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Effect of genetic variation in the nicotinic receptor genes on risk for posttraumatic stress disorder

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Abstract

The present study examined the association between genetic variation in the nicotinic receptor gene family (CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNA10, CHRNB2, CHRNB3, CHRNB4) and the occurrence of posttraumatic stress disorder (PTSD). Clinical interviews were used to diagnose PTSD in 925 non-Hispanic Black (NHB) and 743 non-Hispanic White (NHW) participants. Trauma history and smoking status were assessed with self-report. No significant main effects or single nucleotide polymorphism (SNP) * smoking interactions were observed among NHB participants; however, among NHW participants, a novel association between rs12898919 in the cholinergic receptor nicotinic alpha-5 (*CHRNA5*) gene and PTSD was observed. No other significant main effects or SNP * smoking interactions were identified among NHW participants. While preliminary, these findings provide continued support for the hypothesis that the *CHRNA5* gene is associated with increased risk for PTSD. Limitations of the present study include cross-sectional design, relatively small sample sizes for genetic research, use of self-report to assess smoking status, and use of different methods to diagnose PTSD. Additional research in other samples of trauma-exposed participants is needed to identify the specific functional variant(s) responsible for the association observed between *CHRNA5* and PTSD risk in the present study.

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1. Introduction

Posttraumatic stress disorder (PTSD) is a complex psychiatric disorder that sometimes develops following exposure to a potentially-traumatic event (PTE; Kessler, 2000; Breslau, 2002). While most individuals exposed to PTEs do not develop PTSD, approximately 6.8-7.6% of individuals will develop PTSD during their lifetime (Kessler et al., 1995, 2005). Although it is clear that traumatic exposure and other environmental factors play a major role in the development of PTSD (e.g., Dedert et al., 2009; Kimbrel et al., 2014), the variability in response to PTEs suggests that genetic factors are also important (Breslau, 2002; Koenen et al., 2008).

Twin studies indicate that approximately 30% of the variability in PTSD can be attributed to genetic influences (Lyons et al., 1993; True et al., 1993; Stein et al., 2002); however, specific genetic risk factors for PTSD remain largely unknown (Cornelis et al., 2010; Pitman et al., 2012). More than 40 candidate gene studies of PTSD have been conducted to date (Pitman et al., 2012), but only a handful of genes have been associated with PTSD in at least two separate studies, such as the serotonin transporter (*SLC6A4*; Kilpatrick et al., 2007; Xie et al., 2009, 2012; Wang et al., 2011; Liu et al., 2015; Kimbrel et al., 2015), FK506 binding protein 5 (*FKBP5*; Koenen et al., 2005; Binder et al., 2008; Xie et al., 2010; Boscarino et al., 2011), catechol-omethyltransferase (*COMT*; Kolassa et al., 2010; Boscarino et al., 2011), and apolipoprotein E (*APOE*; Lyons et al., 2013; Kimbrel et al., 2015) genes. In addition, while genome-wide association studies (GWAS) studies of PTSD have emerged in recent years (e.g., Guffanti et al., 2013; Logue et al., 2013; Nievergelt et al., 2015; Xie et al., 2013; Ashley-Koch et al., in press), the most significant associations from these studies have had little overlap. Thus, there remains a critical need for replication of genes previously associated with PTSD as well as exploration of novel genes to advance this important area of research.

1.1 Nicotinic Receptor Genes and PTSD

Given the well-documented association between smoking and PTSD (e.g., Fu et al., 2007) and between smoking and the nicotinic receptor genes (e.g., Berrettini et al., 2008), the present study aimed to examine whether genetic variation within the nicotinic receptor gene family might also influence risk for PTSD. To date, the nicotinic receptor gene family has received relatively little evaluation for a role in PTSD, despite the fact that a single nucleotide polymorphism (SNP; rs16969968) in one of the nicotinic receptor genes—the cholinergic receptor nicotinic alpha-5 (*CHRNA5*) gene—has been associated with PTSD in two previous studies (Boscarino et al., 2011, 2012).

