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Shared Genetic Factors Influence Risk for Bipolar Disorder and Alcohol Use Disorders

Nasdia Carmiol¹, Juan M Peralta^{1,2}, Laura Almasy², Javier Contreras¹, Adriana Pacheco¹, Michael A Escamilla³, Emma E Knowles^{5,6}, Henriette Raventós^{1,4}, and David C Glahn^{5,6}

¹Centro de Investigación en Biología Molecular y Celular, Universidad de Costa Rica, San José, CR

²Department of Genetics, Texas Biomedical Research Institute, San Antonio, TX, USA

³Center of Excellence for Neurosciences, Texas Tech University Health Science Center, El Paso, TX, USA

⁴Escuela de Biología, Universidad de Costa Rica, San José, CR

⁵Olin Neuropsychiatry Research Center, Institute of Living, Hartford, CT, USA

⁶Department of Psychiatry, Yale University School of Medicine, New Haven, CT USA

Abstract

Bipolar disorder and alcohol use disorder (AUD) have a high rate of comorbidity, more than 50% of individuals with bipolar disorder also receive a diagnosis of AUD in their lifetimes. Although both disorders are heritable, it is unclear if the same genetic factors mediate risk for bipolar disorder and AUD. We examined 733 Costa Rican individuals from 61 bipolar pedigrees. Based on a best-estimate process, 32% of the sample met criteria for bipolar disorder, 17% had a lifetime AUD diagnosis, 32% met criteria for lifetime nicotine dependence, and 21% had an anxiety disorder. AUD, nicotine dependence and anxiety disorders were relatively more common among individuals with bipolar disorder than in their non-bipolar relatives. All illnesses were shown to be heritable and bipolar disorder was genetically correlated with AUD, nicotine dependence and anxiety disorders. The genetic correlation between bipolar and AUD remained when controlling for anxiety, suggesting that unique genetic factors influence risk for comorbid bipolar and AUD independent of anxiety. Our findings provide evidence for shared genetic effects on bipolar disorder and AUD risk. Demonstrating that common genetic factors influence these independent diagnostic constructs could help to refine our diagnostic nosology.

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Corresponding Author: David C Glahn Ph.D., Olin Neuropsychiatry Research Center, Whitehall Research Building, Institute of Living, 200 Retreat Ave, Hartford, CT 06106, Office (860) 545-7298, Fax (860) 545-7797, david.glahn@yale.edu.

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Keywords

bipolar disorder; alcohol use disorder; family studies; heritability; genetic correlation; Central Valley of Costa Rica

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Introduction

Bipolar disorder is a debilitating psychiatric condition with profound negative impact on patients and their families. Although bipolar disorder is among the leading cause of disability world-wide [Kessler and others 2005; Murray and Lopez 1996], the causes of the illness are largely unknown. This illness has a high rate of comorbidity with anxiety disorders [Castilla-Puentes and others 2011; Prisciandaro and others 2011], personality disorders [Grant and others 2005; Nery and others 2008] and substance use disorders [Jaworski and others 2011; Lagerberg and others 2010]. Comorbidity between bipolar disorder and alcohol use disorder (AUD) is exceptionally high, with more than 50% of individuals with bipolar disorder receiving an AUD diagnosis in their lifetimes [Levander and others 2007; Prisciandaro and others 2011]. As comorbid AUD worsens so does the course of mental illnesses which in turn complicates treatment response [Chang and others 2012], therefore clarifying the nature of the relationship between bipolar disorder and AUD could improve clinical outcomes. Unfortunately, it is unclear if overlapping bipolar disorder and AUD are due to common biological or environmental elements. The goal of this manuscript is to determine if shared genetic factors influence risk for bipolar disorder and AUD, thereby providing evidence that the high comorbidity between these illnesses is related to common biology.

