Twin Research and Human Genetics
Volume 18 ▌ Number 6 ▌ pp. 727–737 ▌ © The Author(s) 2015 ▌ doi:10.1017/thg.2015.77

Variants Near CCK Receptors are Associated With Electrophysiological Responses to Pre-pulse Startle Stimuli in a Mexican American Cohort

Trina M. Norden-Krichmar,[1,2] Ian R. Gizer,[3] Evelyn Phillips,[1] Kirk C. Wilhelmsen,[4] Nicholas J. Schork,[5] and Cindy L. Ehlers[1]

[1]*Department of Molecular and Cellular Neuroscience, The Scripps Research Institute, La Jolla, CA, USA*
[2]*Department of Epidemiology, University of California, Irvine, CA, USA*
[3]*Department of Psychological Sciences, University of Missouri, Columbia, MO, USA*
[4]*Department of Genetics and Neurology, University of North Carolina, Chapel Hill, N.C., USA*
[5]*Department of Human Biology, J. Craig Venter Institute, La Jolla, CA, USA*

Neurophysiological measurements of the response to pre-pulse and startle stimuli have been suggested to represent an important endophenotype for both substance dependence and other select psychiatric disorders. We have previously shown, in young adult Mexican Americans (MA), that presentation of a short delay acoustic pre-pulse, prior to the startle stimuli can elicit a late negative component at about 400 msec (N4S), in the event-related potential (ERP), recorded from frontal cortical areas. In the present study, we investigated whether genetic factors associated with this endophenotype could be identified. The study included 420 (age 18–30 years) MA men ($n = 170$), and women ($n = 250$). DNA was genotyped using an Affymetrix Axiom Exome1A chip. An association analysis revealed that the *CCKAR* and *CCKBR* (cholecystokinin A and B receptor) genes each had a nearby variant that showed suggestive significance with the amplitude of the N4S component to pre-pulse stimuli. The neurotransmitter cholecystokinin (*CCK*), along with its receptors, *CCKAR* and *CCKBR*, have been previously associated with psychiatric disorders, suggesting that variants near these genes may play a role in the pre-pulse/startle response in this cohort.

■ **Keywords:** Mexican Americans, startle response, EEG, ERP, alcohol dependence

The identification of neurophysiological endophenotypes associated with psychiatric disorders may help in determining the causal relationship between clinical phenomena associated with the disorder and basic molecular processes that are in large part determined by genetic factors. One psychophysiological measure that has been used as a potential endophenotype for a number of psychiatric disorders is the acoustic startle reflex (ASR) and pre-pulse inhibition of the startle (PPI). The startle reflex is a constellation of responses usually indexed by eye blink responses (Swerdlow et al., 1992), but also by electrophysiological recordings from cortical areas that may index cognitive responses to startle (Ehlers et al., 2011; Ford et al., 1994, 1999; Putnam & Roth, 1990). PPI refers to the fact that if a weak stimulus is presented prior to the presentation of the startle stimuli (pre-pulse) the response to the startle is reduced in amplitude. It has been suggested that pre-pulse inhibition is an index of automatic sensorimotor gating (Geyer & Swerdlow, 2001). In pre-pulse facilitation (PPF), the response to the startle is enhanced by short or long delay pre-pulses. PPF has been suggested to reflect a combination of alerting, attention and/ or arousal (Filion et al., 1998; Hsieh et al., 2006; Ludewig et al., 2003).

The anatomical substrates of the neurobehavioral responses (ASR/PPI/PPF) to the presentation of the startle stimuli have been extensively investigated in clinical and pre-clinical studies (Braff et al., 2001a, 2001b; Kumari et al., 2005; Swerdlow et al., 1994). Startle responses involve a complex neural network extending from brainstem nuclei via the thalamus to higher order cortical areas that may regulate cognitive responses to startle (Campbell et al., 2007; Fendt et al., 2001; Kumari et al., 2005; Neuner et al., 2010; Schall et al., 1999). There is some evidence that the cognitive response to ASR/PPI may share a common

RECEIVED 4 August 2015; ACCEPTED 3 September 2015. First published online 26 November 2015.