1.2 Objectives

The first objective of the present study was to replicate the finding by Boscarino et al. (2011, 2012) associating *CHRNA5* with PTSD. The second objective was to explore whether

common variants in other genes from the nicotinic receptor gene family (CHRNA2, CHRNA3, CHRNA4, CHRNA6, CHRNA7, CHRNA9, CHRNA10, CHRNB2, CHRNB3, and *CHRNB4*) might also be associated with PTSD. To our knowledge, no previous candidate gene study has examined this entire gene family in relation to PTSD.

2. Methods

2.1 Participants and Procedures

Participants were drawn from the VA Mid-Atlantic Mental Illness Research, Education and Clinical Center (MIRECC) Post-Deployment Mental Health (PDMH) Study and the Traumatic Stress and Health Genetics (TSHG) Study at the Durham VA and Duke University Medical Center. The PDMH Study is a registry study of Veterans who served in the United States military since September 11, 2001. The TSHG study is a genetic study of PTSD that recruited participants from a variety of other trauma research studies at the Durham VA and Duke University Medical Center. Whereas the PDMH is restricted to Iraq/Afghanistan-era Veterans, the TSHG includes Veterans from a variety of eras as well as community civilians who agreed to donate a blood sample for genetic analyses. All studies received IRB approval, and all participants provided consent prior to participating.

Participants in the PDMH were primarily recruited through recruitment letters that invited them to participate in their respective studies; however, participants were also recruited through advertisements and clinician referrals. Participants in the TSHG were recruited from a variety of other trauma research studies at the Durham VA and Duke University Medical Center. The PDMH and TSHG studies used identical methodologies to obtain blood samples from participants and to assess traumatic exposure; however, different methods were used for diagnosing psychiatric disorders. The PDMH study used the Structured Clinical Interview for DSM-IV (SCID; First et al., 1994) to diagnose PTSD, whereas the Clinician-Administered PTSD Scale (CAPS; Blake et al., 1995) was used in the TSHG Study.

To be eligible for the current analyses, participants had to report at least one PTE on the Traumatic Life Events Questionnaire (TLEQ; Kubany, 2000) that caused them fear, helplessness, or horror. We also restricted the analyses to the two largest racial groups in the combined sample—non-Hispanic Blacks (NHB) and non-Hispanic Whites (NHW)—because of the potential effects of admixture on the genetic analyses. Finally, participants were required to have genetic, smoking, diagnostic, and trauma history data available for analysis in order to be included in the present study. After these selection criteria were applied, a final sample of 925 NHB participants and 743 NHW participants (total $N = 1668$) were available for analysis.

2.2 Measures

As noted above, the SCID (First et al., 1994) was used to diagnose PTSD during the past month (i.e., current) in the MIRECC PDMH sample ($n = 1433$), whereas the CAPS (Blake et al., 1995) was used in the TSHG Study ($n = 235$). Scores on the Davidson Trauma Scale (DTS; Davidson et al., 1997) were used to categorize participants as either cases (DTS ≥ 75) or controls (DTS ≤ 24) in the small number of instances ($n = 91$) where neither SCID nor

CAPS data was available. The DTS is a 17-item self-report measure of DSM-IV-TR PTSD symptoms that has consistently demonstrated strong psychometric properties, including excellent diagnostic efficiency (e.g., Davidson et al., 1997; McDonald et al., 2014). The specific cut-offs that were chosen for the current study were based on findings from McDonald and colleagues (2014) which found that a cut-off score of 75 or more on the DTS produced a positive predictive value of 0.96, whereas a cut-off score of 24 or less produced a negative predictive value of 0.96. Thus, by using cut-off scores of DTS ≥ 75 for cases and DTS ≤ 24 for controls we hoped to maximize identification of true cases and true non-cases. Trauma exposure was assessed with the TLEQ (Kubany, 2000), a 23-item self-report measure of traumatic experiences.