There is substantial evidence supporting the notion that both bipolar disorder [Smoller and Finn 2003] and AUD [Kaprio and others 1987] are heritable. While the last decade has seen significant progress delineating the genetic architecture these illnesses [Agrawal and others 2006; Bierut and others 2010; Purcell and others 2009], causal genes have yet to be identified. Indeed, there is some initial evidence from candidate gene studies suggesting that specific genetic variants may increase risk for both illnesses [Le-Niculescu and others 2008; Lydall and others 2011; Neves and others 2011]. Neves and colleagues (2011) recently reported that two haplotypes of the BDNF gene are significantly more common in individuals with comorbid bipolar disorder and AUD compared with individuals with bipolar disorder alone. Lydall and colleagues (2011) used a gene-burden approach to associate bipolar disorder to several genes putatively associated with AUD, including CDH11, COL11A2, NMUR2, XP07 and SEMA5A. Similarly, in a series of articles, Le-Niculescu and colleagues showed that the clock gene D-box binding protein (Dbp) appears to influence risk for both bipolar disorder and AUD [Le-Niculescu and others 2008; Niculescu and others 2000]. While these experiments suggest that common genetic factors influence bipolar disorder and AUD, they do not provide an estimate of the magnitude of shared genetic effects on these illnesses.

Anxiety disorders are often found in patients with bipolar disorder [Freeman and others 2002; Simon and others 2004] and in individuals with AUD [Kendler and others 1995; Petry

and others 2005]. Comorbidity between bipolar disorder and anxiety disorders is associated with increased AUD and poorer treatment outcome [Strakowski and others 1998]. It is possible that the genetic factors that increase risk for anxiety disorders also increase risk for bipolar disorder and/or AUD. Similarly, nicotine dependence is common among individuals with bipolar disorder [Heffner and others 2011; Waxmonsky and others 2005] and common genetic factors are associated with risk for nicotine dependence and AUD [Fowler and others 2007; Zhang and others 2012]. Thus, it is possible that a genetic overlap exists between all four disorders, including bipolar disorder, alcohol use disorder, nicotine dependence and anxiety disorders. Demonstrating that common genetic factors influence these putatively independent diagnostic constructs will support the idea that shared biological pathways predispose these illnesses. If so, this information could be used to refine our current diagnostic nosology using empirically defined indicators [Cuthbert and Insel 2010], consistent with NIMH's Research Domain Criteria initiative (RDoC; <http://www.nimh.nih.gov/research-priorities/rdoc/index.shtml>).

While there is limited evidence for common genetic factors influencing AUD and bipolar disorder [Winokur and others 1996], there is substantial support for claims that major depression and AUD have common genetic roots [Kendler and others 2003; Prescott and others 2000]. Indeed, we recently documented shared genetics effects on major depression and alcohol use disorders in extended Mexican-American pedigrees from the San Antonio region [Olvera and others 2011]. Here, we implement a conceptually similar approach with extended pedigrees selected for bipolar disorder living in the Central Valley of Costa Rica, an established genetic isolate with a high degree of genetic homogeneity [Mathews and others 2004; Segura-Wang and others 2010]. Previously, in an independent Costa Rican sample, we documented high rates of AUD in bipolar pedigrees [Escamilla and others 2002], noting that the majority of substance abuse/dependence cases predated the onset of manic episodes.

The aims of this study are to document the prevalence of AUD in previously acquired bipolar pedigrees and, using bivariate genetic correlations, determine if common genetic factors influence risk for bipolar disorder and AUD. In addition, we will examine the relationship between bipolar disorder and nicotine dependence and between bipolar disorder and anxiety disorders.

Methods

Sample

A total of seven hundred and thirty-three individuals from sixty-one extended pedigrees (range 3–46 members) with at least two siblings diagnosed with bipolar disorder participated in the study. Participants were 40.62±16.24 years old on average (range 14–85) and 59% were female (n=429). All participants live in Central Valley of Costa Rica. Probands were recruited through systematic screening of outpatient and inpatient facilities. Once an affected sibling pair provided informed consent, attempts were made to extend the family and recruit all 1st, 2nd and 3rd degree relatives.