ADDRESS FOR CORRESPONDENCE: Cindy L. Ehlers, Department of Molecular and Cellular Neuroscience, The Scripps Research Institute, La Jolla, CA 92037 USA. E-mail: cindye@scripps.edu

underlying neurophysiology with some behavioral and clinical measures of cognition that require response inhibition (Filion et al., 1999). For instance, both performance on the Wisconsin Card Sorting Task and PPI of startle have been suggested to reflect pre-frontal cortical function and dysfunction (Filion et al., 1999; Swerdlow & Geyer, 1999). Impairments in frontal lobe function and associated behaviors, such as executive functioning, have been an important theoretical construct in the understanding a number of behavioral disorders, such as schizophrenia (Bagney et al., 2013; Chan et al., 2014; Eisenberg & Berman, 2010; Holmen et al., 2012; Owens et al., 2010), bipolar disorders (Erol et al., 2014; Kulkarni et al., 2010; Yen et al., 2009; Zimmerman et al., 2006) and substance use disorders (Fernandez-Serrano et al., 2010; Gierski et al., 2013; Loeber et al., 2009; Maurage et al., 2014; van der Plas et al., 2009; Zorko et al., 2004). If frontal cortical responses to the startle stimuli index some aspect of frontal lobe functioning involving higher cognition, then psychiatric disorders postulated to involve some aspects of frontal lobe dysfunction should also have startle deficits, such as anxiety disorders (De Pascalis et al., 2013), schizophrenia (De Koning et al., 2014; Swerdlow et al., 2014), post-traumatic stress disorder (Grillon et al., 1996), and alcoholism (Ehlers et al., 2011; Marin et al., 2012).

The present investigation used a startle paradigm with short delay pre-pulse-plus-startle stimuli, which elicits a large frontal negative slow wave designated the N4S component (Ehlers et al., 2011). In the present study, we used this endophenotype in an association analysis using an Affymetrix Axiom Exome1A array to explore potential genetic factors underlying the N4S component response to pre-pulse startle stimuli in a young adult MA cohort that has been previously well-characterized clinically (Criado & Ehlers, 2007; Criado et al., 2014; Ehlers & Phillips, 2007; Ehlers et al., 2009, 2010, 2011, 2012, 2014).

Materials and Methods

Sample Ascertainment

To investigate risk and protective factors for the pre-pulse inhibition and startle response in a select population of MA young adults, we investigated a cohort of 420 (age 18–30 years) MA men ($n = 170$) and women ($n = 250$). Participants were recruited using a commercial mailing list that provided the addresses of individuals with Hispanic surnames in 11 zip codes in San Diego County. The mailed invitation stated that potential participants must be of MA heritage, between the ages of 18 and 30 years, residing in the United States legally, and able to read and write in English. Based on a phone interview, participants were excluded if they were pregnant, were nursing, or currently had a major medical or neurological disorder or head injury. All participants were identified as having over 20% Hispanic heritage, with 92% reporting over 50% Hispanic heritage. The Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994) was used to make lifetime substance use and other psychiatric disorder diagnoses, according to DSM-III-R and DSM-IV criteria. There have been several studies that have evaluated the concurrent diagnostic validity of the SSAGA across alcohol and drug dependencies, major depression, anxiety disorders, and antisocial personality disorder (Bucholz et al., 1994; Hesselbrock et al., 1999). These findings indicate that the SSAGA is a highly reliable and valid instrument for use in studies of psychiatric disorders, including substance dependence. The protocol for the study was approved by the Institutional Review Board (IRB) at the Scripps Research Institute, and written consent was obtained for all participants. Participants were asked to refrain from alcohol and drug usage for 24 hours prior to the testing.

Startle ERP Collection and Analysis

Recordings were obtained from participants who were seated on a hospital bed in a sound-attenuated room. Acoustic startle stimuli were presented binaurally through headphones. The behavioral response to the startle (eye blink) is recorded using electrodes placed below and lateral to the eye as described (Braff et al., 2001b). The auditory stimuli consist of 45 trials. These trials include randomly presented startle stimuli (115 dB white noise burst for 40 msec $n = 30$) and pre-pulse-startle stimuli (85 dB white noise burst for 20 msec-duration) immediately (<5 msec) followed by the startle (115 dB white noise burst for 40 msec $n = 15$). Each individual startle and/or pre-pulse startle trial is separated by an interval of 15 seconds. Background white noise was presented for the entire session at a level of 60 dB. The behavioral variables assessed included: ASR magnitude on startle trials and pre-pulse trials as determined by quantification of the eye blink response as described below.

Seven channels of ERP data (FZ, CZ, PZ, F3, F4, F7, and F8, referenced to linked ear lobes with a forehead ground, international 10–20 system) were obtained using gold-plated electrodes with impedance held below 5 KΩ. Frontal electrodes were emphasized in the montage as previous data had suggested that ERP decrements in frontal areas distinguished subjects with a risk for alcohol dependence (Bauer, 1997). An electrode placed left lateral infraorbitally and reference to the left earlobe was used to monitor both horizontal and vertical eye movements. ERP signals were amplified (time constant 0.3 s, 35 Hz low pass) using a Nihon Kohden EEG machine and were transferred online to a PC. The combined gain of the EEG amplifiers and the analog-to-digital multiplexer amplifier was 50 K.