2.3 Genotyping and Imputation

Whole blood samples were obtained through venipuncture. DNA was extracted from these samples using the Puregene system (Gentra Systems, Minneapolis, MN). Briefly, whole-genome data was generated across three different platforms, including the Illumina HumanHap650 Beadchip, the Illumina Human1M-Duo Beadchip, and the Illumina HumanOmni2.5 Beadchip (Illumina, San Diego, CA) as part of a larger GWAS study on the genetics of PTSD (Ashley-Koch et al., in press). Quality control procedures included the use of Centre d'Etude du Polymorphism Humain (CEPH) samples as well as masked sample duplicates as controls. Probes were required to have a call rate > 98% and Hardy-Weinberg Equilibrium (HWE) p-values > 10^{-6} in controls. Missing genotypes were imputed using a global reference panel from The 1000 Genomes Project (www.1000genomes.org) in order to increase genomic coverage and obtain a concordant set of SNPs across the samples genotyped using different chips. Additional details regarding our imputation approach are available in Ashley-Koch et al. in press.

2.4 Data Analytic Plan

The NHB and NHW individuals were analyzed separately to minimize the potential effects of population stratification. NHB and NHW status was initially determined by self-report. Within each racial group, we further controlled for population substructure by including principle components (PCs) derived from genome-wide data using the smartpca program from the software package EIGENSOFT (Patterson et al., 2006). Three PCs were necessary to adequately control for remaining population substructure in the NHB subset. Six PCs were retained in the NHW subset. Logistic regression was used to determine the effects of SNPs in the nicotinic receptor genes on risk for current PTSD in the NHB and NHW subsets separately using PLINK (Purcell et al., 2007). All available SNPs from the 11 nicotinic receptor genes (CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNA10, CHRNB2, CHRNB3, and *CHRNB4*) were initially extracted from the imputed genome-wide data for analysis in the current study. SNPs in high linkage disequilibrium (LD; $R^2 \geq 0.5$) were removed using PLINK. Following LD pruning, 77 SNPs remained available for analysis in the NHB sample and 33 SNPs remained in the NHW sample. To control for multiple testing, spectral decomposition (Li and Ji, 2005) was used to determine the “effective” number of tests within each racial subset, which resulted in 76 effective tests within the NHB sample and 33 within the NHW sample. A Bonferroni

correction using the effective number of tests was then applied, resulting in a multiple testing threshold of 0.0007 for the NHB sample and 0.0015 for the NHW sample.

An additive genetic model was employed in all logistic regression models. Covariates included age, population stratification PCs, TLEQ total scores, cohort (PDMH vs. TSHG study), and smoking status. Smoking status was defined categorically as never smoker, ex-smoker, or current smoker based on participants' self-report. Two separate models were run: (1) A main effects model which examined only the direct effects of each SNP, smoking status, age, PCs, study, and TLEQ total score on current PTSD status; and (2) a gene * environment (G*E) model which examined the SNP * smoking status interaction term for each SNP, controlling for the covariates listed above.

3. Results

Sample characteristics by case-control status are provided in Table 1. TLEQ total sum, lifetime major depressive disorder (MDD), drug abuse/dependence, alcohol abuse/dependence, and smoking status were all significantly different between the cases and controls for each racial group. Additionally, cohort (PDMH vs. TSHG study) was significant in the NHB sample and age was significant in the NHW sample (p's < 0.05).

No main genetic effects or G*E interactions were statistically significant among NHB participants at the multiple testing threshold of 0.0007 (Table 2), including the main effect for rs16969968 from *CHRNA5* (p = 0.0858). This SNP was also not associated with PTSD among the NHW participants (p = 0.6153); however, a different SNP (rs12898919) in the *CHRNA5* gene provided evidence for a main effect on PTSD risk in the NHW sample, and this association met correction for multiple testing (Table 3).

