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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.

Keywords

GABRA2; *KIBRA*; *CHRM2*; *ANKK1*; *BDNF*; gene; relapse; substance use disorder; treatment outcome

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Conflict of Interest

The authors have no conflicts of interest.

Contributors

Dr. Bauer designed the study and wrote the grant application as well as this report. Advice on these tasks was provided by Drs. Covault and Gelernter. Drs. Covault and Gelernter also participated in the genetic analyses.

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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. However, 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.

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. In 2009, Wojnar and colleagues (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. In 2007, we (Bauer et al., 2007) tested the association between alcohol treatment outcome and a different gene, *GABRA2*. The analysis employed 812 alcohol-dependent patients who had participated in Project MATCH, an NIH-funded comparison of the relative efficacy of three psychosocial treatments. We 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 neurotrophic 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 study (Wojnar et al., 2009). The *KIBRA* SNP was another logical choice because it had previously been associated with poor cognitive control (Zhang et al., 2009a), 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 yrs of education. Their age range was 20–56 yrs. 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 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

minutes, 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™, Psychomedics 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, 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, 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, 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 *GABRA2* (rs279858), *CHRM2* (rs36210735), *ANKK1* (rs4938012), *BDNF* (rs6265), and *KIBRA* (rs17070145) chromosomal regions. The success rate was 100%. The counts for the 5 SNPs

all adhered to Hardy-Weinberg equilibrium expectations: 32/78/36 (*GABRA2*; GG/GA/AA), 29/77/40 (*CHRM2*; TT/TC/CC), 68/57/21 (*ANKK1*; GG/GA/AA), 102/42/2 (*BDNF*; GG/GA/AA), and 64/63/19 (*KIBRA*; CC/CT/TT).

Because of statistical concerns about dividing our modest sample size across the 3 cells or levels of each SNP genotype, the smallest cell--consisting of minor allele homozygotes--was combined with the heterozygotes and then compared to the remaining cell, consisting of major allele homozygotes. The only exception to this strategy was the *KIBRA* genotype. For its analysis, minor T allele homozygotes were compared to major allele carriers (Zhang et al., 2009b).

2.5 Data Analysis

The initial analyses used simple ANOVA and χ^2 tests to examine intake differences between the outcome groups, Relapse- and Abstinence-prone, on various demographic, psychological, and psychiatric variables. A related set of analyses used multivariate logistic regression models to examine the association of outcome group with each SNP genotype as well as age, sex, and BDI-II, DAST-20, and MAST scores. Statistically significant logistic regressions were followed by Receiver Operating Characteristic (ROC) analyses to describe the accuracy (sensitivity/specificity) of the regression equations in predicting outcome.

The next set of analyses used Cox regression models and age, sex; number of intake alcohol, drug use, and depression symptoms, and SNP genotypes to predict outcome over time. A similar analysis was performed to clarify the importance of specific SNP genotypes (*GABRA2* and *KIBRA*) that the Cox analysis had shown to be important. Unlike the initial Cox analysis, this analysis used forward selection instead of simultaneous entry of predictors. Accordingly, it could test the χ^2 change, or added value, of predictors as they were sequentially entered.

3. Results

Table 1 presents the results of simple comparisons of the Relapse-Prone and Abstinence-Prone groups on their intake characteristics. The comparisons revealed no significant group differences in age [$F=2.3$], years of education [$F=3.8$], days of abstinence at study entry [$F=0.3$], or the sex ratio [$\chi^2=0.2$]. The groups were also similar in the number of adult anxiety [$F=0.8$] and childhood Conduct Disorder symptoms [$F=0.4$]. However, four other intake characteristics did differentiate the groups: IQ [$F=10.3$, $p<0.002$], depression symptoms reported on the BDI-II [$F=10.7$, $p<0.001$], and the number of alcohol [$F=8.5$, $p<0.004$] and drug [$F=12.4$, $p<0.001$] use problems respectively reported on the MAST and DAST-20. Patients who later relapsed exhibited a lower IQ, and reported more symptoms of depression, alcohol, and drug use than their successfully abstinent peers.

The next two tables (Tables 2a and 2b) present the results of two logistic regression analyses using predictors hypothesized to be relevant to outcome: age, sex, BDI-II, DAST-20 and MAST. These analyses also entered the SNP genotypes in separate iterations. The analyses showed that the *GABRA2* and *KIBRA* SNPs were the only significant genetic predictors. The remaining genotypes did not yield significant associations and are therefore not presented. Table 2a reveals a significant association between the "low substance dependence risk" *GABRA2* genotype and abstinence [$B=1.1$, Wald=4.4, $p=0.03$, OR=3.1 (95% CI: 1.1–9.1)]. Table 2b reveals a separate association between the "low risk for impaired cognitive control" *KIBRA* genotype and abstinence [$B=1.3$, Wald=4.7, $p=0.02$, OR=3.8 (95% CI: 1.1–12.9)]. In both the *GABRA2* and *KIBRA* analyses, age and DAST-20 score were significant negative predictors of an abstinent outcome.