The eye blink and ERP trials were simultaneously digitized at a rate of 256 Hz (bandwidth 0.5–35 Hz). Individual trials where the EEG or eye blink exceeded ±250 microvolts (<5% of the trials) were eliminated before averaging. The N4S component of the ERP was quantified

https://doi.org/10.1017/thg.2015.77 Published online by Cambridge University Press

using a computerized peak detection routine that identifies baseline-to-peak amplitudes (in μV) within the specified latency window (350–500 msec). The eye blink amplitude was also assessed using this routine. The latency window for the eye blink was 50–120 msec. The baseline was determined by averaging the 150 ms of pre-stimulus activity obtained for each trial. The routine is user-driven, and each peak detection must be verified by the user. All peaks were quantified by one investigator, and verified by a second investigator, both of whom were blind to participants' characteristics.

The N4S component of the ERP was also evaluated to determine if it was altered as a function of alcohol dependence, antisocial personality disorder/conduct disorder (ASPD/CD), affective/anxiety disorders (ANYAXAF), and any other drug dependence (AnyDrugDep). In this analysis, regionally averaged N4S component responses to startle and pre-pulse/startle were compared between those participants with and without the psychiatric disorders using ANCOVA (co-varying for gender).

Sample Preparation and Genotyping

For all subjects, DNA was extracted from blood samples, followed by genotyping using an Affymetrix Exome1A chip. The DNA samples were prepared and the exome chip genotyping was performed on the Affymetrix Axiom Exome 1A Array according to the Affymetrix Axiom 2.0 Assay Manual Workflow documentation. The Affymetrix Exome 1A chip contains 247,222 markers. Variant quality from the exome chip genotyping was initially assessed according to Affymetrix best practices (Affymetrix, 2011). Plink version 1.07 (Purcell et al., 2007) was used to calculate Hardy-Weinberg (HWE) p values on the set of unrelated samples, followed by the removal of 653 variants with an HWE $p < 10^{-10}$.

Association Analysis

PLINK was used to test for genome-wide association for the N4S component of the ERP in response to acoustic startle stimuli following the presentation of a pre-pulse. PLINK was run with linear regression model parameters and with one million permutations. Gender and age were included as covariates. To determine the effect of extreme outliers in the phenotypic values, custom R code was written to generate winsorized phenotype values at 5% and 95% cut-offs, which were then used as the phenotype values in PLINK. Manhattan plots were generated using Manhattan R library (Stephen Turner, http://gettinggeneticsdone.blogspot.com/2011/04/annotated-manhattan-plots-and-qq-plots.html). Annotations of the variants were obtained from the Affymetrix Exome 1A chip description file. Multiple test correction p-value thresholds were calculated for the Affymetrix Exome1A chip using the Genetic Type 1 Error Calculator (GEC) software (Li et al., 2012). The UCSC Genome Browser (Kent et al., 2002) was also utilized to visualize the genomic region containing the significant SNPs.

In order to determine if the SNPs that were significantly associated with the pre-pulse response phenotype were shared with the alcohol dependence trait, we used the multivariate version of the PLINK software (Ferreira & Purcell, 2009) with covariates age and gender.

LD Analysis

In order to check for linkage disequilibrium (LD) across the *CCKAR* and *CCKBR* gene regions, PLINK was utilized to extract a subset of variants for analysis based on the physical position of these genes on chromosomes 4 and 11, respectively. In particular, a region of chromosome 4 from genomic location 25,450,000–28,000,000 and chromosome 11 from genomic location 6,100,000–6,500,000, were extracted from the data set. Haploview (Barrett et al., 2005) was used to calculate the LD statistics and visualize the haplotype block structure of the gene regions.

Results

Demographics of the Mexican American Population

The demographics for the full sample of individuals ($N = 420$) that were included in the association analysis are shown in Table 1. The subjects were a mean age of 23.6 (range 18–30) years at the time of interview, with 40% of the sample being male and 60% of the sample being female. Participants had a mean of 13.3 years of education ($SD = 1.8$), and a mean income of $30,000–$49,000. Using self-reported ancestry based on grandparent origin, 92% of the participants reported at least 50% Hispanic heritage. The mean BMI was 27 ($SD = 7$, range 17–64). Approximately 29% ($n = 123$) of the participants were diagnosed with alcohol dependence according to DSM-III-R guidelines, indicating that these subjects had symptoms from three or more symptom groups, out of nine possible symptom groups. Eleven percent ($n = 45$) of the participants were diagnosed with conduct disorder or ASPD/CD. Thirty-one percent ($n = 132$) of the participants has a lifetime diagnosis of affective and/or anxiety disorder. Twenty-seven percent ($n = 115$) of the participants had a diagnosis of another drug disorder (nicotine, cannabis, hallucinogens, stimulants, sedatives, opioids).

