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Whole Genome Sequence Association and Ancestry-Informed Polygenic Profile of EEG Alpha in a Native American Population

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Abstract

EEG alpha activity is the dominant oscillation in most adult humans, is highly heritable, and has been associated with a number of cognitive functions. Two EEG phenotypes, low- and high-voltage alpha (LVA & HVA), have been demonstrated to have high heritabilities. They have different prevalence depending on a population's ancestral origins. In the present study we assessed the influence of ancestry admixture on EEG alpha power, and conducted a whole genome sequencing association analysis and an ancestry-informed polygenic study on those phenotypes in a Native American (NA) population that has a high prevalence of LVA. Seven common variants, in LD with each other upstream from gene *ASIC2*, reached genome-wide significance ($p=2\times 10^{-8}$) having a positive association with alpha voltage. They had lower minor allele frequencies in the NAs than in a global population sample. Overall correlations between lower degrees of NA (higher degree European) ancestry and HVA, and higher degrees of NA and LVA were also found. Additionally a rare-variant gene-based study identified gene *TIA1* being negatively associated with LVA. Approximately 3% of SNPs exhibited a 15-fold enrichment that explained nearly half of the total SNP-heritability for EEG alpha. These regions showed the most significant anti-correlations between NA ancestry and alpha voltage, and were enriched for genes and pathways mediating cognitive functions. Our findings suggested that these regions likely harbor causal variants for HVA, and lacking of such variants could explain the high prevalence of LVA in this NA population, possibly illuminating the ancestral origin and genetic basis for EEG alpha.

Keywords

Low coverage sequencing; Admixture; Genome-wide association; Gene based rare variant analysis; Heritability enrichment

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CONFLICT OF INTEREST

None of the authors have any conflicts of interest.

INTRODUCTION

The EEG is a highly heritable, quantitative phenotype that can be accurately and reliably indexed and it has been suggested to be closer to gene function than diagnostic and psychological measures of brain function [Anokhin, 2014]. Several features of the resting EEG have been shown to be genetically influenced, and EEG phenotypes based on frequency and amplitude characteristics that may be useful in genetic analyses have been suggested [Iacono et al., 2014; Rangaswamy et al., 2002; Rangaswamy et al., 2004; Vogel, 1962]. Evidence from twin studies has determined that a significant proportion of the variance in the EEG is genetically determined [Christian et al., 1996; Juel-Nielsen and Harvald, 1958; Lykken et al., 1982; Stassen et al., 1987; van Beijsterveldt and Boomsma, 1994]. EEG patterns appear to remain highly stable over most of an adult's lifespan, with variation within an individual studied on two different occasions being not greater than that observed between monozygotic twins [Lykken et al., 1982].

EEG alpha oscillations are the single most salient feature of the waking EEG of humans, and are most prominently seen in occipital areas when the eyes are closed. Resting state alpha oscillations are associated with relaxation or non-focused attention and are reduced in amplitude during cognitive or sensorimotor stimulation or replaced by slower waves during drowsiness [Ba ar, 2012; Bazanova and Vernon, 2014; Niedermeyer and Lopes da Silva, 2004]. Over the last decade, a prevailing theory has emerged that has viewed alpha oscillations as an important top-down mechanism of neuronal inhibition that exerts control over the timing of neuronal discharges in nearby populations [Klimesch, 2012; Klimesch et al., 2007]. Alpha activity reflects processes related to controlled access to and retrieval from the "knowledge system" that underlies many cognitive processes such as attention and memory [Klimesch, 2012]. It has also been suggested that, through inhibitory and timing mechanisms, alpha oscillations help maintain selective attention to environmental stimuli. Alpha oscillations have been shown to change during memory-related tasks [Ba ar et al., 2001; Ba ar et al., 1997; Klimesch, 1997, 1999; Klimesch et al., 2007; Klimesch et al., 1994]. For instance, long-term memory demands lead to task-specific desynchronization in alpha and working memory demands can lead to increase in alpha activity [Jensen et al., 2002; Klimesch, 1999]. Alpha enhancement has also been frequently observed during mental imagery, internal attention, and various creativity-related demands such as imagination and ideation [Cooper et al., 2003; Fink and Benedek, 2014]. Changes in alpha activity have also been associated with select mental and behavioral disorders [Ba ar, 2013; Ba ar and Güntekin, 2013; Ba ar et al., 2016; Ducci et al., 2009; Enoch et al., 1999; Herning et al., 1994; Loo and Makeig, 2012; Mazaheri et al., 2014].

Many authors have suggested that several EEG measures may serve as potential endophenotypes for certain psychiatric disorders including alcohol and other substance use disorders [Kamarajan and Porjesz, 2015]. For instance,, low EEG Alpha power has been reported in individuals with different subtypes of alcohol use disorders with other comorbid disorders [Ducci et al., 2009; Enoch et al., 1995; Enoch et al., 1999]. In a previous study of a Native American population, low voltage alpha was found to be associated with a larger number of maximum alcohol drinks ever consumed in a 24-hour period, and a less intense response to alcohol, both factors that have been shown to be associated with an increased

risk for the development of alcohol use disorders [Ehlers et al., 2015]. Therefore understanding the genetic underpinnings of the EEG alpha may help illuminate the biological process underlying some cognitive activities, as well as some mental health conditions.

The amplitude of the alpha rhythm is a robust trait variable that varies greatly between individuals. In some individuals it is of very high amplitude and can be continuously present irrespective of the level of arousal (so called monomorphic alpha). Whereas, in other individuals alpha waves are virtually absent [Niedermeyer and Lopes da Silva, 2004]. This low voltage EEG phenotype (LVEEG) was first described by Adrian and Matthews in 1934 [Adrian and Matthews, 1934] based on visual inspection of loss of alpha waves, and overall low voltage in the EEG. Early genetic studies also identified LVEEG as being highly heritable, and suggested it might have an autosomal dominant mode of inheritance, and provided data in a few families for linkage to a marker on chromosome 20q (see [Anokhin et al., 1992; Steinlein et al., 1992; van Beijsterveldt and Boomsma, 1994; Vogel, 1970] for review).

Although there have been a number of studies that have investigated associations between candidate genes and power in different EEG frequency bands [Ducci et al., 2009; Enoch et al., 2008; Lee et al., 2011a; Lee et al., 2011b; Lee et al., 2012a, b; Porjesz et al., 2002], there have only been a few genome-wide association studies (GWAS) using EEG phenotypes. In one study, conducted in American Plains Indians, a significant association was found between theta band EEG power and a SNP in the *SGIP1* gene, and a similar trend was observed in a Caucasian sample that did not reach significance [Hodgkinson et al., 2010]. In another study, a family-based GWAS was conducted in Caucasians and an association was found between several SNPs in *KCNJ6* and theta oscillations [Kang et al., 2012]. More recently, a genome wide search, using several different electrophysiological measures, did not result in any significant associations in common or rare variants in a population of over thirteen-hundred subjects [Vrieze et al., 2014b]. With substantially increased sample sizes, a similar study focusing on nonsynonymous exonic variants identified a variant in gene *PARD3* associated with EEG theta power; and another study identified several genes associated with EEG delta power [Malone et al., 2014; Vrieze et al., 2014a]. Both studies employed around four thousand predominantly Caucasian subjects from the Minnesota Twin Family Study. Although neither found significant variants or genes for EEG alpha, EEG alpha was shown to be significantly heritable, consistent with a polygenic inheritance model [Malone et al., 2014].