Inclusion and exclusion criteria for probands required a previous clinical diagnosis of bipolar disorder and at least one sibling meeting criteria for bipolar I disorder or schizoaffective disorder, bipolar type. Affected individuals were excluded if they did not provide written consent to contact family members, had a history of mental retardation, neurological disorder, or severe head trauma. Inclusion and exclusion criteria were identical for all family members, with the exception of requiring a personal history of bipolar disorder. All participants provided written informed consent on forms approved by the Internal Review Boards at the University de Costa Rica and the University of Texas Health Science Center San Antonio.

Diagnostic Assessment

All participants, regardless of diagnostic or family status, received the Diagnostic Interview for Genetic Studies (DIGS; [Nurnberger and others 1994]) and the Family Interview for Genetic Studies (FIGS; [Maxwell 1992]) by psychiatrists with an established diagnostic reliability ($\kappa=0.85$). Final DSM-IV diagnoses were determined through a best estimate consensus process where two psychiatrists reviewed all available records (DIGS, FIGS and medical records), arrived at diagnoses individually and reached a consensus after discussion (if necessary). If consensus was not reached, a third best estimator reviewed the case independently (this occurred once in this sample). Six phenotypes were derived from this process: (1) a broad bipolar phenotype comprised of the bipolar I disorder, bipolar II disorder, bipolar not otherwise specified (NOS), and schizoaffective disorder bipolar subtype lifetime diagnoses; (2) a lifetime bipolar I disorder phenotype; (3) an alcohol use disorder (AUD) phenotype comprised of a lifetime alcohol abuse or dependence diagnoses; (4) a substance use disorder phenotype comprised of lifetime substance abuse or dependence diagnoses; (5) an anxiety disorder phenotype comprised of lifetime diagnoses of general anxiety disorder, obsessive compulsive disorder, panic disorder with/without agoraphobia, social phobia, and/or post traumatic stress disorder; and (6) lifetime nicotine dependence diagnosis.

Statistical Genetic Analyses

Heritability and bivariate correlations were estimated with SOLAR [Almasy and Blangero 1998], using a standard threshold model for dichotomous phenotypes [Duggirala and others 1997]. SOLAR employs maximum likelihood variance decomposition methods to estimate genetic and environmental influences by modeling the covariance among family members as a function of genetic proximity (kinship).

Heritability (h^2) represents the portion of the phenotypic variance accounted for by the total additive genetic variance ($h^2 = \sigma_g^2 / \sigma_p^2$). Phenotypes exhibiting larger covariances between genetically more similar individuals than between genetically less similar individuals have higher heritability.

To examine the relationship between bipolar disorder and AUD, phenotypic correlations were decomposed into genetic and environmental correlations [Williams and Blangero 1999]. More formally, bivariate polygenic analyses were performed to estimate phenotypic (ρ_p), genetic (ρ_g) and environmental (ρ_e) correlations between bipolar disorder and AUD

with the following formula: $\rho_p = \rho_g \sqrt{(h^2_{\text{bipolar}}) \sqrt{(h^2_{\text{AUD}})} + \rho_e \sqrt{(1-h^2_{\text{bipolar}}) \sqrt{(1-h^2_{\text{AUD}})}}$. The significance of these correlations was tested by comparing the $\ln$ likelihood for two restricted models (with either ρ_g or ρ_e constrained to 0) against the $\ln$ likelihood for the model in which these parameters were estimated. Specifically, a likelihood ratio test assuming a χ^2 distribution with a single degree of freedom was used to generate p-values for the bivariate analyses. Similar analyses were conducted between bipolar disorder and nicotine dependence and between bipolar disorder and anxiety disorders. A significant genetic correlation is evidence for shared genetics effects, that a gene or set of genes influences both phenotypes [Almasy and others 1997].

Given that families were ascertained for a sibling pair concordant for bipolar disorder, the prevalence of bipolar disorder and related illnesses are considerably higher in this sample than those reported in unselected populations. To correct for our ascertainment strategy [Falconer and Mackay 1996], the population estimate for the broad bipolar phenotype was set to 4.4%, reflecting the lifetime prevalence for the illness reported the National Comorbidity Survey Replication [Merikangas and others 2007]. Similarly, for analyses focused on bipolar I disorder, the prevalence rate was set to 1.0%. Correction for potential ascertainment bias ensures that heritability estimates and bivariate correlations are generalizable to other populations. See the Supplementary Materials for heritability estimates and bivariate analyses without corrections for ascertainment.