The mean N4S amplitude was evaluated using ANCOVA (co-varying with gender) as a function of alcohol dependence, ASPD/CD, any affective and/or anxiety disorder, and any other drug dependency. Participants with a lifetime diagnosis of alcohol dependence had significantly increased amplitude N4S responses to pre-pulse/startle stimuli as compared to participants with no alcohol dependence diagnoses ($F = 6.535$; $p = .011$). There were no significant associations between the N4S amplitude to pre-pulse

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TABLE 1

Demographics for Mexican American Study Participants

	Male	Female	Total
Participants	170 (40%)	250 (60%)	420
Age: mean(*SD*), [range]	23.7 (3.9), [18–30]	23.5 (3.8), [18–30]	23.6 (3.8), [18–30]
Self-reported MA heritage ≥ 50%	90.60%	92.60%	91.60%
BMI: mean(*SD*), [range]	27.6 (6.0) [17.3–52.3]	27.2 (7.4) [16.9–64.4]	27.3 (6.9) [16.9–64.4]
Education in years: mean(*SD*), [range]	13.2 (1.7), [9–17]	13.4 (1.8), [7–18]	13.3 (1.8), [7–18]
Income: mean(*SD*), [range]	4.8 (2.1), [1–9]	4.2 (2.1), [0–9]	4.4 (2.2) [0–9]
Alcohol dependence, # of subject affected	63 [63/170 = 37%]	60 [60/250 = 24%]	123 [123/420 = 29.3%)
Pre-pulse inhibition: mean(*SD*), [range]	13.07 (8.38), [0.01–50.63]	15.48 (9.18), [0.01–60.12]	14.51 (8.93), [0.01–60.12]
Startle: mean(*SD*), [range]	12.28 (6.70), [0.01–36.28]	15.12 (8.00), [0.01–47.09]	13.97 (7.62), [0.01–47.09]

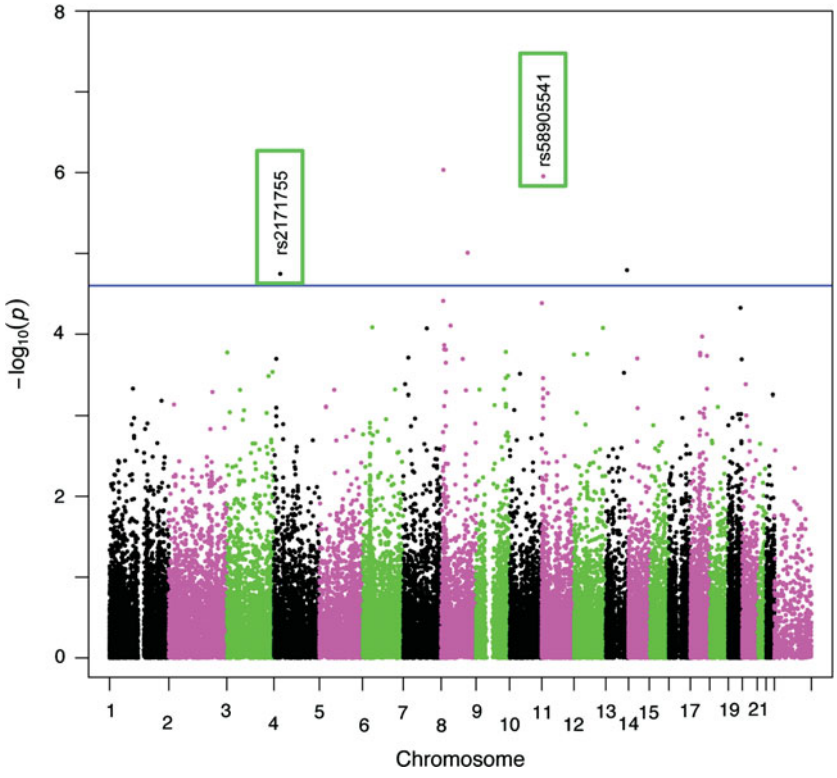

FIGURE 1

(Colour online) Manhattan plot for pre-pulse phenotype.
Note: Manhattan plot across all chromosomes, using covariates age and gender. Minor allele frequency cut-off of 0.01 applied to the plot. Suggestive significance line calculated from GEC software. Green rectangles in plot highlight SNPs rs2171755 and rs58905541.

stimuli phenotypic trait and ASPD/CD, ANYAXAF, or AnyDrugDep diagnoses.