There are several reasons why some studies may identify significant genetic variants and others not. Most studies evaluating genetic associations with the awake resting EEG have used, as a phenotype, the transformed amplitude (power) of the EEG signal in a specific frequency band (e.g. delta, theta, alpha, beta, gamma). Depending on the transformation, some studies may normalize power so that overall differences in power between individuals may be diminished. Another difference between studies may be that LVEEG is not highly prevalent in most populations (approximately 4% in EuroAmerican populations) [Anokhin et al., 1992; Niedermeyer, 1986] so that large scale EEG screening would be required to obtain a relatively small number of cases, leaving power for detection of variants in GWAS

very low. We have previously reported that LVEEG is more prevalent in an American Indian community sample than what has been documented in other selected Asian, African, or EuroAmerican populations [Ehlers et al., 1999; Ehlers and Phillips, 2003, 2007; Ehlers et al., 2015]. We have also demonstrated that alpha EEG phenotypes in this population are substantially heritable ($h^2 = 0.62$ frontal, 0.67 posterior scalp locations) [Ehlers et al., 2010b].

Genetic studies of complex phenotypes such as EEG alpha have additional advantages when they are conducted in well-defined populations such as Native Americans living on reservations as these populations may have greater genetic and environmental homogeneity than general population or clinical samples. Using data from a rural dwelling community sample of Native Americans several fundamental questions regarding EEG phenotypes were evaluated in the present study: i) we assessed the influence of the overall ancestral background on EEG alpha and the presence of low-voltage and high-voltage alpha, and determined whether the EEG alpha is associated with areas of the genome that are more or less associated with a person's Native American or European American ancestry; ii) we conducted a whole genome sequence association, a gene-based rare variant association, and polygenic studies on these phenotypes using low coverage whole genome sequencing data; and iii) conducted pathway and functional analyses on the identified variants.

MATERIALS AND METHODS

Participants and Phenotypes

The protocol of the study was approved by the Scripps Research Institute Institutional Review Board and Indian Health Council, a tribal review group overseeing health issues for the reservations where recruitments took place. Written informed consent was obtained from each participant after study procedures had been fully explained. Participants were compensated for their time spent in the study.

Eight hundred and fifty eight (858) Native Americans from extended pedigrees participated in the study. The population characteristics and the recruitment procedures have been previously described [Ehlers et al., 2011; Ehlers et al., 2010a]. Six hundred and ninety two sequenced samples ($n = 692$) were eventually used in this study. The average age of the analyzed samples was 31.2 years old (range 18–81, s.d.=13.0 yrs.), with 42.9% being male. 42.3% of participants ($n = 293$) had at least 50% self-reported Native American heritage as indicated from their federal Indian blood quantum.

Six channels of bipolar EEG (10–20 system) were collected using an electrode cap and analyzed using spectral analyses. Signals were transformed using Fourier analyses and the power in the alpha frequency band (7.5–12 Hz) was determined (See supplementary method for further details on EEG collection and analysis). The distribution of the alpha voltage measurement was skewed with a long right tail: mean = 40.92, median = 21.72, range = 0.743 to 594.4, skewness = 3.51, and Pearson's measure of kurtosis = 24.41. The distribution was close to lognormal, reflecting the distinctiveness of the NA population with respect to this phenotype. For subsequent analysis, we used three alpha voltage derived phenotypes: winsorized alpha voltage at 10% at each tail, dichotomous low-voltage alpha

(LVA) and high-voltage alpha (HVA). Note that we explicitly studied LVA rather than the overall low voltage EEG (LVEEG). Low-voltage alpha was defined as having an EEG power in the alpha frequency range at or below 10 microvolts squared/octave in the posterior leads (set to 1 if ≤ 10 , 0 if > 10). High-voltage alpha was defined as EEG power at or above 50 microvolts squared/octave (set to 0 if < 50 , 1 if ≥ 50). These cutoffs resulted in roughly one-quarter of the participants being defined as having low-voltage alpha (27%) or high-voltage alpha (26%).

Sequencing and Variants Calling

Blood derived DNA was sequenced using Illumina low-coverage whole genome sequencing (LCWGS), as well as genotyped using an Affymetrix Exome1A chip. The pair-end sequencing was performed on HiSeq2000 sequencers (Illumina). About 80% of the samples had coverage between 3X and 12X, approximately evenly distributed. Reads from whole genome sequencing were aligned using BWA, and realigned near indels (inserts and deletions) with GATK. Variants were called using both GATK Unified Genotyper following the best practices for low-coverage samples [DePristo et al., 2011] and the Linkage Disequilibrium (LD)-aware variant caller Thunder [Li et al., 2011]. The human genome reference GRCh37 was used. Imputation was carried out using the program Thunder. Qualities of variant calling were assessed through a comparison between the sequencing results to genotypes generated on the exome array for the same set of subjects. The assessment showed that LD-aware variant caller Thunder performed the best and correctly called nearly all of common variants and a high percentage of rare variants in the samples. The median concordance rate was 97.5%. The median false positive rate was 0.3% [Bizon et al., 2014].

Ancestry Estimates and Admixture Analysis

We used a supervised clustering approach implemented in the ADMIXTURE software [Alexander et al., 2009] to assess ancestry and admixture proportions in the samples, and clustered subject data into four clusters corresponding to four major continental populations: African, East Asian, European, and Native American. These populations were defined by the individuals in a reference panel containing genotype information at about 300k strand-unambiguous SNPs. The admixture estimates were further refined through a noise reduction approach via bootstrapping [Libiger and Schork, 2012]. Multiple linear regression was used to assess the relation between the degrees of NA ancestry and the EEG alpha power.

In addition to the global ancestries estimated for each individual with SNPs spanning entire genomes, we also estimated local ancestry admixtures. A sliding window of 200 consecutive SNPs in the reference panel moved across each chromosome at the step of 50 SNPs. Local ancestry and admixture proportions were estimated using SNPs within each window for all samples. A fixed-width window with respect to the number of ancestry-informative markers was used to assure sufficient number of such markers to yield meaningful local admixture estimates. For each fixed-width window, the winsorized alpha voltage was regressed onto the local NA ancestry. Windows associated with local NA ancestries were selected at various significant *p*-value thresholds for heritability analysis. Consecutive windows were merged into one region.

Whole Genome Association Analysis

Most participants had a mixed ethnic background, indicated both by self-report and by the admixture analysis. In addition, the sample was composed of 159 families of variable sizes. A variance component model approach as implemented in EMMAX [Kang et al., 2010] with global ancestry estimates further incorporated as covariates was used in the association test to control for admixture and familial relatedness. The covariates for the association analysis included gender, age, age-squared, and three of the four ancestry components: Native American, European, and African (The four ancestry components sum up to one). Note that in the variance component model, the covariance matrix is the kinship coefficient matrix that is derived from the genotypes. This matrix captures, to a certain extent, the relatedness and population structure. We used a conservative approach that included ancestry estimates as covariates in order to further control for population structure. We also performed a second set of association analysis excluding the three ancestry components from covariates, in order to account for potential overcorrection for ancestry.

While this unique population may offer us certain genetic insights into EEG alpha power that have been hard to detect in other populations, the sample size of this population is albeit moderate. The statistical power to detect genomic association for small effect sizes is therefore limited. A power calculation was conducted using the Genetic Power Calculator [Purcell et al., 2003] that is based on a variance component model derived in [Sham et al., 2000]. The genetic power for the given sample size as a function of effect size is shown in supplemental Figure S1. Desired sample sizes to reach 80% power are also presented in Figure S1.