Specifically, we found that rs12898919 of the *CHRNA5* gene was significantly associated with having a current PTSD diagnosis, such that for each additional C allele, the odds of PTSD increased by 2.35 [95% confidence interval (CI): 1.44 – 3.83, p = 0.0006114; Table 3]. The rate of current PTSD was 39.9% (260/652) among homozygotes for the major allele, 60.2% (53/88) among heterozygotes, and 100% (1/1) among the sole participant homozygous for the minor (C) allele of rs12898919. Because there was only one participant with the rare homozygous genotype, an *ad hoc* allele test was conducted to ensure the genotype of the one participant that was homozygous for the C allele was not driving the observed association with this SNP. The association remained significant in the allele test (C allele vs. G allele), such that those with the C allele were 2.22 times as likely as those with the G allele to have PTSD (95% CI: 1.380 – 3.578, p = 0.0010). No other main effects or G*E effects were statistically significant at the multiple-testing threshold among NHW participants; however, a number of nominally significant associations (p < .05) were observed in both the NHW and NHB samples (see Tables 2 and 3).

4. Discussion

The findings from the present study provide continued support for the role of the *CHRNA5* gene in risk for PTSD. We did not replicate the association between rs16969968 of the *CHRNA5* gene and PTSD reported by Boscarino et al. (2011, 2012) in either the NHB (p =

0.0858) or NHW (p = 0.6153) sample. We did, however, identify a novel association between rs12898919 of the *CHRNA5* gene and PTSD among NHW participants that remained statistically significant after accounting for smoking status, age, PCs, cohort, and trauma exposure. While this finding is in need of further replication, our results are consistent with those of Boscarino et al. (2011, 2012) and suggest that CHRNA5 may play a role in the pathogenesis of PTSD.

The exact mechanism through which CHRNA5 might influence susceptibility to PTSD is unclear at the present time. One possibility is that its effects on PTSD are mediated through its influence on smoking and nicotine dependence. For example, we know that nicotinic receptors influence the reward system and cognitive functioning (Zhang et al., 2010). We also know that CHRNA5 is critically involved in controlling the drive to obtain nicotine (Fowler et al., 2011), and that it is implicated in vulnerability to smoking, substance dependence, and lung cancer (e.g., Berrettini et al., 2008; Erlich et al., 2010; Kuryatov et al., 2011). Given that smoking is associated with PTSD (e.g., Fu et al., 2007), we suspect that the effect of CHRNA5 on PTSD is mediated through its influence on smoking and nicotine dependence. Unfortunately, the cross-sectional design of the current study did not allow for a rigorous test of this hypothesis. Thus, additional longitudinal research is needed to properly address this question.

4.1 Strengths and Limitations

The current study had several strengths and limitations. Notable strengths included use of trauma-exposed control participants, structured clinical interviews to diagnose the majority of participants, and inclusion of important covariates such as population stratification PCs, trauma exposure scores, and smoking status. Limitations included the cross-sectional design, relatively small sample sizes for genetic research, use of self-report to assess smoking status, and use of different methods to diagnose PTSD.

4.2 Conclusion

The objective of the present research was to explore whether common variants in the nicotinic receptor gene family (CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA9, CHRNA10, CHRNB2, CHRNB3, and *CHRNB4*) might be associated with PTSD, as no previous candidate gene study has examined this entire gene family in relation to PTSD. Our findings provide continued support for the hypothesis that the *CHRNA5* gene plays a role in the pathogenesis of PTSD; however, the specific genetic variant that we found to be associated with PTSD in the current study (rs12898919) differs from the variant previously identified by Boscarino and colleagues (2011, 2012; rs16969968). Taken together, these findings suggest that the functional variant(s) within *CHRNA5* that are contributing to the association with PTSD are still unknown. Thus, additional research on the association between *CHRNA5* and PTSD will be necessary to identify this causal variation to better understand this association.

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Highlights

- We examined the association between the nicotinic receptor gene family and PTSD
- No significant effects were observed among non-Hispanic Black participants
- A novel SNP in the *CHRNA5* gene was associated with PTSD in non-Hispanic Whites