Association Analysis

Figure 1 contains the Manhattan plot for the amplitude of the N4S response to pre-pulse stimuli phenotypic trait tested in the association analysis across the entire genome, using covariates age and gender, and applying a minor allele cut-off of 0.01. Although there were five total variants which exhibited p values ≤ E-05 after association, as shown in Table 2, there were only two variants (rs2171755 and rs58905541) that showed suggestive significance and possessed plausible gene functions for this phenotype. One protective variant (rs2171755; NC_000004.12:g.26502338T>C) is located 12 kb upstream from the *CCKAR* gene in a MIRb class SINE repetitive element, and is common in our sample, with an allele frequency of 0.36. The rs58905541 variant is a risk variant (NC_000011.10:g.6296157C>T) located 24 kb downstream from the *CCKBR* gene in a DNaseI hypersensitivity cluster, with an allele frequency of 0.018. The variant retained its significance through permutation and winsorization and the exclusion of covariates age and gender. The association values for these two variants, along with the allele and genotype frequencies, are shown in Table 3. The minor allele frequencies of these variants in the 1,000

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TABLE 2

Significant Variants for Pre-pulse Phenotype

Chr	Position	dbSNP RS ID	Association *p* value	MAF	Location of nearest gene	Description of nearest gene
4	26503960	rs2171755	1.79E-05	0.3607	12 kb upstream, CCKAR	Cholecystokinin A receptor
8	9649769	rs7830613	9.25E-07	0.4485	9 kb downstream, TNKS	Tankyrase, TRF1-interacting ankyrin-related ADP-ribose polymerase
8	111264112	rs1403843	9.83E-06	0.4613	83 kb downstream, CSMD3	CUB and Sushi multiple domains 3
11	6317387	rs58905541	1.11E-06	0.0176	24 kb downstream, CCKBR	Cholecystokinin B receptor
13	108518444	rs1771137	1.61E-05	0.1518	FAM155A	Family with sequence similarity 155 member A

TABLE 3

Allele Frequencies, Genotype Frequencies, and Association Analysis Results

dbSNP RS ID	rs2171755	rs58905541
Minor Allele	C	T
1000GENOMES AF (ALL)	0.455	0.129
1000GENOMES AF (AMR)	0.403	0.044
Present study sample		
Overall MAF	0.361	0.018
Genotype counts	59/185/176	0/15/405
Frequency	0.1405/0.4405/0.419	0/0.03571/0.9643
HWE *p* value	0.3463	1
Association analysis with no covars		
Beta +/− SE	−2.512 +/− 0.6165	11.56 +/− 2.283
T-stat	−4.0750	5.0650
p value	5.517E-05	6.15E-07
Association following winsorization		
Beta +/− SE	−1.947 +/− 0.5209	8.738 +/− 1.934
T-stat	−3.7380	4.518
p value	2.116E-04	8.14E-06
Permutation testing		
Number of permutations performed	901,000	1,000,000
Empirical adaptive *p* value	4.44E-05	1.30E-05
Association analysis with covars		
(Unscaled beta, *p* value)		
Additive	−2.658, 1.789E-05	11.24, 1.114E-06
Sex	2.675, 2.155E-03	2.167, 1.207E-02
Age	−0.07525, 0.5007	−0.06604, 0.5519
(Scaled beta, *p* value)		
Additive	−0.2068, 1.789E-05	0.2337, 1.114E-06
Sex	0.1471, 2.155E-03	0.1192, 1.207E-02
Age	−0.03204, 0.5007	−0.02812, 0.5519

Note: The minor allele frequencies from the 1000 Genomes project, 1000GENOMES AF (ALL = total subjects and AMR = Admixed American subjects) were obtained from the 1000Genomes website (http://www.1000genomes.org/). Abbreviations: MAF = minor allele frequency, HWE = Hardy–Weinberg equilibrium, SE = standard error.

Genomes project was obtained from the dbSNP website (http://www.ncbi.nlm.nih.gov/SNP/).

From the multivariate association analysis of the N4S response to pre-pulse stimuli phenotypic trait and alcohol dependence diagnosis phenotype, we found that the inclusion of the alcohol dependence phenotype did not significantly alter the association of the SNPs with the pre-pulse phenotype. That is, the *p* values were significant whether we used univariate PLINK (rs2171755 *p* value = 1.79E-05; rs58905541 *p* value = 1.11E-06), or multivariate PLINK (rs2171755 *p* value = 9.36E-05; rs58905541 *p* value = 5.77E-06). Additionally, the weights determined by multivariate PLINK demonstrated that the pre-pulse phenotype had a strong correlation to the SNPs (rs2171755 weight for pre-pulse = 0.995; rs58905541 weight for pre-pulse = 0.999), while the alcohol dependence phenotype had a very weak correlation (rs2171755 weight for alcohol dependence = 0.026; rs58905541 weight for alcohol dependence = 0.109). These results suggest that the pre-pulse phenotype is driving the significance of the association for these two SNPs.