Low Frequency and Rare Variant Association Analysis

Low frequency ($0.5\% \leq \text{MAF} < 5\%$) and rare ($\text{MAF} < 0.5\%$) variants were analyzed with the combined multivariate and collapsing (CMC) method [Li and Leal, 2008] using a variance component model as implemented in EMMAX. Low frequency variants and rare variants were grouped by genes. Only variants on exons, 5' and 3' UTRs, upstream and downstream of a gene were considered. A gene was excluded if there were fewer than three such markers, or if there were less than 1% of the samples that had at least one of such variants on the gene. A total of 27403 genes were included in the test. The gene-based burden test was performed on winsorized EEG alpha, low-voltage alpha and high-voltage alpha. We used Bonferroni correction and set the p -value of $0.05/27403$ (number of genes) = 1.8×10^{-6} as the significant threshold.

Brain eQTL

The brain eQTL dataset was from BRAINEAC (UK Brain Expression Consortium) [Ramasamy et al., 2014]. The dataset consists of genotypes and gene expression datasets of ten post-mortem brain tissues from each of the 134 individuals of European descent. All individuals were neurologically normal during life [Trabzuni et al., 2011]. The eQTL signals were assessed at the exon level. A significant association between genotype markers and gene expression levels was established through permutation testing. An eQTL signal was defined as being significant using a false discovery rate (FDR) $< 1\%$ [Ramasamy et al.,

2014]. Top variants from the whole genome association analysis were tested against this database.

Polygenic Analysis

In addition to the association analysis, we used the variance component model to estimate various components of heritability of alpha voltage in our NA samples. In this case we use the term *heritability* to refer to the portion of the phenotypic variance that is explained by the additive genetic effects. The genetic variance captured by all SNPs was estimated by comparing the phenotypic similarity of pairs of distantly related individuals to their SNP-derived genetic similarity [Yang et al., 2011]. If the genome is partitioned into two parts, the phenotype variance can be written as: $\Sigma = A_1\sigma_{g1}^2 + A_2\sigma_{g2}^2 + I\sigma_e^2$, where Σ is the variance structure of phenotypic observations, A_1, A_2 are the covariance matrices derived using the SNPs within each respective genomic partition, $\sigma_{g1}^2, \sigma_{g2}^2$ are the genetic variance of each partition, and σ_e^2 the residual variance. The heritability of each genomic partition i through a joint estimate is then given by: $h_{gi}^2 = \frac{\sigma_{gi}^2}{\sigma_{g1}^2 + \sigma_{g2}^2 + \sigma_e^2}$. The enrichment for heritability of partition i is defined as: $\frac{h_{gi}^2 / (h_{g1}^2 + h_{g2}^2)}{N_{SNP_i} / N_{SNP}}$, where N_{SNP_i} / N_{SNP} is the proportion of the total SNPs in the i -th partition.

When there are related individuals, such estimates of heritability may be potentially inflated due to common environment and epistatic interactions. A joint estimate using identity-by-descent (IBD) covariance matrix (approximated by thresholding on the full genetic relationship matrix) together with genetic covariance matrices was used to control such bias [Zaitlen et al., 2013]. (See Supplemental Method for further details.)

We used the restricted maximum likelihood (REML) method as implemented in GCTA [Yang et al., 2011] to estimate the heritability of the overall additive genetic effects and the portions explained by various genomic partitions. The phenotype was winsorized alpha voltage; covariates included age, age-squared, gender and the global ancestry estimate. The genome was partitioned into two parts in each setting by one of the following criteria: i) the genomic regions having less than the median local Native American ancestry were in one partition, while those above the median local NA in another; ii) the regions where alpha voltage was significantly associated with the local NA ancestry were in one partition, while the remaining in the other (the level of significant threshold was set at various p -values); and iii) The genic regions including 20k upstream and downstream were in one partition while the remaining intergenic regions in the other.

Functional and Pathway Analyses

Once the partitioned heritability analysis identified the most enriched genomic regions for EEG alpha heritability, we then investigated functional annotations of the variants within those regions. The Database for Annotation, Visualization and Integrated Discovery (DAVID) version 6.7 [Dennis et al., 2003] was used for the functional and pathway analyses. The variants were first annotated with SGAdviser [Pham et al., 2015]. The list of genes was then submitted to DAVID. A modified Fisher exact test p -value, or EASE score, was used to

identify enriched annotation terms derived from gene ontology (GO), tissue expression, or pathway. The EASE score threshold was 0.1. The Benjamini corrected p -value was used to establish significance [Dennis et al., 2003]. For the GO terms, we used the lower levels of biological process ontology (GOTERM_BP_FAT). For gene expression localization, two sources were used: UniProt tissue list (based on literature mining and reports for each gene that found to be expressed in tissues by using a curated vocabulary), and the more comprehensive GNF_U133A_QUARTILE tissue list, from which the genes expressing higher than 3rd quartile of their expressions were reported.

RESULTS

Whole Genome Association Analysis

Whole genome association analysis was performed on: the continuous trait, EEG alpha voltage (winsorized), and the dichotomous traits, low-voltage alpha and high-voltage alpha (see Figure S2 for Manhattan plots of the associations). The analysis identified variant rs2368697, together with six neighboring variants that were in complete or near complete linkage disequilibrium (LD), as being significantly associated with the EEG alpha voltage ($p = 2.0 \times 10^{-8}$), as shown in Table I. No variant passed the significant threshold for low or high voltage alpha. The significant variants were at approximately 7kb upstream of the acid-sensing ion channels gene *ASIC2/ACCN1* (see Supplemental Figure S3). The acid-sensing ion channels are neuronal voltage-insensitive cationic channels activated by extracellular protons. The finding that the associations were positive indicates that the variants were associated with high-voltage alpha, which was confirmed by association analysis using the dichotomous high-voltage alpha phenotype ($p = 2.1 \times 10^{-7} - 3.0 \times 10^{-7}$). Note that the associations that included ancestry estimates as covariates yielded slightly lower significances for most of the top variants than the associations without the ancestry covariates (see Table I). Although the findings essentially remained the same, to be conservative, we refer to the former in the text. While the variants had minor allele frequencies (MAF) of near 16% in the NA samples, they had higher MAFs of 24–27% in the default global population in the 1000 Genomes database [1000 Genomes Project Consortium et al., 2012]. We further examined the ancestral compositions of individuals having different forms of the genotypes. As illustrated in Figure 1A, individuals having rs2368697 genotype GA had significantly lower degree of NA ancestry than those with the wild-type genotype GG (Tukey's multiple comparison test adjusted $p = 0.0015$; ANOVA test for three genotype forms $p = 4.6 \times 10^{-4}$). Variant rs76103505, which had a slightly lower p -value and was in complete LD with the top hits, resides within transcription binding sites *CTCF*, *SMC3*, *RAD21* and *SPI1*.

Using the brain expression quantitative trait loci (eQTLs) database BRAINEAC [Ramasamy et al., 2014], we found evidence of *cis*-eQTL signals for the top 13 variants upstream of *ASIC2/ACCN1* that were associated with EEG alpha in our study at significant or suggestively significant levels. Of the ten human brain regions, the most significant eQTL signals were in the occipital cortex ($p = 9.7 \times 10^{-4} - 1.2 \times 10^{-3}$), followed by the putamen ($p = 4.9 \times 10^{-3} - 1.4 \times 10^{-2}$). The significant brain eQTL signals remain unchanged if we restricted

only to the top 7 variants that were significantly associated with EEG alpha. The complete details are given in Supplemental Tables S-I and S-III.

