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Research paper

Quantitative genetic analysis of anxiety trait in bipolar disorder

J. Contreras[a,*], E. Hare[c], G. Chavarría[b], H. Raventós[a,b]

[a] Centro de Investigación en Biología Celular y Molecular, Universidad de Costa Rica, Costa Rica
[b] Escuela de Biología, Universidad de Costa Rica, Costa Rica
[c] Genetics and Genomics Research and Breeding Program Planning, Dog Genetics LLC., Sunnyside, NY, United States

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ABSTRACT

Background: Bipolar disorder type I (BPI) affects approximately 1% of the world population. Although genetic influences on bipolar disorder are well established, identification of genes that predispose to the illness has been difficult. Most genetic studies are based on categorical diagnosis. One strategy to overcome this obstacle is the use of quantitative endophenotypes, as has been done for other medical disorders.

Methods: We studied 619 individuals, 568 participants from 61 extended families and 51 unrelated healthy controls. The sample was 55% female and had a mean age of 43.25 (SD 13.90; range 18–78).

Heritability and genetic correlation of the trait scale from the Anxiety State and Trait Inventory (STAI) was computed by using the general linear model (SOLAR package software).

Results: we observed that anxiety trait meets the following criteria for an endophenotype of bipolar disorder type I (BPI): 1) association with BPI (individuals with BPI showed the highest trait score ($F = 15.20$ [5,24], $p = 0.009$), 2) state-independence confirmed after conducting a test-retest in 321 subjects, 3) co-segregation within families 4) heritability of 0.70 (SE: 0.060), $p = 2.33 \times 10^{-14}$ and 5) genetic correlation with BPI was 0.20, (SE $= 0.17$, $p = 3.12 \times 10^{-5}$).

Limitations: Confounding factors such as comorbid disorders and pharmacological treatment could affect the clinical relationship between BPI and anxiety trait. Further research is needed to evaluate if anxiety traits are specially related to BPI in comparison with other traits such as anger, attention or response inhibition deficit, pathological impulsivity or low self-directedness.

Conclusions: Anxiety trait is a heritable phenotype that follows a normal distribution when measured not only in subjects with BPI but also in unrelated healthy controls. It could be used as an endophenotype in BPI for the identification of genomic regions with susceptibility genes for this disorder.

1. Introduction

Estimates of the prevalence of bipolar I disorder have ranged from 0.8% to 1.6% of the general population (Berns and Nemeroff, 2003). Although the genetic participation is well established, the identification of genes has remained elusive. Imprecision of the phenotype might explain the failure of genetic research to identify genes that contribute to susceptibility of BPI. Psychiatric disorders lack objective clinical and biological markers, and there are substantial disagreements on specific criteria to define diagnostic categories (Freedman et al., 2013). The need for a new approach to psychiatric genetics has led to the increasing popularity of endophenotypes (internal phenotypes that lie intermediate between the gene and the disease itself) (Gottesman and Shields, 1973). It is assumed that genes involved in endophenotypic variation are likely to represent more elementary phenomena than those involved in complex psychiatric diagnostic entities. It is also used interchangeably with the term 'intermediate trait,' describing a heritable quantitative phenotype believed to be closer in the chain of causality to the genes underlying the disease.

Many patients with BPI show anxiety symptoms that can be very disabling. Anxiety symptoms are caused by an interaction of biopsychosocial factors, including genetic vulnerability, stress, and trauma, which produce clinically significant syndromes. High comorbidity rates for anxiety have been documented (Shim et al., 2016). However, subclinical levels of anxiety (defined as anxiety trait) have also been associated with BPI (Mantere et al., 2008). These individuals have poor outcomes with longer, more frequent, and more difficult to treat mood episodes, are less responsive to lithium therapy, have earlier onset of symptoms and have greater functional impairment (McElroy et al., 2001).

Many candidate endophenotypes for BPI (e.g. neurocognitive functions, behavioral traits, sleep abnormalities) have been proposed

* Corresponding author.
E-mail address: dr.javiercontreras@gmail.com (J. Contreras).

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(Gottesman and Gould, 2003; Hasler et al., 2006). As reported by Glahn et al. (2014), the number of genetic research using endophenotype approach has rapidly increased during the last decade. To our knowledge, none of these studies has identified a gene with a significant major effect on any psychiatric disorder. To date, few studies have assessed anxiety as a quantitative phenotype for bipolar disorder? (Wozniak et al., 2002).

Our hypothesis is that subclinical anxiety as a heritable trait genetically correlates with BPI. To determine whether quantitative anxiety symptomatology is a candidate endophenotype for BPI, we tested heritability of the trait (measurement of the general level of anxiety experienced over the lifetime) from the STAI in a sample of extended pedigrees from the Central Valley of Costa Rica (CVCR) with BPI disorder, and the genetic correlation between anxiety and BPI. We followed the same methodology of our pilot study (Contreras et al., 2010).

2. Methods

2.1. Participants

Subjects were originally recruited for the study Anxiety traits in Bipolar I Disorder in the Costa Rican population (NIMH 1R01TW008290-01A1). This study was reviewed and approved by the Institutional Review Board of the University of Costa Rica following the international guidelines for genetic research with human samples. The research project was explained to each participant before obtaining written consent.