Multiple Test Correction

Multiple test correction *p* value thresholds were calculated for the Affymetrix Axiom Exome1A chip using the GEC software (Li et al., 2012), and the thresholds generated were thereby used to determine that the variants could be characterized to possess suggestive significance. In particular, for the Affymetrix Axiom Exome1A chip at a minor allele frequency of 0.01 or greater, the threshold for a suggestive *p* value was calculated as 2.53E-05, significant *p* value as 1.27E-06, and highly significant *p* value as 2.53E-08.

LD Analysis

The LD was calculated across the *CCKAR* and *CCKBR* gene regions. The average D' value across the SNP pairs in the *CCKAR* region was 0.77 in this data set. No other SNPs

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on the Affymetrix chip were found to be in high LD with the variant near the *CCKAR* gene. The average D' value across the SNP pairs in the *CCKBR* region was 0.85 in this data set. While no SNP was found to be in complete LD with rs58905541, the SNP with highest LD was rs1462983 ($D' = 0.837$, r2 = 0.023, LOD = 2.19, CI = 0.37–0.95). This SNP was located in OR56B4 (olfactory receptor, family 56, subfamily B, member 4) and possessed a positive beta value, suggesting it is a risk factor. However, rs1462932 was not significantly associated with the pre-pulse inhibition response phenotype in our sample when using PLINK for the analysis.

Discussion

The present study confirmed previous observations in this population of an increase in PPF of the N4S ERP component to the acoustic pre-pulse stimuli (Ehlers et al., 2011). In the present study, we used this endophenotype in an association analysis using an Affymetrix Axiom Exome1A array to explore potential genetic factors underlying the N4S component response to pre-pulse startle stimuli in this young adult MA cohort. The results of the present study suggest that variants located near *CCKAR* and *CCKBR* (cholecystokinin A and B receptor) genes are suggestive to be associated with the N4S ERP response to pre-pulse startle stimuli in this MA cohort. The rs2171755 variant (NC_000004.12:g.26502338T>C) is located 12 kb upstream from the *CCKAR* gene in a MIRb class SINE repetitive element. Interestingly, a variant in a MIRb class SINE repetitive element has been reported to be associated with human cognition (Gosso et al., 2007). The rs58905541 variant (NC_000011.10:g.6296157C>T) is located 24 kb downstream from the *CCKBR* gene in a DNaseI hypersensitivity cluster. Variants in regulatory regions of the genome, such as DNase I hypersensitive sites, have been found to be associated with a number of diseases (Encode Project Consortium, 2012; Maurano et al., 2012). Additionally, both SNPs show phylogenetic conservation in the UCSC Genome Browser alignment tracks in Figure 2. Since, it has been reported that phenotype-associated variants occur more frequently in evolutionarily constrained regions of the genome (Parker et al., 2009), it suggests that these SNPs are likely to be real and functional. Therefore, it is feasible that the non-coding variants found in this present study could potentially play a role in the N4S ERP response to pre-pulse stimuli.

The neurotransmitter cholecystokinin (*CCK*) is widely present in the human body and in the central nervous system, where it modulates the dopaminergic system (Crawley & Corwin, 1994). Because of its potential modulation of the dopaminergic system and associated reward pathways, *CCK* has been investigated in a number of studies as a candidate gene for substance dependence and other behavioral disorders. *CCK*, along with its two receptors, *CCKAR* and *CCKBR*, have been previously associated with anxiety and panic disorders (Maron et al., 2008; Wilson et al., 2012), schizophrenia (Christoforou et al., 2007; Sanjuan et al., 2004), nicotine dependence (Takimoto et al., 2005), and alcohol dependence (Miyasaka et al., 2004; Okubo & Harada, 2001; Okubo et al., 2002). Although one study reported no association between *CCK* and *CCKBR* with alcohol dependence (Vanakoski et al., 2001), the study was performed using a Finnish population and did not examine the same significant SNPs that were determined in our study. Besides possible neurological influences of *CCK* on alcohol addiction, it has also been found that *CCK* through activation of CCKA receptors protects the gastric mucosa against ethanol-induced gastric damage in rats (Konturek et al., 1995). In the context of alcoholism, variation in CCK activity in the gut could allow for the ingestion of greater or lesser amounts of alcohol, which in turn could influence liability towards alcoholism.