In addition to the genome-wide significantly associated variants, variants with suggestive significances ($p = 5 \times 10^{-7}$) are also reported in Table I. Of note, rs11014588 resides within gene *GPR158* (G protein-coupled orphan receptor 158). Due to the moderate sample size, we primarily restricted our genome-wide findings to common variants (MAF $\geq 5\%$). To emphasize and illustrate the differential allele frequencies in different ancestral origins, however, we included some variants in Table I that were considered common in the 1000 Genomes global population but are rare in our NA sample (See Supplemental Table S-I for a complete list of top variants including low frequency variants with MAF $\geq 0.5\%$). Some of these variants exhibited suggestive significance of association with the high-voltage alpha phenotype. Specifically, the top such variant rs73994652 is located within gene *CACNG5*, a neuronal voltage-gated calcium channel gamma-5 subunit. Figure 1B shows distributions of NA ancestry of individuals having different genotype forms for rs73994652: individuals having the CT genotype had significantly lower degree of NA ancestry than those having the wild-type CC genotype ($p = 4.9 \times 10^{-5}$). Note that although the African subpopulations of the 1000 Genomes had a much higher MAF for this variant, we did not detect significant difference between the two genotypes for the African ancestral component in our sample ($p = 0.09$). The additional rare variant shown is rs61583023, which resides on gene *LINGO2*. Interestingly, while there was no significant difference for Native American or European ancestral components between the two genotypes, the African ancestry exhibited a significant difference between individuals possessing the two genotypic forms GG and GT ($p < 2.2 \times 10^{-16}$), as shown in Figure 1D. This is consistent with the fact that in the 1000 Genomes database, the minor allele of this variant is found almost exclusively in African subpopulations.

Overall, except for one variant (rs11014588), all variants exhibiting at least suggestive significance of association with high-voltage alpha had consistently higher MAF in the 1000 genomes global population than in the NA samples in our study. The individuals with minor alleles, in the NA population, had either significantly lower NA ancestral components and/or higher degree of other ancestral components. The only variant that was associated with low-voltage alpha at a level above suggestive significance was rs78245818, which had lower MAF in the 1000 Genomes than in our NA samples. As expected, the individuals with minor alleles had a significantly lower degree of European ancestry than those with both major alleles (GG genotype): ANOVA test $p = 5.8 \times 10^{-8}$, with Tukey's test GG vs. GC: $p = 5.0 \times 10^{-6}$, GG vs. CC: $p = 4.3 \times 10^{-4}$, and GC vs. CC: $p = 0.13$ (see Figure 1C).

Since the genome sequencing was performed at low coverage, we also verified whether the top variants reported here that were associated with EEG phenotypes were of good genotype quality. The genotype-call qualities (GQ) of the variants in Table I are listed in Supplemental Table S-II. All variants except two had mean GQ score coded as a Phred score above 30. The exceptions were rs138338934 and rs78245818, with mean GQ of 25.5 and 19.5 respectively.

Rare Variants Association Analysis

Low frequency ($0.5\% \leq \text{MAF} < 5\%$) and rare ($\text{MAF} < 0.5\%$) variants were analyzed using a combined multivariate and collapsing (CMC) methodology [Li and Leal, 2008]. A gene-based burden test was performed on the EEG alpha voltage (winsorized), low-voltage alpha and high-voltage alpha phenotypes. Table II lists the genes that exhibited significant ($p \leq 1.8 \times 10^{-6}$) or suggestively significant association with those phenotypes. The only gene that passed the significant threshold was *TIA1* that was negatively associated with low-voltage alpha, or 'protective' against LVA. *TIA1* encodes a stress granules-nucleating protein. Among the top genes that were suggestively associated with low-voltage alpha was *PROK1*, a prokineticin 1 gene that is an endocrine-gland-derived vascular endothelial growth factor. The top gene that was trending toward association with high-voltage alpha is *SCN9A*, a sodium channel, voltage gated, type IX alpha subunit gene. No gene passed the significance threshold for the continuous EEG alpha trait.

Global Admixture-Phenotype Correlation

The ancestry estimate of the NA samples indicates that most individuals have an admixture of Native American and European ancestries. The degree of the NA ancestry of the individuals had a sample mean of 46.8% with standard deviation (s.d.) 19.2%. The samples had a mean of 48.9% European ancestry with s.d. 19.9%. Eight individuals each had at least a quarter of African ancestry or East Asian ancestry respectively. The samples overall had a mean of 2.93% African ancestry with s.d. 5.56%, and a mean of 1.34% East Asian ancestry with s.d. 5.65%.

EEG alpha power showed a significantly negative association with the overall estimate of the NA ancestry, as shown in Figure 2, when alpha power was regressed onto the NA ancestry, with or without covariates. Both the original measure of alpha voltage and the winsorized alpha voltage phenotypes showed significant anti-correlations. Correlation analyses were also performed on the two dichotomous EEG phenotypes. The low-voltage alpha exhibited a positive correlation with Native American ancestry with a point-biserial correlation coefficient of 0.092 ($p = 0.016$). The high-voltage alpha was positively correlated with European ancestry with a point-biserial correlation coefficient of 0.133 ($p = 4.6 \times 10^{-4}$). These results were consistent with the high prevalence of low-voltage alpha in the NA population comparing to other ethnicities, and with our genome-wide association findings.

Local Admixture-Phenotype Correlation

The estimates of an individual's ancestral composition were averaged over the whole genome. Using the same method that was employed to estimate the global ancestry makeup, we estimated local admixtures of 4396 sliding-overlapping windows along the whole genome for each individual. Some portions of the genome did not harbor a sufficient number of ancestry-informative markers to allow for an estimate, and those regions were excluded from the analyses. Figure 3 shows the estimated local Native American ancestry along the chromosomes averaged over all individuals. The average degree of local NA ancestry had a range of 27%–54% with a mean of 43%.

To further investigate which genomic segments might have an enriched genetic effect on alpha power that depended on local ancestry, we computed the correlations between local NA ancestry estimates and EEG alpha voltage for each of the 4396 genomic windows. The results are shown in Figure 4. Most of the regions were negatively correlated with the local NA ancestry, as expected. There was no apparent correlation between the correlation coefficients and the degrees of the local ancestry.

SNP-Heritability Enrichment Analysis

For these analyses we partitioned the genome based on the results of the admixture analysis. The first set of partitions was based on the averaged degree of local NA ancestry alone, independent of phenotype. The second sets of partitions were determined by the significant levels of the association found between the local ancestries and alpha voltage. Four p -values were chosen as thresholds: 0.0001, 0.001, 0.01 & 0.03 (p of 0.03 was so chosen that two parts were roughly even). We partitioned the genomes in two disjointed parts in each setting and estimated the SNP-heritability for each part using a joint estimation method. In addition, the genome was also partitioned based on functional annotation into genic (along with upstream and downstream) and intergenic regions. Table III lists the partition parameters and proportions of each partition. Notice that the partitions that were determined by the median local NA ancestry did not sum up to 100% of the genomic markers. As noted earlier, this was due to a small fraction of the genome being excluded because there were not enough ancestry-informative markers to allow for a local admixture estimate. Figure 5A shows the partitioned heritability estimates for each genomic partition setting. Figure 5B shows the joint estimates of the two partitions of the genome together with the thresholded genetic relationship matrix that controlled for relatedness. Our estimate, without genomic partitions, yielded an overall SNP-heritability of 0.45 ± 0.10 ($p = 1.78 \times 10^{-5}$). A similar estimate of SNP-heritability for EEG alpha power in a European American population gave a range of 0.48 – 0.77 depending on the threshold of genetic relatedness [Malone et al., 2014].