Table 1

Participant Characteristics by Case-Control Status and Racial Group

	NHB *n* = 925			NHW *n*= 743		
	Cases	**Controls**	**p-value**	**Cases**	**Controls**	**p-value**
TSHG study (%)	24.1%	14.2%	0.0001	10.8%	7.7%	0.1538
Gender (% Male)	69.5%	70.6%	0.7246	85.8%	85.5%	0.9146
Age in years (S.D.)	38.7 (9.8)	39.4 (9.6)	0.2497	35.2 (9.6)	37.2 (10.9)	0.0108
TLEQ total sum*	24.6 (16.3)	14.0 (10.1)	<0.0001	27.6 (16.1)	15.6 (11.8)	<0.0001
DTS total score	79.4 (31.8)	20.6 (27.7)	<0.0001	80.0 (31.5)	19.0 (25.9)	<0.0001
Lifetime major depression diagnosis	66.8%	23.7%	<0.0001	65.1%	23.0%	<0.0001
Lifetime drug abuse/dependence	29.2%	16.9%	<0.0001	24.7%	13.9%	0.0003
Lifetime alcohol abuse/dependence	56.0%	30.0%	<0.0001	55.3%	37.2%	<0.0001
Smoking status			<0.0001			<0.0001
current smoker	41.4%	25.2%		47.5%	25.3%	
ex-smoker	15.2%	17.2%		20.3%	26.2%	
never smoker	43.3%	57.5%		32.3%	48.5%	

*variable was log-transformed for analysis due to non-normality.

Table 2

Summary of Nicotinic Receptor Gene Effects on PTSD Risk in Non-Hispanic Blacks (n = 925)

Gene	CHR	SNP	HWE p-value	A1	MAF	Main Effect p-value	G×E p-value
CHRNB2	1	1-154533463	0.6474	C	0.01315	0.2068	0.1084
CHRNB2	1	rs115411271	0.1634	A	0.07538	0.8443	0.218
CHRNA9	4	rs10024518	0.5969	A	0.03761	0.9377	0.8081
CHRNA9	4	rs116380416	0.0898	G	0.01364	0.4925	0.2434
CHRNA9	4	rs112422052	0.1074	T	0.01414	0.2727	0.8644
CHRNA9	4	rs115327085	0.4755	A	0.06853	0.6206	0.3173
CHRNA9	4	rs7655828	0.328	C	0.02783	0.05445	0.5747
CHRNA9	4	4-40345413	0.5636	A	0.01654	0.1956	0.4409
CHRNA9	4	4-40346053	0.615	C	0.01446	0.5716	0.06904
CHRNA9	4	rs112305367	0.6464	A	0.01323	0.7818	0.6261
CHRNA9	4	rs78800928	0.5091	C	0.01906	0.6115	0.09041
CHRNA9	4	rs114867797	0.4638	T	0.02099	0.9848	0.3046
CHRNA9	4	rs6818856	0.9262	A	0.04259	0.2528	0.898
CHRNA9	4	rs114929155	0.6131	A	0.1646	0.582	0.8293
CHRNA9	4	rs11946727	0.8589	G	0.03896	0.5511	0.4818
CHRNA9	4	rs57973150	0.1766	C	0.03797	0.4362	0.08437
CHRNA9	4	4-40356646	0.3772	C	0.01917	0.16	0.3149
CHRNA2	8	rs112587531	0.8132	A	0.09812	0.1597	0.7221
CHRNA2	8	8-27319038	0.5526	A	0.01704	0.6115	0.7362
CHRNA2	8	rs9314347	0.6841	G	0.06588	0.1561	0.7584
CHRNA2	8	rs116429685	0.4595	A	0.0205	0.8037	0.7495
CHRNA2	8	rs747111	0.7128	A	0.08241	0.3243	0.6916
CHRNA2	8	rs60646603	0.007	G	0.01792	0.03028	0.7831
CHRNA2	8	8-27330227	0.3823	A	0.01933	0.7335	0.4855
CHRNA2	8	rs10104133	0.5597	T	0.03866	0.7681	0.04795
CHRNA2	8	rs73679204	0.1248	C	0.04314	0.01487	0.1744
CHRNA2	8	rs114817081	0.1801	C	0.0378	0.2509	0.5356
CHRNA2	8	rs80025940	0.653	T	0.02352	0.2362	0.877
CHRNB3	8	rs9643891	0.9786	T	0.2254	0.1954	0.6677
CHRNB3	8	rs113888748	0.6247	G	0.04451	0.843	0.9919
CHRNB3	8	rs75431302	0.0028	C	0.02365	0.0908	0.039
CHRNB3	8	rs60719005	0.594	G	0.01531	0.05669	0.5208
CHRNB3	8	rs6651365	0.668	T	0.0359	0.2326	0.2893
CHRNB3	8	8-42571417	0.5523	A	0.01706	0.07868	0.1492
CHRNB3	8	8-42578842	0.3005	T	0.01792	0.499	0.8099
CHRNB3	8	8-42579668	0.3321	G	0.01855	0.9841	0.2012
CHRNB3	8	8-42583990	0.3062	T	0.02904	0.1526	0.9026
CHRNB3	8	rs16891563	0.8709	C	0.02711	0.9977	0.5092
CHRNA6	8	8-42605906	0.5216	G	0.01841	0.3783	0.06368