Further evidence of the role of *CCK* in the regulation of startle responses is supported by studies where the administration of *CCK*-related peptides has been found to influence the startle response in rats and humans. In particular, infusion of *CCK* has been found to enhance the acoustic startle response in rats (Feifel & Swerdlow, 1997; Feifel et al., 2001; Fendt et al., 1995), and some CCK antagonists attenuate startle responses (Feifel et al., 1999; Josselyn et al., 1995). In human subjects, CCK infusion has also been demonstrated to increase eye-blink startle as well as produce a mild increase in anxiety and heart rate as well as increases in plasma concentrations of ACTH, cortisol, prolactin, and growth hormone (Shlik et al., 1999). Since, CCK peptides have been demonstrated to enhance anxiety, several studies have investigated the role of the CCK system in anxiety and panic disorders, using CCK-related peptide administration as a challenge method (Koszycki et al., 2012; Maron et al., 2008). These CCK challenge studies were able to explore genetic factors in panic disorders by performing candidate gene analyses to find alleles that may be associated with greater sensitivity to the CCK peptides. One study found an association of the tryptophan hydroxylase gene isomer 2 (*TPH2*) with subjects experiencing panic attacks after CCK infusion (Maron et al., 2008). Another study found an association to the *CCKBR* gene in subjects with greater pre-challenge anxiety (Koszycki et al., 2012). Additional studies have utilized CCK-peptide infusion to determine its effects on EEG and ERP measures in healthy human subjects (Knott et al., 2002, 2003). CCK-4 infusion was found to delay the latencies of N100 and P200 components of the ERP that was elicited during an auditory oddball task (Knott et al., 2002). During EEG recording of resting subjects, CCK-4 infusion was also found to increase asymmetry and reduce coherence of the slow-wave activity at mid-temporal recording sites (Knott et al., 2003). Taken together, these studies suggest a plausible role for CCK variants in the regulation of brain activity and behavior.

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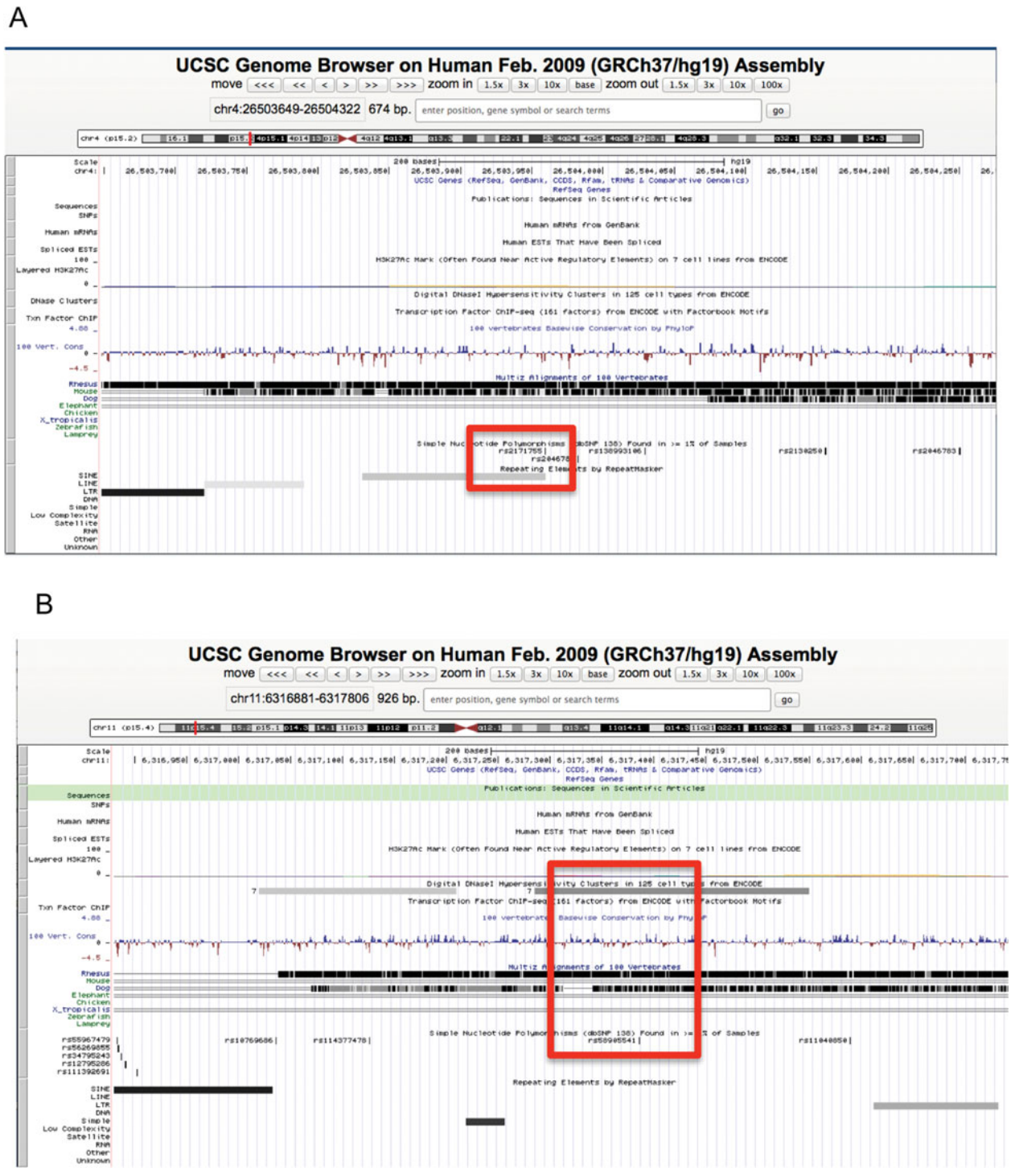