Heritability and bivariate analyses were conducted with simultaneous estimation for demographic covariates including age, sex, age x sex interaction, age², and age² x sex interaction. Tests were Bonferroni corrected for multiple comparisons: six heritability estimates (nominal $p=0.05/6=0.008$); three bivariate models (nominal $p=0.05/6=0.02$).

Results

Sample Characteristics

Two hundred and thirty-three participants (32% of the sample) exhibited a broad bipolar phenotype: 186 with bipolar I disorder (25%), 9 with bipolar II disorder, 21 with bipolar NOS and 18 with the bipolar subtype of schizoaffective disorder (see Table 1). One hundred and twenty-five participants (17%) had a lifetime AUD (30 alcohol abuse and 95 alcohol dependence). Two-hundred and thirty-seven reported nicotine dependence (32%) and 13 individuals presented with a lifetime substance use disorder (2%). Given the very low prevalence of substance use disorders, analyses were not conducted with this phenotype. The anxiety phenotype was present in 152 individuals (21%): 6 with generalized anxiety disorder, 15 with obsessive-compulsive disorder, 123 panic attack disorder, 22 social phobia, and 9 post traumatic stress disorder. Two hundred and fifty-two individuals did not meet criteria for a lifetime DSM-IV diagnosis (34%).

Among individuals with the broad bipolar phenotype, 66 had a lifetime AUD (28% of the group), indicating a significant over-representation of AUD among these individuals compared to the remaining sample given the pedigree structure (see Table 2). A similar pattern was observed for nicotine dependence and anxiety disorders. Complementary results

were observed when the sample was restricted to individuals with bipolar I disorder (see Table 2).

Heritability

The heritability estimate, after controlling for possible ascertainment bias, for the lifetime broad bipolar phenotype was $h^2=0.636$ (see Table 1). When restricting the analysis to bipolar I disorder, the resulting heritability estimate was $h^2=0.548$. The heritability estimate for lifetime alcohol use disorder was $h^2=0.752$. The heritability estimate for lifetime alcohol dependence alone has slightly higher ($h^2=0.809$, $p=1.6\times10^{-6}$) than for the broader AUD trait, with similar covariates (age ($p=9.8\times10^{-8}$), sex ($p=2.5\times10^{-8}$), age x sex interaction ($p=0.0003$), and age² ($p=0.02$)). The anxiety disorder phenotype was heritable at $h^2=0.361$. Nicotine dependence was heritable at $h^2=0.464$. Supplementary Materials Table S1 reports heritability estimates without corrections for ascertainment.

Bivariate Analyses

As can be seen in Table 3, the broad bipolar phenotype was significantly phenotypically correlated with AUD, nicotine dependence and anxiety disorders. These phenotypic correlations appear to have been primarily driven by genetic rather than environmental effects, as the genetic correlations were consistently higher than the environmental correlations and significant. The genetic correlation between AUD and nicotine dependence ($\rho_g=0.991$, $p=5.8\times10^{-8}$) suggests that these traits reflect a single, or at least strongly overlapping, genetic pathway [True and others 1999]. The anxiety disorders and AUD phenotypes were genetically correlated at $\rho_g=0.696$ ($p=0.003$), suggesting genetic overlap between these traits as well. A very similar pattern of results was observed without correction for ascertainment (see Supplementary Materials Table S2).

To determine if AUD and the broad bipolar phenotype share genetic factors that are independent of those shared with anxiety disorders, the anxiety disorders phenotype was included as a covariate (with age, sex, age² and their interactions) in a bivariate model. Even when anxiety disorders were included as a covariate the genetic correlation between AUD and bipolar disorder remained significant ($\rho_g=0.416$, $p=0.024$) suggesting that not all of the genetic relationship between these illnesses could be explained by anxiety disorders.

