European Psychiatry 29 (2014) 282–287

Available online at ScienceDirect www.sciencedirect.com

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Original article

Shared genetic factors influence risk for bipolar disorder and alcohol use disorders

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ARTICLE INFO

Article history:
Received 23 August 2013
Accepted 7 October 2013
Available online 8 December 2013

Keywords:
Bipolar disorder
Alcohol use disorder
Family studies
Heritability
Genetic correlation
Central Valley of Costa Rica

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 the 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.

1. Introduction

Bipolar disorder is a debilitating psychiatric condition with profound negative impact on patients and their families. Although bipolar disorder is among the leading causes of disability worldwide [28,39], the causes of the illness are largely unknown. This illness has a high rate of comorbidity with anxiety disorders [7,48], personality disorders [20,40] and substance use disorders [23,31]. Comorbidity between bipolar disorder and alcohol use disorder (AUD) is exceptionally high, with more than 50% of the individuals with bipolar disorder receiving an AUD diagnosis in their lifetimes [33,48]. As comorbid AUD worsens so does the course of mental illnesses, which in turn complicates treatment response [8], 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 the 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 [52] and AUD [24] are heritable. While the last decade has seen significant progress delineating the genetic architecture of these illnesses [1,6,49], 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 [32,35,42]. Neves et al. recently reported that two haplotypes of the BDNF gene are significantly more common in individuals with comorbid bipolar disorder and AUD compared to individuals with bipolar disorder alone. Lydall et al. 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 et al. showed that the clock gene D-box binding protein (Dbp) appears to influence the risk for both bipolar disorder and AUD [32,43]. While these experiments suggest that common

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http://dx.doi.org/10.1016/j.eurpsy.2013.10.001

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 [18,51] and in individuals with AUD [26,46]. Comorbidity between bipolar disorder and anxiety disorders is associated with increased AUD and poorer treatment outcome [53]. 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 [21,56] and common genetic factors are associated with risk for nicotine dependence and AUD [17,60]. 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 [11], 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 [58], there is substantial support for claims that major depression and AUD have common genetic roots [27,47]. Indeed, we recently documented shared genetics effects on major depression and alcohol use disorders in extended Mexican-American pedigrees from the San Antonio region [45]. 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 [36,50]. Previously, in an independent Costa Rican sample, we documented high rates of AUD in bipolar pedigrees [14], 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 the 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.

2. Methods

2.1. 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.

2.2. Diagnostic assessment

All participants, regardless of diagnostic or family status, received the Diagnostic Interview for Genetic Studies (DIGS; [44]) and the Family Interview for Genetic Studies (FIGS; [37]) by psychiatrists with an established diagnostic reliability (κ = 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:

- 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;
- a lifetime bipolar I disorder phenotype;
- an alcohol use disorder (AUD) phenotype comprised a lifetime alcohol abuse or dependence diagnoses;
- a substance use disorder phenotype comprised of lifetime substance abuse or dependence diagnoses;
- an anxiety disorder phenotype comprised lifetime diagnoses of general anxiety disorder, obsessive-compulsive disorder, panic disorder with/without agoraphobia, social phobia, and/or post traumatic stress disorder;
- and lifetime nicotine dependence diagnosis.

2.3. Statistical genetic analyses

Heritability and bivariate correlations were estimated with SOLAR [2], using a standard threshold model for dichotomous phenotypes [13]. 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 ($h^2 = \sigma^2_g/\sigma^2_p$). 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 [57]. 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:

$$\rho_p = \rho_g\sqrt{(h^2_{bipolar})}\sqrt{(h^2_{AUD})} + \rho_e\sqrt{(1-h^2_{bipolar})}\sqrt{(1-h^2_{AUD})}$$

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 evidenced for shared genetics effects, that a gene or set of genes influences both phenotypes [3].

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