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GABRA2 and *KIBRA* genotypes predict early relapse to substance use

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ABSTRACT

Background: Numerous single nucleotide polymorphisms (SNPs) within different genes have been associated with alcohol and drug involvement or known risk factors for involvement, such as impaired cognitive control. The ability of these SNPs to predict re-involvement, defined here as abstinence failure during treatment, has not been thoroughly tested.
Methods: We studied a small sample ($n = 146$; 49% female) of residential substance abuse treatment program patients who had maintained 2–6 months of abstinence. They were followed for 4 months thereafter for the purpose of counting days until the first abstinence violation. The analysis used logistic and Cox regression methods to evaluate the contributions of age; sex; number of intake alcohol, drug use, and depression symptoms; and either *GABRA2*, *CHRM2*, *ANKK1*, *BDNF*, or *KIBRA* SNP genotypes to outcome.
Results: GABRA2 and *KIBRA* genotypes, as well as the number of intake drug abuse problems and a younger age, were associated with an increased risk of relapse. Importantly, these genotypes were found to add value to relapse prediction: the χ^2 statistic evaluating their residual contribution, after age and the number of previous drug use problems were entered, was significant.
Conclusions: Genetic analyses may add value to outcome prediction. Future studies should evaluate the sensitivity and specificity of *GABRA2* and *KIBRA* genotypes for this purpose in other racial/ethnic groups and treatment settings.

1. Introduction

Before and since the era of Project MATCH (Project MATCH Research Group, 1993), researchers have recognized that a "one-size-fits-all" approach to Substance Use Disorder (SUD) treatment is unwise. It is unwise because no single treatment is so powerful as to overshadow all of the dispositional factors that can influence outcome. Also, not every patient requires the most intensive and expensive option. The challenge for psychiatry is to identify reliable dispositional factors and, with them in mind, assign patients to an appropriate type and level of treatment. The end result may be a better outcome at a lower cost.

The present study was conducted with the goal of identifying dispositional variables that might later be used for treatment matching. Many previous studies have been directed toward this goal. For example, they have shown that poor self-efficacy, high substance use severity, comorbid psychiatric disorders (Ciraulo et al., 2003), and a family history of a substance use disorder (Milne et al., 2009) are all correlated with treatment failure or relapse. Our interest is in outcome predictors of a different type. More specifically, we are focused on biological variables that point to the dysfunctional processes underlying these psychological and family history differences.

There are several important criteria to consider as we pursue this interest. The criteria are items that can be applied in determining which of the many possible biological predictors are worthy of further investigation and application. Among the items on this list, sensitivity and specificity hold a particularly prominent position. But, good reliability and stability are likewise critical. Indeed, given the heterogeneous presentation of substance abusers, who may vary markedly in quantity or frequency of use, duration of abstinence, medication usage, and other state variables, excellent signal-to-noise characteristics are necessary. Economy and practicality (e.g. portability) are relevant criteria if the predictor is ever to be implemented clinically – for example, to guide patients toward one type of treatment versus another. The final criterion is added value. The predictive validity of the variable should exceed that of other variables which are more easily and less expensively measured.

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Applying these evaluative criteria to the biological predictors described to date eliminates many possibilities. For instance, although abnormal functional magnetic resonance imaging (fMRI) contrast patterns during the performance of cognitive tasks have been associated with relapse to cocaine (Kosten et al., 2006) and methamphetamine (Paulus et al., 2005) use, the predictive validity of these patterns for relapse to other categories of substance abuse is unknown. An additional weakness of fMRI is its disappointing within-subject test–retest reliability during cognitive (i.e. non-motor) tasks. In fact, the average intraclass correlation coefficient of whole brain fMRI data from test to retest varies between 0.33 and 0.66, and the average test–retest overlap (Jaccard index) of activated voxels is only 29% (Bennett and Miller, 2010). fMRI is also too expensive and impractical for routine clinical use. Furthermore, its sensitivity to state variables, such as medications and mood, is understudied (Shah and Marsden, 2004) and therefore unknown.

Electroencephalographic (EEG) techniques have likewise been employed in studies of relapse prediction. Some studies using these techniques have identified longer sleep onset latency and poor sleep efficiency as correlates of poor outcomes (Brower et al., 1998; Brower and Perron, 2010). Other studies have revealed elevations in spontaneous fast beta activity (Bauer, 2001) and decrements in P300 potentials (Bauer, 1997) in awake patients that predict poor outcome. EEG techniques are less costly, more portable, and more reliable (Hall et al., 2006; Napflin et al., 2007, 2008) than fMRI. But, the extant EEG studies are similarly complicated by the effects of psychoactive drugs.

A third category of studies has examined the predictive validity of various measures of endocrine or neurotransmitter activity, including prolactin levels (Markianos et al., 2001), growth hormone or cortisol (Adinoff et al., 2005) responses, and serotonin and opioid activity. Unfortunately, the results of these studies have been inconsistent and difficult to interpret. Endocrine and neurotransmitter measures are easily confounded by sleep schedule, time-of-day, and drugs or medications (Perreau-Lenz et al., 2004).

In this article, we pursue a fourth area of study, in which we examine the association between SUD treatment outcome and biological measures that are reliable, practical, and inexpensive to assay. Importantly, the measures are also impervious to the pharmacological effects of medications and substance use. They are single nucleotide polymorphisms (SNP) within five candidate genes.