Gene	CHR	SNP	HWE p-value	A1	MAF	Main Effect p-value	G×E p-value
CHRNA10	11	11-3687104	0.6243	G	0.01413	0.3535	0.8495
CHRNA10	11	rs74049384	0.339	T	0.04565	0.9315	0.8491
CHRNA7	15	rs74463288	0.5229	G	0.0183	0.9835	0.3866
CHRNA7	15	rs11071503	0.2916	C	0.2753	0.9514	0.9924
CHRNA7	15	rs7178564	0.6012	C	0.01514	0.5566	0.8751
CHRNA7	15	rs4779969	0.9506	A	0.2402	0.4794	0.2481
CHRNA7	15	rs114569889	0.6911	G	0.01143	0.1093	0.875
CHRNA7	15	rs111865782	0.5519	G	0.01709	0.3256	0.3563
CHRNA7	15	rs116613835	0.9737	T	0.04174	0.7345	0.1074
CHRNA7	15	rs114087523	0.6326	T	0.02332	0.878	0.4071
CHRNA7	15	rs4779565	0.3965	T	0.2525	0.8295	0.7356
CHRNA7	15	rs8029400	0.7818	T	0.2383	0.393	0.184
CHRNA7	15	15-32400467	0.0892	G	0.01361	0.9123	0.8645
CHRNA7	15	rs11852956	0.095	C	0.1319	0.1422	0.3518
CHRNA7	15	rs13329490	0.9629	C	0.08657	0.9447	0.1001
CHRNA7	15	rs75010965	0.519	C	0.01863	0.9959	0.6491
CHRNA7	15	rs904952	0.0162	C	0.294	0.8154	0.329
CHRNA7	15	15-32421322	0.6343	C	0.01376	0.4029	0.6598
CHRNA5	15	rs116297933	0.8832	G	0.04855	0.2636	0.5876
CHRNA5	15	15-78861349	0.6458	C	0.01327	0.2715	0.6187
CHRNA5	15	rs7165657	0.8893	G	0.1154	0.7337	0.988
CHRNA5	15	15-78862485	0.119	G	0.04359	0.3321	0.6221
CHRNA5	15	rs588765	0.9069	T	0.2975	0.1427	0.3985
CHRNA5	15	rs112234596	0.8403	T	0.1159	0.9207	0.7649
CHRNA5	15	rs12903839	0.702	G	0.01102	0.5432	0.9433
CHRNA5	15	rs80087508	0.4857	G	0.02089	0.01196	0.9147
CHRNA5	15	rs16969968	0.0331	A	0.05833	0.08577	0.4467
CHRNA3	15	rs7359276	0.5059	C	0.4553	0.07964	0.8799
CHRNA3	15	rs1051730	0.0166	A	0.1178	0.2913	0.1057
CHRNA3	15	rs7179998	0.6237	A	0.01418	0.6284	0.2225
CHRNA3	15	rs2869547	0.3868	T	0.02458	0.2501	0.6004
CHRNA3	15	15-78912604	0.6256	T	0.01403	0.2019	0.981
CHRNA3	15	15-78912699	0.6118	C	0.01471	0.3163	0.06271
CHRNB4	15	rs76652377	0.5032	T	0.01917	0.07824	0.2616
CHRNB4	15	15-78926497	0.0305	T	0.01154	0.7415	0.3759
CHRNB4	15	rs57728226	0.7852	C	0.1025	0.7906	0.7297
CHRNA4	20	rs4809540	0.202	C	0.1808	0.2881	0.6872
CHRNA4	20	rs12624510	0.6117	A	0.01472	0.8296	0.1748

Note: CHR = Chromosome; SNP = Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; A1 = minor allele; MAF = minor allele frequency; G×E = gene × environment. Imputed SNPs without reference SNP numbers are denoted by chromosome-base pair location from NCBI build 37.