The total study sample was 619 individuals from the Central Valley of Costa Rica (CVCR). The sample was comprised of 61 extended families (568 subjects, average family size 31 members, range: 4–41) and 51 unrelated healthy controls. Each family had at least one member diagnosed with BPI. The sample was 55% female and had a mean age of 43.25 (SD 13.90; range 18–78).

2.2. Diagnostic assessment

The subjects were diagnosed based on the diagnostic criteria of DSM-IV through a best estimation process (Leckman et al., 1982), utilizing clinical information obtained from the Diagnostic Interview for Genetic Studies (Nurnberger et al., 1994), a Family Interview for Genetic Studies (Maxwell, 1992) and psychiatric records. Final diagnoses were determined through a consensus process where two independent psychiatrists reviewed all available information. The Lifetime Dimensions of Psychosis Scale (LDPS) was used to capture affective and psychotic symptoms over the lifetime in addition to the consensus diagnoses (Levinson et al., 2002). LDPS was utilized as a proxy for bipolarity using the item that provide a quantitative measurement of lifetime mania.

2.3. Assessment of the anxiety trait

We measured subclinical anxiety in each subject regardless of the categorical diagnosis using the STAI. The STAI is a self-rated instrument that contains two subscales to measure anxiety. Each subscale has 20 items (4 response choices per item, higher scores indicate higher anxiety) (Spielberger et al., 1983). One scale measures state anxiety (i.e. the extent to which respondents experience anxiety symptoms at the time of measurement) (Vigneau and Cormier, 2008). The second scale measures trait anxiety (i.e. the extent to which respondents generally experience of anxiety symptoms as a behavioral trait). This instrument has been validated in Spanish (Rodrigo and Lusiardo, 1988).

The instrument was applied within the same month period after the initial psychiatric evaluation in 390 subjects, while 229 individuals were assessed with the STAI at a different time (later than a month after psychiatric interview) due to availability of the participants. We were also able to reassess 321 subjects after at least one year of the first evaluation of anxiety. The goal of this second evaluation was to test independency of the trait at a different moment of life.

2.4. Statistical analysis

We used a general linear model (GLM) to test endophenotype criteria (e.g. heritability, genetic correlation). Heritability and genetic correlation was assessed with variance component methods implemented in the SOLAR package software. We created an index representing mania based on the quantitative symptoms score from the item M-1 (duration × severity) of the LDPS as described before. We included in each model the covariates age, sex, the square of age, and interactions between age and sex, to allow for different age effects in males and females and non-linear change with age. Bivariate analyses provide genetic and environmental correlations as a means of examining how BPI and anxiety varies together. Such analysis allowed us to ask whether anxiety score correlated with mania in subjects with BPI.

To test association of anxiety trait with BPI, we examined multiple dependent, independent and covariate variables (e.g. age, sex). We tested the anxiety scores of individuals with BPI and their relatives to determine whether their scores are different compared to controls. The differences between groups would suggest an underlying genetic correlation between anxiety and BPI. This hypothesis was tested through GLM methods, modeling anxiety as function of genetic proximity to an affected individual (BPI > relatives with other psychiatric illness - different than BPI- > healthy relatives > healthy unrelated controls). All calculations of clinical and demographic variables were adjusted for age and gender by using the Statistical Package for the Social Sciences (SPSS) Software v.20.

3. Results

3.1. Sample characteristics

The primary DSMIV psychiatric diagnosis of the 568 subjects from the extended pedigrees were: BPI 151 (26%), major depressive disorder 59 (10%), specific phobia 10 (1%), panic disorder 11 (1%) and no axis I disorder 100 (18%). Out of the 61 families, 90% had one or more relatives with BPI, 77% had more than two members with BPI and 26%, four or more affected members. Out of the 618 participants, 340 (55%) were female. The mean age at interview was 43.25 (SD 13.90; range 18–78). The average dimensional index of lifetime mania (M-1 severity × duration of the LDPS) was 2.61. The average anxiety trait score was 28.15 (SD = 7.1) out of a maximum of 60. Detailed clinical and demographic characteristics of the sample are described in Contreras-Rojas and Raventós-Vorst (2014).

3.2. Heritability analysis

Since we observed in our pilot study that only anxiety trait is independent of clinical status in subjects with BPI, we restricted all the following analyses to anxiety trait without considering anxiety state. The heritability is 0.70 (SE: 0.060), $p = 2.33 \times 10^{-14}$ and the genetic correlation between anxiety and BPI is 0.20, (SE = 0.17, $p = 3.12 \times 10^{-05}$, p: correlation is different from zero = 0.02 and p: correlation is different from one = 1.10×10^{-06}).

As seen in Fig. 1, subjects with BPI showed significantly higher anxiety trait scores than their healthy relatives and healthy controls ($F = 15.20$ [5,24], $p = 0.009$), (BPI patients > healthy relatives > unrelated healthy controls). Anxiety trait correlated with lifetime mania (LDPS M-1 duration x severity) $r = 0.30$ ($p < 0.0001$) after controlling for sex and age.

Of the 618 individuals, 390 (90%) were evaluated at the same time (within a month period after psychiatric evaluation), 62 (10%) met criteria for a current depressive syndrome (five or more depressive symptoms within the last two weeks of psychiatric assessment) and 18