Discussion

Risk for bipolar disorder was significantly genetically correlated with alcohol use disorder, nicotine dependence and anxiety disorders. Evidence for shared genetic factors between bipolar disorder and AUD does not appear to be entirely driven by liability for anxiety disorders. Given the very strong genetic correlation between alcoholism and nicotine dependence, these phenotypes probably represent a single genetic pathway [Goldman and others 2005; True and others 1999]. Indeed, our results are consistent with those reported by Zhang and colleagues (2012) who reported a common genetic vulnerability for tobacco and alcohol use in healthy male Chinese twins. While others have reported somewhat lower genetic overlap between AUD and nicotine dependence (e.g. [Young and others 2006]), nonetheless these addictive disorders consistently show genetic overlap. In this way the

findings in this study, despite the relatively low rates of substance misuse identified in the employed sample, represent an extension of previous findings showing high rates of comorbidity between bipolar disorder, AUD, nicotine dependence and anxiety disorders [Contreras and others 2010; Jaworski and others 2011; Lagerberg and others 2010; Levander and others 2007; Prisciandaro and others 2011; Waxmonsky and others 2005]. Thus, our findings are best conceptualized as evidence for shared genetic effects between bipolar disorder and addictive disorders. Based upon our observed genetic correlations, 47–57% of the genetic variance predisposing bipolar disorder also influence risk for AUD, providing an estimate and upper bound for candidate gene studies examining the influence of single variants on both illnesses. Searching for the common genetic influences for bipolar disorder and AUD combined, rather than focusing on each illness separately, may provide insight into psychopathology. Thus, it is possible that biomarkers sensitive to risk for both illnesses could be identified, which in turn could be used to refine our diagnostic nosology [Cuthbert and Insel 2010].

As the current sample was ascertained in the Central Valley of Costa Rica, a known population isolate with a high degree of genetic homogeneity [Mathews and others 2004; Segura-Wang and others 2010], it is possible that our heritability estimates could be biased. However, our heritability estimate for the broad bipolar phenotype ($h^2=0.64$) and bipolar I disorder ($h^2=0.55$) are strikingly similar to others reported in the literature using different populations and different experimental designs (e.g. sibling or discordant twin pairs). For example Lichtenstein and colleagues (2009) used an unselected sample of Swedish families ($n=40,487$) to estimate heritability for bipolar disorder, reporting $h^2=0.59$ [Lichtenstein and others 2009]. Smoller and Finn's 2003 review on the subject reported heritability derived from twin sample ranging from 0.59 to 0.87. Hence, it appears that heritability estimates derived in the current study are remarkably similar to previously published estimates, suggesting that around 60% of the variance associated with risk for bipolar disorder is under genetic control. Having heritability estimates that are consistent with the larger literature implies that our findings of a strong genetic correlation between bipolar disorder and addiction may also generalize to other populations.

The finding that bipolar disorder and addictive disorders share common genetic factors is consistent with the observation that the two illnesses share similar brain networks [Bearden and others 2001; Koob and Volkow 2010]. Neuroanatomic and functional activation models of bipolar disorder focus on alterations in inferior and dorsolateral prefrontal regions coupled with disruptions in the limbic system associated with emotional processing [Chen and others 2011; Delvecchio and others 2013; Strakowski and others 2004], potentially due to aberrant connectivity between these regions [Anticevic and others 2013]. Similarly, neuroanatomic and neurophysiological models of addictive disorders often focus on orbital and medial prefrontal cortex and dopamine rich subcortical regions like the amygdala, striatum, thalamus and hippocampus involved in reward processing and impulsivity [Everitt and others 1999; Hyman and others 2006; Koob and Le Moal 2001]. The substantial overlap between brain circuits associated with addictive and affective disorders suggests that some of the neurophysiological mechanisms in these diseases may overlap [Nestler and Carlezon 2006]. Our findings suggest that common genes may influence these putatively shared

neural processes. While this supposition is tentative, it provides a framework for subsequent investigation.

