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No association between common variations in the neuronal nicotinic acetylcholine receptor alpha2 subunit gene (CHRNA2) and bipolar I disorder

Falk W. Lohoff*, Thomas N. Ferraro, Leilah McNabb, Candice Schwebel, John P. Dahl, Glenn A. Doyle, Russell J. Buono, Wade H. Berrettini

School of Medicine Center for Neurobiology and Behavior, Department of Psychiatry, University of Pennsylvania, Clinical Research Building, Room 135a, 415 Curie Boulevard, Philadelphia, PA 19104-6140, USA

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Abstract

The neuronal nicotinic acetylcholine receptor alpha2 subunit gene (CHRNA2) maps to the bipolar susceptibility locus on chromosome 8p21–22. Given the biological role of the neuronal nicotinic acetylcholine receptors and the substantial comorbidity of nicotine dependence in psychiatric disorders, the CHRNA2 gene is a plausible candidate gene for bipolar disorder (BPD). We tested the hypothesis that variations in the CHRNA2 gene confer susceptibility to bipolar I disorder in a case-control association study. Genotypes of one amino acid substitution polymorphism (Ala125Thr) and five non-coding variations across the CHRNA2 gene were obtained from 345 unrelated bipolar I patients and 273 control samples. Genotypes and allele frequencies were compared between groups using chi-square contingency analysis. Linkage disequilibrium (LD) between markers was calculated, and estimated haplotype frequencies were compared between groups. We observed no statitistically significant difference in genotype and allele frequencies for all six variations between bipolar patients and controls, but we did demonstrate strong LD throughout the gene. Haplotype analysis showed that no combinations of alleles were associated with illness. Our results suggest that common variations in the CHRNA2 gene are unlikely to confer susceptibility to BPD in this sample. Further studies are required to elucidate the susceptibility locus for BPD on chromosome 8p21–22.

Keywords: Polymorphism; Genetics; Association study; Chromosome 8p

1. Introduction

Bipolar disorder (BPD) is a common psychiatric disorder, which affects approximately 1% of the general population and is characterized by episodes of mania and depression. Family, adoption and twin stud-

* Corresponding author. Tel.:+1 215 746 7229; fax: +1 215 573-2041.
E-mail address: lohoff@mail.med.upenn.edu (F.W. Lohoff).

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ies show that BPD has a strong genetic component (Craddock and Jones, 1999). However, genetic causes have been difficult to elucidate due to the complex mode of inheritance and genetic heterogeneity. Linkage studies have suggested a susceptibility locus for BPD on chromosome 8p21–22 (Cichon et al., 2001; Ophoff et al., 2002; Park et al., 2004). The neuronal nicotinic acetylcholine receptor alpha2 subunit gene (CHRNA2) maps to this bipolar susceptibility locus on chromosome 8p21 (Wood et al., 1995) and is expressed in the brain (Talib et al., 1993; Martin-Ruiz et al., 2002).

Neuronal nicotinic acetylcholine receptors (nAChR) belong to a large family of ligand-gated ion channels with diverse structures and properties (Lindstrom, 2003). Clinical and laboratory data indicate the involvement of nAChR in complex brain functions such as memory, attention and cognition but also in the pathogenesis of neurological and psychiatric disorders such as schizophrenia and mood disorders (Mihailescu and Drucker-Colin, 2000; Weiland et al., 2000; Araki et al., 2002; McEvoy and Allen, 2002). Experiments in animal models of depression show that inhibition of nAChRs by mecamylamine has antidepressant-like effects in the forced swim test and potentiates the antidepressant activity of amitriptyline (Caldarone et al., 2004). Other experiments with the centrally acting nAChR antagonist mecamylamine reduced symptoms of depression and mood instability in patients with comorbid depression and bipolar disorder (Shytle et al., 2002a,b; Lopez-Valdes et al., 2002). Given the substantial comorbidity of nicotine dependence in psychiatric disorders (Lasser et al., 2000; Leonard et al., 2001; Faraone et al., 2004) and the emerging data on the involvement of nAChR in mood disorders, the CHRNA2 gene is a plausible candidate gene for BPD not only based on its chromosomal location, but also based on its biological function.

In this study we tested the hypothesis that variations in the CHRNA2 gene, including the potential functional amino acid substitution polymorphism Ala125Thr, confer susceptibility to BPD.

2. Methods

2.1. Participants

Three hundred and forty-five unrelated bipolar I patients participated in this study. Patients were collected at centers participating in the NIMH Genetics Initiative on Bipolar Disorder and carried a diagnosis of Bipolar I disorder (BPI) defined by DSM-IV criteria. The key criterion for admission of a family to the study was a working diagnosis of BPI in two or more siblings. Background and detailed methodology for the NIMH Genetics Initiative are described elsewhere (NIMH Genetics Initiative Bipolar Group, 1997). All subjects were assessed with the Diagnostic Instrument for Genetic Studies (DIGS) (Nurnberger et al., 1994). Family history information was obtained through the Family Interview for Genetic Studies, and medical records were requested. A final best estimate diagnosis was made using all available information including medical records, information from relatives, and the

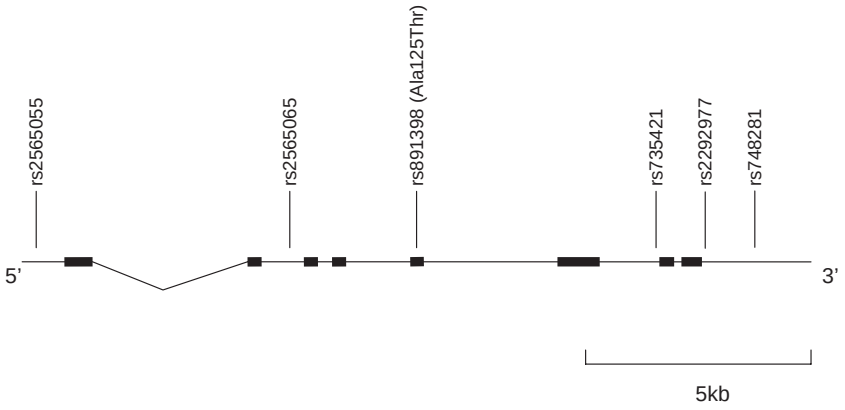

Fig. 1. Variations in the CHRNA2 gene.