Taken together, the results of these analyses suggest that the genomic regions with higher degrees of European ancestry accounted for more variance of the alpha power than those regions that were primarily of American Indian ancestry. This observation was consistent with the finding that European ancestry is correlated with high-voltage alpha. The regions that exhibited negative correlation between alpha power and the degree of local NA ancestry at a significant level lower than p -value of 0.0001 encompassed 25 contiguous genomic segments spanning over 14 chromosomes (see Table S-IV). These regions accounted for slightly over 3% of the SNPs. Yet they appeared to explain nearly half of the total SNP-heritability of the alpha power, representing a 15-times enrichment (Table III). As we reduced the level of correlation significance and included more of the regions and the number of SNPs, the heritability enrichment gradually decreased.

We used the regions of the genome that showed the most significant negative correlation ($p = 0.0001$) between alpha power and local NA ancestry to perform logistic regressions of the low-voltage alpha and the high-voltage alpha respectively onto the degree of local NA ancestry. These regions consisted of 78 sliding windows. The regressions from the low-voltage alpha all had a positive β , with p -values ranging from 4.4×10^{-4} to 0.47 with a

median p -value 0.02. The regressions from the high-voltage alpha all had a negative β , with p -values ranging from 5.4×10^{-7} to 2.1×10^{-3} with a median p -value 3.2×10^{-5} (See Figure 6). In all of the 78 windows, the high-voltage alpha exhibited higher levels of significance than the low-voltage alpha. The finding that these genomic regions showing the most significant negative correlations between local degree of NA ancestry and alpha voltage accounted for almost half of the SNP-heritability of the EEG alpha, and that the local NA ancestry was negatively associated with high-voltage alpha at a much higher significant levels than their positive associations with the low-voltage alpha, together suggest that these regions likely harbor causal variants for high-voltage alpha. Additionally, the relative absence of such variants might explain the high prevalence of low-voltage alpha in this Native American population.

Functional and Pathway Analyses on Heritability-Enriched Regions

We further examined the variants in the 25 genomic regions that were most enriched for EEG alpha heritability. Interestingly, the significant variants in the association study are located outside of these regions. The variant that exhibited the most significant association with alpha power in the regions was rs7031763, a common variant located upstream of gene *LINGO2* ($p = 5.4 \times 10^{-7}$, see Table I). There were 576 variants in these regions that had p values at least 5×10^{-4} in the association analysis. They corresponded to 112 genes or predicted gene models (including ncRNAs), of which 85 were recognized by the DAVID database for further functional annotations [Dennis et al., 2003; Huang et al., 2007].

The gene ontology (GO) enrichment analysis yielded 13 clusters for the 85 genes. Although none of the GO terms were statistically significant after multiple-testing correction, it might still be noteworthy that the top GO term was memory, and the three most enriched clusters consisted of categories related to: i) cell growth and proliferation; ii) response to hormones and endogenous stimuli; and iii) memory, learning, cognition and behavior (see Table S-V). The results of the pathway analysis are shown in Table IV. The most significantly enriched pathways were vascular smooth muscle contraction, long-term potentiation, followed by GnRH signaling pathway. Further, when the genes were categorized by the tissues in which they were expressed, the most significant tissue was brain based on UniProt tissue expression database: 48 genes out of 85 were expressed in the brain. A more specific tissue expression profile is shown in Table V. A region-specific enrichment was found with statistical significance ($p < 0.05$) in four areas of the central nervous system (CNS): cerebellar peduncles, pituitary, subthalamic nucleus, and the occipital lobe. Of the 24 tissues that were enriched with a nominal p value less than 0.1, near half of the tissues are part of the central nervous system or peripheral nervous system, and one quarter belong to the endocrine system.

DISCUSSION

Twin and family studies suggest that quantitative characteristics of the waking EEG are strongly influenced by genetic factors and it may be one of the most heritable human traits (see [Anokhin, 2014] for review). Twin studies comparing different EEG frequency bands have demonstrated that power in the alpha frequency band tends to yield the highest

heritability estimates [Anokhin et al., 2006; Christian et al., 1996; Lykken et al., 1974; Smit et al., 2007; van Beijsterveldt et al., 1996; Vogel, 1970]. However studies employing multivariate genetic analyses have shown high phenotypic and genetic correlations between different frequency bands suggesting the existence of a common genetic factor that may influence overall EEG amplitude [Anokhin, 1989; Zietsch et al., 2007]. Overall EEG amplitude also shows considerable variation over different human populations and ethnic groups [Anokhin et al., 1992; Ehlers et al., 1999; Ehlers and Phillips, 2003; Ehlers et al., 2004]. One EEG pattern of overall low voltage (LVEEG) has been demonstrated to be of low prevalence in Asians and EuroAmericans [Anokhin et al., 1992], and of higher prevalence in selected African and Native American populations [Ehlers et al., 1999; Ehlers and Phillips, 2003]. Because of these differences, the use of selected populations that are enhanced for certain EEG variants may offer greater statistical power to detect potential genes affecting these phenotypes. Additionally, admixture analyses may shed further light on the ancestral origins of these phenotypes. In the present study we used an admixed population to assess the influence of ancestral background in a Native American population that had been demonstrated previously to have a high prevalence of LVEEG [Ehlers et al., 2004].

As reviewed in the introduction, although recent studies have identified several variants and genes associated with various EEG phenotypes, no significant variant or gene has been found for EEG alpha. In the present study, in addition to assessing the influence of ancestral background on EEG alpha, we also conducted a low coverage whole genome scan on alpha EEG phenotypes in a Native American population. A dozen common variants in LD were identified on chromosome 17 to be positively associated with alpha voltage and the dichotomous high-voltage alpha phenotype with a genome-wide significance or suggestive level of significance. These variants were at 6–7kb upstream of gene *ASIC2/ACCNI*. Acid-sensing ion channels (*ASICs*) are neuronal voltage-insensitive cationic channels activated by extracellular protons, and have been identified as potential therapeutic targets for pain and central nervous system diseases [Sluka et al., 2009]. *ASIC2* is in particular expressed in both peripheral and central nervous systems. It has been known to contribute to neurotransmission. *ASIC2* has also been suggested to play a role in determining the defensive response to aversive stimuli and might affect fear and panic [Price et al., 2014]. The top variants also showed evidence for acting as a *cis*-eQTL for *ASIC2/ACCNI*, most significantly in the occipital cortex and followed by the putamen region of the human brain. The resting state EEG alpha is most prominently seen in the occipital areas when the eyes are closed. Additionally, a variant residing within the gene *GPR158* (G protein-coupled orphan receptor 158) was found to be associated with alpha voltage at a suggestively significant level. *GPR158* is specifically expressed in brain where it binds to *RGS7* that may play a role in the rapid regulation of neuronal excitability and cellular responses to short-lived stimuli [Saitoh et al., 1999]. *RGS7* has also been shown to be associated with panic disorder in a German population [Hohoff et al., 2009].