Certain limitations of the current work should be considered. Families in the current sample were selected for a sibling-pair concordant for bipolar disorder. While it is possible to control for this ascertainment scheme when estimating heritability or calculating genetic correlations, the sample selected for this study could be biased in other ways. For example, many of the families selected for this study had two siblings with bipolar I disorder. It is possible that such families have a virulent form of the illness, reducing the number of individuals that experience hypomania relative to mania, resulting in the low number of bipolar II and bipolar NOS subjects in the sample. This hypothesis should be tested in other data sets in other racial groups. In addition, common and unique environmental were not modeled independently, as is typical in twin studies. Given that this sample utilizes large, multigenerational pedigrees, common environmental factors are considerably less pronounced than in twin studies. Moreover the modeling of common environment can be problematic under the twin design. The equal environments assumption, the idea that mono- and dizygotic twins share equal environments, is crucial to the veracity of twin findings. However, if environmental factors are dissimilar between mono- and dizygotic twin pairs, then variance ascribed to genetic effects may be due instead to environmental ones [Kendler 1993].

In summary, we confirmed a high level of comorbidity between bipolar disorder and AUD and furthermore showed that this comorbidity has a genetic basis. These findings improve our understanding of the shared genetic factors underlying these illnesses and could enhance the development of novel approaches to improve illness course, response to treatment, and treatment adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sample Characteristics (n=733) and Heritability Estimates

Phenotype	Affected	Female	Heritability (h^2)	p-value	Significant Covariate*
Broad Bipolar Phenotype*	233	55%	0.635	1.6×10^{-10}	sex (1.0×10^{-5}); sex x age ² (6.1×10^{-10})
Bipolar I Disorder*	186	51%	0.548	1.9×10^{-9}	sex (9.9×10^{-37}); age (5.8×10^{-13}); sex x age ² (3.3×10^{-15})
Alcohol Abuse Disorder (AUD)	125	22%	0.752	3.0×10^{-7}	age (9.6×10^{-7}); sex (1.2×10^{-10}); sex x age (0.005)
Substance Abuse Disorder (SUD)	13	15%			
Nicotine Dependence	237	52%	0.464	3.6×10^{-6}	age (5.2×10^{-7}); sex (3.5×10^{-8})
Anxiety Disorder	152	74%	0.361	6.1×10^{-4}	sex (0.002)
No DSM-IV Diagnosis	252	62%			

* Heritability estimates after correcting for ascertainment strategy; Covariate (p-value)

Table 2

Comorbidity within Bipolar Disorder

	Prevalence Among Non-Bipolar Participants	Prevalence Among Broad Bipolar Phenotype*	Prevalence Among Bipolar I Disorder*
Alcohol Abuse Disorder	59	66; 33.16 (8.5×10 ⁻⁹)	60; 33.16 (8.5×10 ⁻⁹)
Nicotine Dependence	131	106; 19.69 (9.0×10 ⁻⁶)	89; 19.69, p=9.1×10 ⁻⁶
Anxiety Disorders	84	68; 9.81 (0.002)	56; 9.81 (0.002)

* Number of subjects; χ^2 comparing bipolar sample to non-bipolar sample (p-value) given the pedigree structure

Table 3

Bivariate Analyses

	Broad Bipolar Phenotype			Bipolar I Disorder		
	Phenotypic	Genetic	Environmental	Phenotypic	Genetic	Environmental
Alcohol Abuse Disorder	0.415, $p=1.3\times10^{-8}$	0.469, $p=0.006$	0.302, $p=0.343$	0.436, $p=2.2\times10^{-9}$	0.500, $p=5.4\times10^{-3}$	0.331, $p=0.275$
Nicotine Dependence	0.304, $p=1.0\times10^{-8}$	0.566, $p=9.8\times10^{-4}$	-0.007, $p=0.971$	0.257, $p=1.5\times10^{-5}$	0.596, $p=3.2\times10^{-3}$	-0.086, $p=0.605$
Anxiety Disorders	0.239, $p=4.6\times10^{-4}$	0.484, $p=0.019$	-0.022, $p=0.903$	0.246, $p=2.0\times10^{-5}$	0.471, $p=8.6\times10^{-6}$	-0.174, $p=0.386$

All bivariate analyses included a correction for ascertainment strategy