We are not the first group to examine candidate genes as predictors of substance use relapse or treatment outcome. Wojnar et al. (2009) examined the association of alcohol treatment outcome with *BDNF*, *TPH2*, *COMT*, *HTR2A*, and *5-HTTLPR* genotypes. They found that only the *BDNF* Val/Val genotype significantly predicted relapse and time-to-relapse. The association was significant in patients with a positive family history of alcohol dependence but not in their family history negative peers. Bauer et al. (2007) tested the association between alcohol treatment outcome and a different gene, *GABRA2*. Their analysis employed 812 alcohol-dependent patients who had participated in Project MATCH, an NIH-funded comparison of the relative efficacy of three psychosocial treatments. They found that the *GABRA2* allele associated with substance dependence (Covault et al., 2004; Edenberg et al., 2004; Fehr et al., 2006; Lappalainen et al., 2005) in previous studies was associated with an increased daily probability of any drinking and heavy drinking during and after treatment in Project MATCH.

In the present study, we re-examined the association of these *BDNF* (brain-derived neurotophic factor) and *GABRA2* (gamma-aminobutyric acid receptor subunit alpha-2) genotypes with outcome in a small ($n = 146$) sample of substance-dependent patients recruited from residential treatment programs. We also tested three other candidate genes: *KIBRA* (kidney, liver, and brain expressed protein; also known by the abbreviation WWC1), *CHRM2* (cholinergic receptor, muscaric 2), and *ANKK1* (ankyrin repeat and kinase domain containing 1). We concluded that *GABRA2*, *CHRM2*, and *ANKK1* SNPs were reasonable candidates for investigation because these same SNPs had been previously associated with the presence of substance dependence (Agrawal et al., 2006; Dick et al., 2007; Luo et al., 2005; Yang et al., 2007) and might therefore be associated with recurrence. The *BDNF* SNP was chosen because it was associated with relapse in Wojnar et al. (2009) study. The *KIBRA* SNP was another logical choice because it had previously been associated with poor cognitive control (Zhang et al., 2009), a known risk factor for substance use and relapse (Kreek et al., 2005).

2. Method

2.1. Participants

On average, the 146 residential treatment program patients had completed 13 years of education. Their age range was 20–56 years. All of the patients included in the present analysis were European-American. The number of patients ($n = 17$) from other ancestral groups was insufficient to support their inclusion in a separate analysis. These other patient groups were therefore dropped.

All patients were in a good medical health. They were not enrolled if they had a lifetime history of seizures, neurosurgery, head injury with loss of consciousness greater than 30 min, schizophrenia, bipolar disorder, mental retardation, dementia, or significant medical disorders, including HIV-1 infection, or cardiovascular, hepatic, immunologic, or renal disease. Patients with uncorrected deficits in vision or hearing were also excluded.

2.2. Recruitment and clinical evaluation procedures

Patients initially deemed eligible for the study were transported to the University of Connecticut Health Center (UCHC) on a weekday morning. An informed consent document, approved by the UCHC Institutional Review Board, was reviewed and signed at that time. Urine and breath samples were then collected and assayed to exclude patients with recent exposure to alcohol, cocaine, amphetamine, marijuana, or heroin. In addition, hair samples were collected to verify self-reports of no drug use during the previous 60 days (PDT-90™, Psychemedics Inc., Cambridge, MA). Patients admitting substance use, suspected by treatment program staff of substance use, or testing positive for alcohol, cocaine, amphetamine, or heroin use during the previous 2 months were excluded. The maximum duration of abstinence allowed by the protocol was 6 months.

Demographic data and psychiatric histories were obtained from all patients to determine final eligibility. The psychiatric history was obtained with the Computerized Diagnostic Interview Schedule for DSM-IV [CDIS-4; Robins et al., 2002]. Additional demographic, medical, psychological, and drug use information was garnered from medical records, interviews, and questionnaires, including the Michigan Alcoholism Screening Test [MAST; Selzer, 1971], Drug Abuse Screening Test [DAST-20; Skinner, 1982], Fagerstrom Test for Nicotine Dependence [FTND; Heatherton et al., 1991], Beck Depression and Anxiety Inventories (Beck et al., 1996; Leyfer et al., 2006), Family History Assessment Module [FHAM; Rice et al., 1995], Wender Utah Rating Scale [WURS; Ward et al., 1993], and the Kaufman Brief Intelligence Test [KBIT; Kaufman and Kaufman, 1990].

2.3. Definition of relapse

Following the assessment and for a subsequent 4-month period, patients were visited frequently (i.e. 1–2x/week) and unpredictably for the purpose of detecting relapse or continued abstinence via interviews, urine (EZ Screen, Editek Inc.), and breath screening. Patients who left the residential treatment facility prior to the expiration of the 4-month monitoring period remained in the study and were monitored via home visits or brought to the Health Center for abstinence monitoring. Each patient was compensated with a gift coupon with a value of $10 for providing each sample. An additional $10 coupon was awarded if urine and breath samples test negative for alcohol, cocaine, heroin, benzodiazepines, and marijuana. A positive urine or breath test, or a self- or collateral report of a lapse, terminated the patient's enrollment in the study.

Interviews with patients and collateral informants (a roommate, significant other, or counselor) were conducted around the time of sample collection. Patients were assigned to the relapse-prone group if they or their collateral informants reported any use of alcohol, cocaine, opiates, or benzodiazepines, or if urine or breath samples tested positive, on one or more occasions during the 4-month tracking period. Patients were assigned to the abstinence-prone group if they verifiably maintained abstinence from these substances over the 4-month tracking period.

2.4. Genotype analysis procedures

DNA was extracted from peripheral blood samples. Duplicate samples were processed for each patient. Using the Taqman technique, SNPs were genotyped within