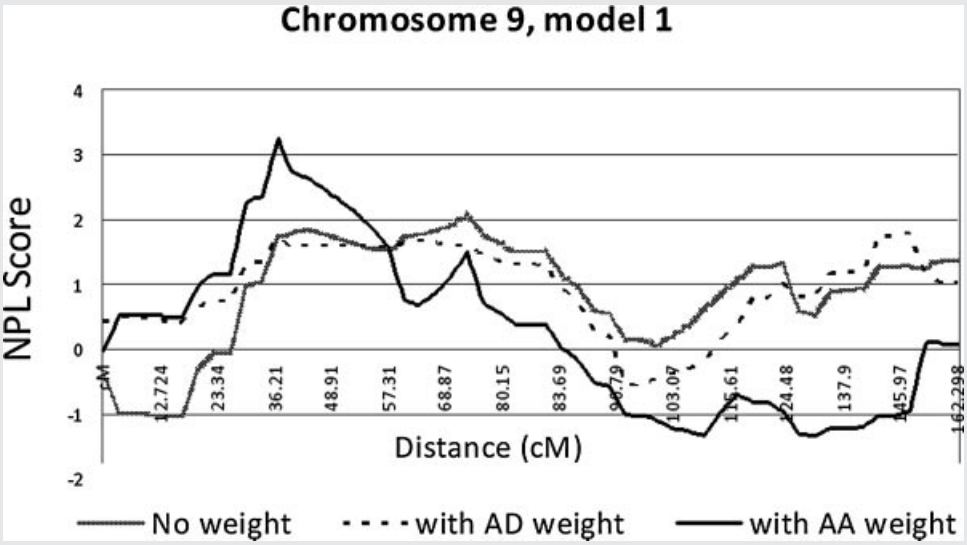

FIG. 2. A suggestive area of linkage at 9p22 (NPL 3.23) with alcohol abuse (AA) weight. This region showed significant difference from the NPL score without weighting or with alcohol dependence (AD) weight.

with strong linkage. The strongest signal we observed using model 3 affectation status was an NPL score of 2.41 found on chromosome 8, p23.2 at 4.30 cM with a corresponding LOD of 2.03. The weighting scheme actually decreased the NPL score; the unweighted score was 2.53.

In summary, we identified a suggestive linkage signal for bipolar disorder on chromosomal region 9p22 after weighting families by frequency of AA. This locus was previously identified as a region of suggestive linkage in bipolar disorder in a recent meta-analysis [Segurado et al., 2003]. This meta-analysis was mostly influenced by two unrelated samples, the Wellcome Trust UK-Irish sample [Bennett et al., 2002], and an unpublished study in Australia. However, further replication is necessary to affirm this finding.

Using permutation, we showed that our weighting scheme significantly enhanced the linkage signal, generating a maximum NPL score that is higher than expected by chance. The statistical significance of the linkage result indicates an increased effect of the detected locus in families with high levels of AA. To further evaluate the nature of this interaction, consider that the weighting scheme included family members with AA regardless of mood disorder. By not restricting the weighting to family members affected by mood disorder, we assumed a risk variant that jointly increases the risk for AA and BP disorder. Such an allele is most likely to segregate in families with large numbers of individuals affected with AA. However, an equally valid interpretation of our results is a risk variant on 9p22 that has a particularly high effect size in a difficult home environment generated by high familial levels of AA. Further investigation is needed to separate these hypotheses.

Remarkably, after weighting for AD, we do not observe any significantly improved linkage signal for BP. This is surprising given the evidence for familiality of AD. In a non-bipolar sample in a study of the genetics of alcoholism, the Collaborative Studies of Genetics of Alcoholism sample, AD but not AA, was demonstrated to be highly familial [Nurnberger et al., 2004]. Several studies of familiality of alcoholism in bipolar samples have not differentiated between AA and AD phenotypes [Winokur et al., 1996; Schulze et al., 2005, 2006; Potash et al., 2008; Saunders et al., 2008]; one study in the NIMH GI dataset revealed that relatives of probands with affective disorders (particularly BPI and SAB) were more likely to have AD, but AA was not studied [Nurnberger et al., 2007]. Given these findings, it is surprising that we detect a signal with AA weighting and not AD weighting. While this result may simply be explained by low power of our approach, this seems unlikely as the number of families with nonzero AD weight is almost twice as high as the number of families with nonzero AA weight. More likely, the interaction between BP and AD is not captured by our weighting scheme. We refrained from testing a wider range of weighting schemes, as applying multiple schemes would require adjusting for multiple testing and we are unlikely to have sufficient power to overcome the associated penalty.

If there truly is a risk variant for BP that is present in AA families and not AD families, it may predispose individuals to impulsive behaviors that then take the form of alcohol abuse during mood episodes. Mood-dependent drinking occurs frequently in BP [reviewed in Goodwin and Jamison, 2007], and is an area of significant concern clinically, as alcohol abuse causes legal and social problems which add to the devastating toll of BP.

AA and AD are both potentially useful markers for defining subtypes of BP and exploring their interaction with genetic risk factors may thus further the understanding of its heterogeneity. Hence, the demonstrated interaction between AA and BP may help identifying subtypes of BP and tailor treatment strategies to the patient.

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