Most of the variants that were associated with high-voltage alpha had higher MAF in the 1000 Genome default global population than in the NA samples. One such variant is located within the gene *CACNG5* that is a neuronal voltage-gated calcium channel gamma-5 subunit. This gene has been reported to be associated with bipolar disorder and schizophrenia [Curtis et al., 2011]. Additional variants of potential interest were found in

gene *LINGO2*, that codes for a Leucine-rich repeat neuronal protein. Of particular interest, *LINGO2* is located within the genomic regions that were identified as the most enriched for EEG alpha heritability based on the admixture-informed heritability analysis. The gene has been found to be associated with both essential tremor and Parkinson's disease [Vilariño-Güell et al., 2010; Wu et al., 2011]. We only identified one variant on chromosome 7 that was associated with low-voltage alpha at a level above suggestive significance, in an intergenic region. The variant had higher MAF in the NA samples than in the global population, in contrast to the variants associated with high-voltage alpha.

TIA1 was the top gene associated with low-voltage alpha and the only gene that passed the significant threshold for any of the phenotypes in the low frequency and rare variant analysis. *TIA1* is an RNA-binding protein involved in nuclear splicing and one of the core proteins that nucleates cytoplasmic stress granules (SGs) [Anderson and Kedersha, 2008]. A recent study has demonstrated that *TIA1* modulates the physiology of tau and it is required for normal interactions of RNA binding proteins in brain tissues. Additionally, it has been shown that its overexpression stimulates neurodegeneration, thus highlighting its potential role in Alzheimer's disease (AD) and other tauopathies [Vanderweyde et al., 2016]. Another study also shows that *TIA1* oxidation suppresses SG formation, which may underlie the neuronal cell death seen in neurodegenerative diseases such as AD and Parkinson's disease [Arimoto-Matsuzaki et al., 2016]. The gene *PROK1* was also found to be associated with low-voltage alpha in the low frequency and rare variant analysis but only at a suggestive significant level. It has been shown that brain modulation of *PROK1*, and several related genes, results in differences in endocrine function that might be related to altered learning and long-term potentiation in aged mice [Lucas et al., 2013]. Additionally, *PROK1* is highly related to gene *PROK2*, which has been shown to potentiate acid-sensing ion channel activity in rat dorsal root ganglion neurons [Qiu et al., 2012]. Another gene of potential interest is *SCN9A*, the top gene associated with high-voltage alpha but at a less significant level. *SCN9A* belongs to the sodium channel gene family and mediates the voltage-dependent sodium ion permeability of excitable membranes. This gene has also been found to be associated with epilepsy [Meisler et al., 2010; Singh et al., 2009].

The individuals in the present sample under study are primarily admixed between Native American and European ancestries [Norden-Krichmar et al., 2014]. Since EEG alpha has previously been shown to be highly heritable in this NA population [Ehlers et al., 2010a], and is most likely polygenic, we performed polygenic analysis using ancestral information in order to compliment the genome-wide association analysis. Individuals who have similar degrees of admixture at a whole genome level may nevertheless have different genomic compositions with respect to ancestral origins in their local chromosomal segments. Therefore, in addition to the global admixture analysis that demonstrated an overall ancestral influence on the alpha voltage phenotypes, we conducted local admixture analysis on individual chromosomal segments. We found that the level of local admixture among individuals varied across chromosomes, as did the correlation between EEG alpha and the level of local ancestry. The correlation between alpha voltage and NA ancestry was negative for most chromosomal segments, which was consistent with the observation from the global admixture analysis. The chromosomal segments that were on average the most European (the least NA) resided on chromosome 16, which showed correlation with alpha voltage as

expected. The regions that exhibited the most significant anti-correlation between alpha voltage and NA ancestry were located on chromosome 17, although interestingly the significant findings from the GWAS were on the same chromosome yet outside of these regions.

Most studies that have identified SNPs that reach genome-wide significance have also found that the SNPs of interest explain only a small amount of the variance in the overall phenotype [Manolio et al., 2009]. We partitioned the genome based on admixture analysis to determine the amount of variance afforded by our genomic analyses. The joint estimates of EEG alpha SNP-heritability of various partitions further suggested that the genomic regions of high European ancestry (low NA ancestry) accounted for the majority of the alpha heritability. Notably, approximately 3% of the SNPs, spanning 25 genomic regions, exhibited a 15-fold of enrichment for EEG alpha heritability by explaining close to half of the total SNP-heritability. These were the regions that showed the most significant anti-correlations between NA ancestry and the alpha power.

Functional and pathway analyses of variants within these EEG alpha heritability-enriched regions led to significant pathway enrichments for long-term potentiation (LTP) and GnRH signaling, as well as gene expression enrichments for some select brain regions. LTP is thought to be one of the cellular and molecular mechanisms of memory and learning [Nabavi et al., 2014; Squire and Kandel, 2009]. This may be important for understanding mechanisms underlying the EEG, as EEG alpha oscillations have been shown to index attention and performance of both long-term and working memory [Escolano et al., 2011; Klimesch, 2012]. It is not clear how gonadotropin-releasing hormone (GnRH), a neurohormone, essential for reproduction, may be important for EEG alpha voltage. However, EEG alpha has been demonstrated to have higher relative spectral power in one study in females as compared to males [Langrova et al., 2012], and gender differences have also been shown in associations between genetic variants and resting state EEG activity [Volf et al., 2015].

Four out of the eight tissues that were significantly enriched for gene expression were part of CNS. They were: cerebellar peduncles, pituitary, subthalamic nucleus (STN), and occipital lobe. There are some data to support associations between these brain areas and EEG alpha production, in particular the occipital lobe, a cortical area where resting state alpha has its highest amplitude when the eyes are closed. For the cerebellar peduncles the data are less clear; however, it has been demonstrated that stimulation of superior cerebellar peduncle increases alpha rhythms at the contralateral motor cortex, in rats [Rubio et al., 2004]. It is also not known how the subthalamic nuclei may control cortical EEG alpha. Yet, the STN is thought to play a prominent role in the pathophysiology of Parkinson's disease (see [Obeso et al., 1997] for review), and when patients with Parkinson's disease received deep brain stimulation of the STN, their EEG alpha accelerates in frequency and decreases in power, mainly in the fronto-central region [Jech et al., 2006]. This data are also consistent with the fact that EEG alpha can be suppressed by motor movements as well as sensory stimulation. The olfactory bulb was also found to be enriched for gene expression in our analysis although at a less significant level. This may be important as with odorant stimulation, alpha power has been shown to increase in different cortical regions depending on the particular

stimulant [Harada et al., 1998]. Taken together, our results suggest that the genomic regions we identified captured important genes mediating certain fundamental cognitive functions whose underlying neuronal activities are reflected in EEG alpha oscillations.

Although our findings are revealing, some limitations need be noted. At n of 692, our sample size is moderate thus has limited power to detect genome wide significant associations (see Figure S1). Given the uniqueness of our sample, there are presently no replication samples available yet for the GWAS study. While some of the variants that were identified as being associated with EEG alpha were located near or within genes that contribute to neuronal transmission or regulation and had been previously associated with certain psychiatric disorders, none of the variants had known disruptive impact on the genes. They were synonymous mutations on introns or intergenic regions. One may postulate that they have potential regulatory functions, as some of the variants exhibited evidence as *cis*-eQTL for the gene in relevant brain regions; but until further evidence, we cannot draw causal conclusions yet about these findings. An additional limitation is that our heritability analysis lacked power due to the moderate sample size, as reflected in the large error bars, particularly when relatedness in the samples was controlled for in order to prevent potential inflation of the estimates. One therefore needs to take caution when making inferences from the estimated SNP-heritability, although the overall patterns that were emerged appeared to be consistent with the observations from association and admixture analyses.