ROC analyses were next used to calculate detection accuracy, i.e., sensitivity/specificity, in predicting abstinent outcomes. The areas under the ROC curves (AUC), estimating the agreement between actual and predicted outcomes, were significantly greater than the 0.5 chance criterion for both *GABRA2* and *KIBRA* (*GABRA2* AUC=0.66, SE=0.05, $p=0.002$, 95% CI= 0.55–0.76; *KIBRA* AUC=0.61, SE=0.05, $p=0.03$, 95% CI=0.51–0.71).

The next set of analyses used Cox regression methods to predict abstinence as the outcome over time. Tables 3a and 3b present the analysis results for *GABRA2* and *KIBRA*. Figures 1 and 2 show the corresponding survival functions. The results of these analyses were consistent with the results shown by the logistic regression analyses. *GABRA2* [B=−0.9, $p=0.03$, Hazard Ratio (HR) =0.39 (95% CI=0.2–0.9)] and *KIBRA* [B=−0.8, $p=0.05$, HR=0.44 (95% CI=0.2–1.0)] were the only SNP genotypes significantly associated with time-to-relapse. In these survival analyses, positive beta weights indicate a poor prognosis—a shorter time-to-relapse.

The final set of analyses were similar to the survival analyses of *GABRA2* and *KIBRA* just described. However, unlike the previous analyses, forward entry was specified as the mode. The results showed that the χ^2 change associated with adding either *GABRA2* [$\chi^2_{df=1}=5.77$, $p=0.01$] or *KIBRA* [$\chi^2_{df=1}=6.02$, $p=0.04$] genotype to a model that already included age and DAST-20 score was significant.

4. Discussion

The present study was founded on the hypothesis of a positive association between various SNPs previously implicated in substance involvement, or known risk factors for involvement, and relapse. The results provided partial support for the hypothesis. Representative SNPs within two of five candidate genes were significantly associated with relapse as well as a more rapid onset of the relapse. Importantly, in the forward selection model, these *GABRA2* and *KIBRA* genotypes brought added value to relapse prediction: the χ^2 increment associated with their addition to the regression equation, after age and severity of dependence (DAST-20) were entered, was significant. This test of incremental value is a major strength of the study.

Our focus on predictors of the genetic variety is a second major strength. In contrast to outcome predictors derived from self-reports, such as SUD symptom severity or self-efficacy ratings, genetic predictors offer almost perfect reliability. Additional advantages are their low cost, simplicity and speed of data collection (e.g., from saliva), and the wide availability of laboratories for DNA extraction and analysis. Also, unlike other biological measures, such as fMRI and EEG, genotypes are impervious to the effects of medications and other variables that affect the patient's state. The unresolved questions about *GABRA2* and *KIBRA* genotypes as predictors of outcome are their sensitivities and specificities, which are unknown outside of our relatively small sample. A study employing more patients than were studied presently is needed to provide a more definitive answer.

A final notable strength of the present study is the intensive method used for relapse monitoring. In many similar studies, relapses are solely determined on the basis of the patient's report during an interview conducted at the end of the monitoring period. Here, we regularly interviewed patients and collateral informants, and also obtained urine and breath samples for drug and alcohol screening biweekly throughout the 4 month monitoring period. Accordingly, misrepresentations by the patient about abstinence could be detected and an outcome could be more accurately assigned. Other advantages associated with intensive relapse monitoring are reduced attrition and lost contact, two situations that raise difficult questions about how a patient's outcome should be coded.

Of course, while contemplating these strengths, we should also contemplate the limitations. The first noteworthy limitation is the modest size (n=146) of our sample. A second limitation is our focus on patients who had psychosocial issues so significant as to bring them to live in a dormitory-like “sober” house, i.e., a residential substance abuse treatment facility. Future studies should test the reliability and generalizability of these genetic predictors in larger samples of substance-dependent patients receiving other forms of treatment, e.g., in outpatient or partial hospitalization settings.

A third limitation of the study is its narrow racial/ethnic composition. The genetic analyses performed presently could only be performed on the majority: patients of European American ancestry. Future studies should examine the predictive power of *GABRA2* and *KIBRA* in other ancestral groups.

The fourth limitation is defining relapse as “any use” versus a return to problematic use, i.e., a reinstatement of abuse or dependence. Although a return to problematic use is the most clinically significant outcome, the former outcome is also significant because episodes of use are often a harbinger of a full relapse to dependence. A sensitive genetic test that predicts this prodrome to dependence may still be useful.

The fifth limitation relates to the unknown mechanisms through *GABRA2* and *KIBRA* may act to promote a poor outcome. An argument can be made that the connection of *GABRA2* to relapse is mediated through effects on conduct problems (Dick et al., 2006), impulsivity (Villafuerte et al., 2011), or anxiety (Enoch et al., 2006). Yet, despite evidence of an effect of *GABRA2* genotype on psychological mediators, we do not yet know how *GABRA2* gene variants operate at a more basic level to affect gene function or expression. It is possible that the rs279858 *GABRA2* synonymous SNP is linked with another, presently unknown genetic polymorphism which more directly affects expression.