FIGURE 2

(Colour online) UCSC Genome browser view of the SNP locations.
Note: This figure shows the genomic location of the SNPs rs2171755 and rs58905541.

Impairments in frontal lobe function and associated behaviors such as executive functioning have been suggested to underlie anxiety disorders (Castaneda et al., 2008), as well as a number of other behavioral disorders such as schizophrenia (Bagney et al., 2013; Chan et al., 2014; Eisenberg & Berman, 2010; Holmen et al., 2012; Owens et al., 2010), bipolar disorders (Erol et al., 2014; Kulkarni et al., 2010; Yen et al., 2009; Zimmerman et al., 2006), and

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substance use disorders (Fernandez-Serrano et al., 2010; Gierski et al., 2013; Loeber et al., 2009; Maurage et al., 2014; van der Plas et al., 2009; Zorko et al., 2004). Interestingly, schizophrenia and bipolar disorders also demonstrate significant clinical comorbidity with substance use disorders (Regier et al., 1990) and may also share genetic susceptibility factors (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; Schuckit et al., 2003). There is also some data to suggest that they may share common endophenotypes such as deficits in some aspects of responses to startle (Kohl et al., 2013), although this hypothesis requires further testing and confirmation.

In summary, in the present study, associations between the N4S ERP responses to acoustic pre-pulse startle stimuli were determined using association analyses. Our results suggest that variants located in regulatory non-coding regions near the cholecystokinin A and B receptors may play a role in the pre-pulse/startle response. However, the results of this study should be interpreted in the context of several limitations. First, the findings may not generalize to the general American population of mixed heritage or all MAs, or all Hispanic young adult Americans. Over half of the participants in the present were women and thus findings many not generalize to previous studies that have focused on samples of entirely male participants. Second, the study was limited to young adults between the ages of 18 and 30 years, and the sample size may limit the interpretation of the results. Despite these limitations, this report represents an important step in an ongoing investigation to determine risk and protective factors associated with development of substance use disorders in this select MA population.

Acknowledgments

We would like to thank and acknowledge the following people for their role in (1) the genotyping effort: Chris Bizon, Scott Chasse, Piotr Mieczkowski, Ewa Patrycja Malc, Joshua Sailsbery, and Phil Owens; and (2) for recruiting participants and collecting the clinical data: David Gilder, Susan Lopez, and Linda Corey. Funding for this study was provided by grants from the National Institutes of Health (NIH); from the National Institute on Alcoholism and Alcohol Abuse (NIAAA) and the National Center on Minority Health and Health Disparities (NCMHD) 5R37 AA010201 and P60 AA006420 (CLE) and the National Institute of Drug Abuse (NIDA) 5 R01 DA030976 (CLE, IRG, KCW, & NJS). NIAAA, NCMHD and NIDA had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. NJS and his lab are supported in part by NIH grants 5 UL1 RR025774, R21 AI085374, 5 U01 DA024417, 5 R01 HL089655, 5 R01 AG035020, 1 R01 MH093500, 2 U19 AI063603, 2 U19 AG023122, 5 P01 AG027734, 1 R21 DA033813.

Conflict of Interest

NJS is a founder and stock holder in Cypher Genomics and paid consultant for the following companies: Human Longevity, Inc., MD Revolution, and Click Therapeutics. All of the authors declare that they have no conflicts of interests.

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