Table 3

Summary of Nicotinic Receptor Gene Effects on PTSD Risk in non-Hispanic Whites (n = 743)

Gene	CHR	SNP	HWE p-value	A1	MAF	Main Effect p-value	G×E p-value
CHRNB2	1	rs4292956	0.9771	T	0.07	0.8366	0.4625
CHRNA9	4	4-40338579	0.6419	C	0.06	0.8366	0.5375
CHRNA9	4	rs7655828	0.8322	C	0.05	0.9886	0.9719
CHRNA9	4	rs114219703	0.8956	T	0.08	0.4272	0.1883
CHRNA9	4	rs112419906	0.9872	T	0.26	0.5949	0.2975
CHRNA2	8	rs9314347	0.6345	G	0.07	0.2087	0.2337
CHRNA2	8	rs117531183	0.7081	A	0.01	0.7155	0.646
CHRNA2	8	rs747111	0.1175	A	0.31	0.9464	0.6913
CHRNA2	8	8-27330791	0.6214	C	0.02	0.565	0.6504
CHRNA2	8	rs2565067	0.2227	A	0.18	0.9635	0.007639
CHRNA2	8	rs80018801	0.4728	A	0.02	0.4684	0.5112
CHRNA2	8	rs55726427	0.6223	A	0.02	0.1325	0.889
CHRNB3	8	rs62516743	0.4078	A	0.03	0.7071	0.03093
CHRNB3	8	rs13261190	0.1067	G	0.09	0.3238	0.4121
CHRNB3	8	8-42589787	0.6583	C	0.01	0.1228	0.7985
CHRNA6	8	rs11995032	0.0724	T	0.03	0.6457	0.199
CHRNA6	8	rs74572794	0.2832	A	0.02	0.1012	0.0152
CHRNA10	11	rs56167171	0.644	A	0.02	0.2844	0.3983
CHRNA7	15	rs4779966	0.0045	A	0.05	0.441	0.1709
CHRNA7	15	rs7178829	0.6443	C	0.17	0.6024	0.2667
CHRNA7	15	rs12914788	0.3299	C	0.1	0.07809	0.7355
CHRNA7	15	rs12899561	0.4962	G	0.05	0.1095	0.5059
CHRNA7	15	rs8035668	0.8893	G	0.19	0.7577	0.4618
CHRNA7	15	rs8036584	0.5663	C	0.22	0.005739	0.5851
CHRNA7	15	rs2878994	0.0406	G	0.14	0.1484	0.8159
CHRNA7	15	rs904951	0.8809	G	0.47	0.4223	0.2614
CHRNA5	15	rs588765	0.9954	T	0.45	0.02006	0.04947
CHRNA5	**15**	**rs12898919**	**0.1692**	**C**	**0.06**	**0.0006114***	**0.4988**
CHRNA5	15	rs16969968	0.5029	A	0.32	0.6153	0.172
CHRNB4	15	rs71528526	0.6842	T	0.01	0.05462	0.5401
CHRNB4	15	rs1316971	0.2625	A	0.19	0.003377	0.6343
CHRNA4	20	rs73155457	0.7184	G	0.26	0.6661	0.5951
CHRNA4	20	rs2093107	0.058	A	0.07	0.7534	0.5202

Note:

* meets multiple testing threshold of 0.0015; CHR = Chromosome; SNP = Single nucleotide polymorphism; HWE = Hardy-Weinberg equilibrium; A1 = minor allele; MAF = minor allele frequency; G×E = gene × environment. Imputed SNPs without reference SNP numbers are denoted by chromosome-base pair location from NCBI build 37.