Another limitation applies only to *KIBRA*. Although SNPs within this gene have been associated with individual differences in hippocampal function (Papassotiropoulos et al., 2006) and episodic memory, as well as perseveration errors on the Wisconsin Card Sorting Task (Zhang et al., 2009b), the direction of the relationship has varied. Several investigations find that noncarriers of the T-allele are impaired. We and a few other groups report the opposite. For this reason, we have less confidence in our *KIBRA* results than the *GABRA2* results. Indeed, the present *GABRA2* results are remarkably consistent with the results of our 2007 outcome prediction analysis involving 812 Project MATCH participants.

A final limitation is the questionable need for *GABRA2* or *KIBRA* genotyping in relapse prediction when a simple assessment of family history might suffice. In a separate set of analyses not described here, we asked this question of our data. The findings were interesting. As expected, the analysis revealed a strong association between the high-risk *GABRA2* and *KIBRA* genotypes and familial density of substance dependence, as well as little or no incremental value of the genotypes over familial density in predicting outcome. But, the analysis also reminded us of a well-recognized problem in family history assessment: familial risk cannot be estimated in many patients because they lack sufficient knowledge or are unreliable reporters. Yet, genotypes could be determined in all cases. The consideration of genotypes is therefore worth the effort. Genotypes can provide information about relapse risk to the clinician or researcher when family history information is missing or unreliable. They add value.

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Figure 1. Probability of abstinence as a function of *GABRA2* genotype and time. High risk, G-carriers are shown by the dashed line. A-allele homozygotes are shown by the solid line.

Figure 2. Probability of abstinence as a function of *KIBRA* genotype and time. Minor T-allele carriers are shown by the dashed line. The T-allele has been associated with impaired cognitive control.

Table 1

Intake characteristics sorted by outcome [Mean (SD) or percent]

Variable	Relapse-Prone (n=52)	Abstinence-Prone (n=94)
Age in yrs (SD)	38.9(10.3)	36.1(10.6)
Yrs Education	12.6(1.8)	13.5(2.1)
% Female	51	46
KBIT IQ *	98.8(11.5)	105.4(11.2)
BDI-II depression *	14.5(8.5)	9.6(8.5)
BAI anxiety	8.2(7.3)	7.0(7.9)
MAST alcohol use problems *	9.9(7.2)	6.4(6.6)
DAST-20 drug use problems *	14.3(5.5)	9.7(8.2)
# Childhood Conduct Disorder Symptoms	2.9(2.6)	2.6(3.1)
# Days Abstinent	110(115)	142(185)

* Group comparison, $p < 0.05$.

Table 2a

Logistic regression analysis results for the prediction of an abstinent outcome.

Predictor	B	S.E.	Wald	df	p	OR (95% CI)
AGE	-.04	.02	5.42	1	.020	.95 (0.91–0.99)
SEX	-.22	.39	.32	1	.570	.79 (0.36–1.73)
BDI-II	-.03	.02	2.44	1	.118	.96 (0.92–1.01)
DAST20	-.08	.03	6.62	1	.010	.91 (0.85–0.97)
MAST	-.03	.03	.66	1	.413	.97 (0.91–1.03)
Low-risk GABRA2 Genotype	1.15	.54	4.46	1	.035	3.15 (1.08–9.17)

Table 2b

Logistic regression analysis results for the prediction of an abstinent outcome.

Predictor	B	S.E.	Wald	df	p	OR(95% CI)
AGE	-.04	.02	4.19	1	.041	.95 (0.92–0.99)
SEX	-.17	.40	.19	1	.657	.83 (0.38–1.83)
BDI-II	-.04	.02	3.72	1	.054	.95 (0.91–1.00)
DAST20	-.08	.03	6.25	1	.012	.91 (0.86–0.98)
MAST	-.03	.03	1.01	1	.314	.96 (0.91–1.03)
Low-risk KIBRA Genotype	1.35	.61	4.75	1	.029	3.85 (1.14–12.98)

Table 3a

GABRA2 survival analysis

Predictor	B	S.E.	Wald	df	p	HR (95% CI)
AGE	.03	.01	4.67	1	.031	1.03 (1.00–1.06)
SEX	.22	.29	.61	1	.432	1.25 (0.71–2.21)
BDI2	.02	.02	1.83	1	.176	1.02 (0.99–1.06)
DAST20	.07	.02	7.32	1	.007	1.07 (1.02–1.12)
MAST	.01	.02	.12	1	.729	1.00 (0.96–1.05)
GABRA2 Genotype	-.93	.43	4.49	1	.034	.39 (0.16–0.93)

Table 3b

KIBRA survival analysis

Predictor	B	S.E.	Wald	df	p	HR (95% CI)
AGE	.03	.01	3.95	1	.047	1.02 (1.00–1.06)
SEX	.25	.29	.73	1	.392	1.28 (0.72–2.28)
BDI2	.03	.02	2.57	1	.108	1.02 (0.99–1.06)
DAST20	.07	.03	7.82	1	.005	1.07 (1.02–1.13)
MAST	.01	.02	.20	1	.651	1.01 (0.96–1.06)
KIBRA Genotype	-.81	.41	3.82	1	.051	.44 (0.20–1.00)