In summary, overall, a lower degree of Native American (higher degree of European) ancestry is associated with high-voltage alpha, and a higher degree of Native American ancestry with low-voltage alpha. The majority of the genetic association findings were in the positive direction for the high-voltage alpha phenotypes (or “protected” against low-voltage alpha). The fact that this Native American population is enriched for low-voltage alpha, in contrast to other populations (e.g. European) where high voltage records are more common, allowed us to have the statistical power to detect genetic variants associated with HVA. Our whole genome sequence association study, global and local admixture analyses, ancestry-informed heritability enrichment analysis, and functional and pathway analyses together suggested that the genomic regions having lower degree of Native American ancestral origins along with the chromosomal segments that we identified to have the most anti-correlation between the degree of NA ancestry and the EEG alpha likely harbor causal variants for the high-voltage alpha. We thus hypothesize that the EEG low-voltage alpha might be a basal state, and lacking of the causal variants for high-voltage alpha might explain the prevalence of low-voltage alpha in our Native American population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ANOVA	Analysis of variance
EEG	Electroencephalogram
GWAS	Genome-wide association study
IBD	Identity-by-descent
LCWGS	Low-coverage WGS
LD	Linkage disequilibrium
LVEEG	Low-voltage EEG
MAF	Minor (alternative) allele frequency
NA	Native American
SNP	Single-nucleotide polymorphism
STN	Subthalamic nucleus
WGS	Whole genome sequencing

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FIG 1.

Ancestry distribution by variant genotypes.

The width of the boxes is proportional to the squared-root of the number of individuals in each group. The genotypes (reference/alternative allele) in each panel are A: G/A, B: C/T, C: G/C, D: G/T, respectively. The variants in panels A, B, and D are positively associated with high-voltage alpha. Variant rs78245818 in panel C is positively associated with low-voltage alpha.

FIG 2.

EEG alpha voltage is anti-correlated with the degree of Native American ancestry.

Left panel: alpha voltage vs. NA, $r = -0.119$ ($p = 0.0017$). If alpha voltage is residualized over age, age-squared and gender, $r = -0.107$ ($p = 0.0049$). Right panel: alpha voltage was winsorized, residualized over age, age-squared and gender, and standardized, $r = -0.132$ ($p = 0.00049$). The fitted lines are from the linear regressions.

FIG 3.

The estimated degrees of local Native American ancestry for 4396 overlapping windows along the chromosomes.

Horizontal lines correspond to mean (μ), mean ± 1 , or 2, or 3 standard deviations (σ) of the correlation coefficients, respectively.

FIG 4. Pearson's correlation coefficients between EEG alpha voltage and the local Native American ancestry, for 4396 overlapping windows along the chromosomes. Horizontal lines correspond to p values at 0.03, 0.01, 0.001, and 0.0001, respectively.

FIG 5.

Joint heritability estimates with genomic partitions.

A. Joint heritability of genome partitions. The first bar on the left is the estimated total SNP-heritability of the whole genome.

B. Joint heritability of genome partitions and thresholded genetic covariance matrix (genetic relation > 0.05). The left bar in each group is the heritability estimate on the thresholded genetic covariance matrix. The second bar in the first group of bars on the left is presumably the estimated total SNP-heritability when controlling for relatedness.

The remaining six groups of bars in each panel correspond to the heritability estimates of the six sets of 2-partitions in the same order detailed in Table III.

FIG 6.
P-values of logistic regressions of the low-voltage alpha, Low10, and the high-voltage alpha, High50, onto the degree of local NA ancestry for the 78 windows that showed most significant negative correlation with $p < 0.0001$ between alpha power and local NA ancestry.

TABLE 1

Variants showing significant association at $p \leq 5 \times 10^{-8}$ or suggestive significant association at $p \leq 5 \times 10^{-7}$ with EEG alpha voltage phenotypes.

Chr	Position	R	A	dbSNP id	Gene	Location	Beta ^a	p-value ^a	p-value ^b	MAF	MAF _{UK} ^c
Alpha ^d											
17	32498200 ^e	G	A	rs2368697	BC062794	Intron5	13.51	2.04E-08	1.61E-08	0.159	0.238
17	32498355 ^e	G	T	rs758292	BC062794	Intron5	13.51	2.04E-08	1.61E-08	0.159	0.237
17	32491138 ^e	G	A	rs17250931	BC062794	Downstream	13.52	2.34E-08	1.71E-08	0.158	0.252
17	32493211 ^e	T	C	rs8077171	BC062794	Downstream	13.52	2.34E-08	1.71E-08	0.158	0.262
17	32495847 ^e	T	G	rs2368698	BC062794	Downstream	13.52	2.34E-08	1.71E-08	0.158	0.266
17	32496620 ^e	C	A	rs3744510	BC062794	Intron5	13.52	2.34E-08	1.71E-08	0.158	0.266
17	32496845 ^e	G	A	rs8082670	BC062794	Intron5	13.52	2.34E-08	1.71E-08	0.158	0.266
17	32490484 ^f	C	A	rs56187645	BC062794	Downstream	13.10	6.96E-08	4.96E-08	0.157	0.227
17	32490858 ^f	G	A	rs76103505	BC062794	Downstream	13.10	6.96E-08	4.96E-08	0.157	0.240
17	32492699 ^f	G	A	rs56100356	BC062794	Downstream	13.10	6.96E-08	4.96E-08	0.157	0.250
17	32492942 ^f	G	T	rs17250938	BC062794	Downstream	13.10	6.96E-08	4.96E-08	0.157	0.214
17	32489873	T	C	rs9911364	ASIC2/ACCN1	Upstream	12.83	1.43E-07	1.02E-07	0.158	0.269
17	32488890	C	T	rs763781	ASIC2/ACCN1	Upstream	12.68	2.20E-07	1.51E-07	0.153	0.220
10	25800019	G	A	rs11014588	GPR158	Intron5	13.40	2.67E-07	2.69E-07	0.133	0.098
9	29205335 ^g	C	G	rs7031763	LINGO2	Upstream	13.92	5.39E-07	3.94E-07	0.114	0.171
21	25737293 ^f	T	A	rs2829013	AK124194	Upstream	9.29	8.76E-07	4.21E-07	0.480	0.565
2	159722256 ^f	T	C	rs55796386	DAPL1	Downstream	19.50	7.30E-07	4.21E-07	0.051	0.053
High ^d											
17	64860340 ^h	C	T	rs73994652	CACNG5	Intron1	0.39	1.45E-07	1.07E-07	0.026	0.057
9	27958999 ^{h,i}	G	T	rs61583023	LINGO2	Intron1/6	0.77	3.09E-07	1.32E-06	0.007	0.062
2	40214752	G	C	rs138338934	BC043380	Intron1	0.16	4.52E-07	5.26E-07	0.168	0.283
Low ^d											
7	3184403	G	C	rs78245818	BC038729	Downstream	-0.16	4.52E-07	2.11E-07	0.185	0.123

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- a* Association significance with ancestry components (Native American, European, and African) incorporated as covariates.
- b* Association significance without ancestry covariates.
- c* Minor/alternate allele frequency (MAF) of the default global population in the 1000 Genomes (1kG).
- d* Phenotypes: Alpha - Winsorized alpha voltage; High - high-voltage alpha; Low - low-voltage alpha.
- e* These seven variants also exhibited suggestive significance ($p = 5 \times 10^{-7}$) in association test with high-voltage alpha with ancestry covariates.
- f* These six variants also exhibited suggestive significance in association with high-voltage alpha without ancestry covariates.
- g* The variant is the top hit in the regions that were enriched for EEG alpha heritability.
- h* Only common variants (MAF ≥ 0.05) are shown, except the two noted variants.
- i* There were additional 11 variants in chr9:27958999–27963623 (see Table S1) that were in high LD with rs61583023 and had same MAF in our NA samples with corresponding 1kG MAF ranging in [0.046, 0.098].

Top genes in low frequency and rare variants association analysis with EEG alpha voltage phenotypes, using gene-based CMC burden test. The significant association is at $p < 1.8 \times 10^{-6}$, and suggestive significant association at $p < 1.8 \times 10^{-5}$.

TABLE II

Chr	Positions	Gene	SNPs ^a	% Rare ^b	Phenotype ^c	p-value	Effect ^d
2	70436758–70475827	<i>TIA1</i>	15	12.57%	Low	6.63E-07	–
1	110993808–110999926	<i>PROK1</i>	7	9.10%	Low	2.83E-06	–
13	37393787–37403143	<i>RFXAP</i>	12	6.94%	Low	6.45E-06	–
2	167051756–167232519	<i>SCN9A</i>	57	35.84%	High	1.90E-05	+
7	44998714–45000549	<i>RP4-647I21.1</i>	11	8.67%	Alpha	6.99E-05	+

^aNumber of SNPs with MAF $\geq 5\%$ in the exons, 5' and 3' UTRs, upstream and downstream regions of the gene. Genes with fewer than three such markers were excluded.

^bPercentage of samples who have one or more of the rare or low frequency variants of the gene. A gene is excluded if the fraction is $\leq 1\%$.

^cPhenotypes: Alpha - Winsorized continuous alpha voltage; High - high-voltage alpha; Low - low-voltage alpha.

^dDirection of effects.

TABLE III

Genomic partitions for SNP-heritability analysis

Partition	Local NA ancestry	p-value of local ancestry & alpha voltage association					Function					
	median	0.0001	0.001	0.01	0.03	>	Genic ±20k	Inter-genic				
%	>	>	>	>	>	>						
SNP	48.80	47.97	3.21	96.79	12.41	87.59	36.75	63.25	53.18	46.82	52.78	47.22
Genome	47.90	46.84	3.49	96.51	13.61	86.39	38.58	61.42	55.44	44.56	52.47	47.53
$h^2_{g1, \text{enrich}^a}$	1.33		15.00		4.41		2.02		1.45		1.34	
$h^2_{g1, \text{enrich}^b}$	2.05		16.73		4.94		2.72		1.88		0.78	

^aEnrichment of heritability. Joint heritability was estimated with genomic partitions.

^bJoint heritability was estimated with genomic partitions and thresholded genetic covariance matrix to control for relatedness (see SI method)

TABLE IV

KEGG Pathway enrichment for variants associated with EEG alpha at level of $p < 5 \times 10^{-4}$ in the genomic regions that are most enriched for alpha heritability as shown in Tables III & S-IV.

KEGG_ID	Pathway	n ^a	% ^a	Enrich ^b	p-value	p-value ^c	Genes
hsa04270	Vascular smooth muscle contraction	6	7.06	12.38	7.28E-05	4.43E-03	RAMP3, AGTR1, ADCY1, PLCB4, PLCB1, MYLK
hsa04720	Long-term potentiation	5	5.88	17.00	1.48E-04	4.49E-03	ADCY1, PLCB4, KRAS, GRIN2B, PLCB1
hsa04912	GnRH signaling	5	5.88	11.79	6.04E-04	1.22E-02	ADCY1, PLCB4, KRAS, PLCB1, MAP2K6
hsa04540	Gap junction	4	4.71	10.39	5.49E-03	6.49E-02	ADCY1, PLCB4, KRAS, PLCB1
hsa04916	Melanogenesis	4	4.71	9.34	7.38E-03	7.26E-02	ADCY1, PLCB4, KRAS, PLCB1
hsa04020	Calcium signaling	5	5.88	6.57	5.23E-03	7.69E-02	AGTR1, ADCY1, PLCB4, PLCB1, MYLK
hsa02010	ABC transporters	3	3.53	15.76	1.38E-02	1.14E-01	ABCA8, ABCA10, ABCA5
hsa04730	Long-term depression	3	3.53	10.05	3.23E-02	2.21E-01	PLCB4, KRAS, PLCB1
hsa04062	Chemokine signaling	4	4.71	4.94	4.00E-02	2.42E-01	ADCY1, PLCB4, KRAS, PLCB1
hsa04810	Regulation of actin cytoskeleton	4	4.71	4.30	5.66E-02	2.99E-01	PAK7, KRAS, FGF12, MYLK
hsa04360	Axon guidance	3	3.53	5.38	9.81E-02	4.36E-01	PAK7, KRAS, EPHB1

^aNumber and percentage of genes in the gene list that belong to the pathway

^bFold enrichment

^cBenjamini corrected p -value

TABLE V

Tissue gene expression enrichment using GNF_U133A_Quartile for variants associated with EEG alpha at level of $p < 5 \times 10^{-4}$ in the genomic regions that are most enriched for alpha heritability as shown in Tables III & S-IV.

Tissue	n ^a	% ^a	Enrich ^b	p-value	p-value ^c
Fetal Liver	26	30.59	2.16	5.23E-05	4.07E-03
Cerebellum Peduncles	17	20.00	2.82	1.39E-04	5.42E-03
Prostate	45	52.94	1.31	1.63E-03	2.51E-02
Appendix	26	30.59	1.78	1.35E-03	2.60E-02
Pituitary	20	23.53	2.12	1.02E-03	2.63E-02
Subthalamicnucleus	21	24.71	1.91	2.64E-03	2.90E-02
Occipital Lobe	19	22.35	2.00	3.09E-03	2.97E-02
Kidney	32	37.65	1.54	2.36E-03	3.03E-02
Uterus Corpus	20	23.53	1.79	7.49E-03	6.31E-02
PB-BDCA4+Dentritic_Cells	7	8.24	3.43	1.45E-02	9.04E-02
Olfactory Bulb	16	18.82	1.91	1.23E-02	9.21E-02
Colorectal Adenocarcinoma	19	22.35	1.71	1.62E-02	9.36E-02
Adrenal Gland	21	24.71	1.65	1.41E-02	9.57E-02
Ovary	12	14.12	1.93	3.70E-02	1.89E-01
Hypothalamus	19	22.35	1.52	4.90E-02	2.30E-01
Testis Interstitial	19	22.35	1.41	9.18E-02	2.69E-01
Pons	28	32.94	1.27	9.08E-02	2.76E-01
Dorsal Root Ganglia	11	12.94	1.73	8.77E-02	2.78E-01
Skin	11	12.94	1.78	7.63E-02	2.78E-01
WHOLE BLOOD	23	27.06	1.38	6.47E-02	2.78E-01
Prefrontal Cortex	14	16.47	1.58	8.42E-02	2.79E-01
Thymus	16	18.82	1.53	7.38E-02	2.83E-01
Ciliary Ganglion	19	22.35	1.42	8.39E-02	2.89E-01
BM-CD105+Endothelial	21	24.71	1.40	7.26E-02	2.92E-01

^aNumber and percentage of genes in the gene list that belong to the pathway

^bFold enrichment

Benjamini corrected p -value

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