# Genome-Wide Association Study of Post-Traumatic Stress Disorder in Two High-Risk Populations

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Mexican Americans (MAs) and American Indians (AIs) constitute conspicuously understudied groups with respect to risk for post-traumatic stress disorder (PTSD), especially in light of findings showing racial/ethnic differences in trauma exposure and risk for PTSD. The purpose of this study was to examine genetic influences on PTSD in two minority cohorts. A genome-wide association study (GWAS) with sum PTSD symptoms for trauma-exposed subjects was run in each cohort. Six highly correlated variants in olfactory receptor family 11 subfamily L member 1 (*OR11L1*) were suggestively associated with PTSD in the MA cohort. These associations remained suggestively significant after permutation testing. A signal in a nearby olfactory receptor on chromosome 1, olfactory receptor family 2 subfamily L member 13 (*OR2L13*), tagged by rs151319968, was nominally associated with PTSD in the AI sample. Although no variants were significantly associated after correction for multiple testing in a meta-analysis of the two cohorts, pathway analysis of the top hits showed an enrichment cluster of terms related to sensory transduction, olfactory receptor activity, G-protein coupled receptors, and membrane. As previous studies have proposed a role for olfaction in PTSD, our results indicate this influence may be partially driven by genetic variation in the olfactory system.

∎ **Keywords:** GWAS, Mexican Americans, American Indians, PTSD, olfaction, enrichment analysis

Post-traumatic stress disorder (PTSD) is an anxiety disorder and unique in that while exposure to a traumatic event is required for diagnosis, not all subjects who experience a traumatic event develop PTSD. PTSD has an overall lifetime prevalence rate of 7–8% and is the fifth most common major psychiatric disorder in the United States (Keane et al., 2006). Multiple psychological and social factors have been shown to influence risk for PTSD, including but not limited to: gender; early life adversity; and the nature, timing, and cumulative burden of traumatic event exposures (Zoladz & Diamond, 2013).

Higher PTSD prevalence and/or symptom severity in Hispanics, relative to their non-Hispanic counterparts, has been reported in several studies (Alcantara et al., 2013; Marshall et al., 2009; Pole et al., 2008). This is particularly true in comparison to Caucasians: individuals from American Indian (AI), African American (AA), Hispanic, and Asian heritages had elevated post-traumatic distress relative to Whites (Santos et al., 2008); and studies of Vietnam veterans have shown that Hispanics were twice as likely as non-Hispanic Caucasians to not only develop PTSD (Kulka, 1990; Schell & Marshall, 2008) but also have more severe symptoms (Marshall et al., 2009; Ortega & Rosenheck,

2000). Although two conflicting studies have reported no difference in PTSD prevalence between non-Hispanic Caucasians and Hispanics (Alegria et al., 2013; Roberts et al., 2011), a recent meta-analysis provided support for higher rates of PTSD onset and severity in Hispanics compared to non-Hispanic Caucasians (Alcantara et al., 2013). Finally, relative to European Americans (EAs), non-Hispanic AAs, non-Hispanic Asians, and Hispanics are less likely to receive treatment for PTSD (Roberts et al., 2011), and are more likely to interpret their symptoms within a cultural context (Liebowitz et al., 1994).

Previous studies have suggested that AIs experience higher rates of traumatic events (Ehlers et al., 2013; Manson et al., 2005; Robin et al., 1997) and PTSD (Beals, Manson

et al., 2005; Beals, Novins et al., 2005) than what is reported in general population surveys (Volpicelli et al., 1999). The prevalence of both one month and lifetime PTSD in Vietnam veterans was found to be higher for two AI samples than for Whites (Beals et al., 2002). However, other studies have shown that AI adults or adolescents do not have higher rates of PTSD (Gnanadesikan et al., 2005; Robin et al., 1997), particularly when accounting for trauma exposure (Beals et al., 2013; Beals et al., 2002). AIs are a unique population in terms of history, culture, and societal position, which may contribute to unique genetic and environmental influences (Szlemko et al., 2006). It is possible that the studies performed thus far do not represent a wide enough range of Indian communities, and tribal differences in PTSD may exist, or differential risk factors for PTSD exist that are trauma-specific (Ehlers et al., 2013).

Twin studies have agreed that genetic factors account for 30–40% of the variance in PTSD (Koenen et al., 2008; Stein et al., 2002; True et al., 1993), although heritability has been estimated to be as high as 72% in some studies (Sartor et al., 2011). These estimates are likely an underestimate as gene–environment interactions have been proposed to play a role in PTSD and are estimated as environmental contributions in twin studies (Almli et al., 2014). Despite the evidence that PTSD is heritable, candidate gene studies and genome-wide association studies (GWAS) have largely been unsuccessful at determining a replicable risk variant for PTSD. In the candidate gene literature, genes in the hypothalamic–pituitary–adrenal (HPA) axis, as well as the serotonergic and dopaminergic systems, have been well investigated but show little evidence of consistent findings (reviewed in Almli et al. (2014)). This is likely due to low power, population differences, sample heterogeneity, or phenotypic assessment. For these same reasons, the six GWAS on PTSD have been similarly contradictory. For instance, Logue and colleagues identified single nucleotide polymorphisms (SNPs) in retinoic acid receptor-related orphan receptor A (*RORA)* that were associated with PTSD in a sample of combat-exposed EAs and a smaller sample of combat-exposed AAs (Logue et al., 2013), whereas cordon-bleu WH2 repeat protein (*COBL*) and tolloid like 1 (*TLL1)* were associated with PTSD in a sample of EAs drawn from substance abuse studies, but not in a corresponding AA sample (Xie et al., 2013). The long intergenic non-coding RNA *AC068718.1* was linked to PTSD (Guffanti et al., 2013) in trauma-exposed females from the community. Meta-analysis of a multi-ethnic study of trauma-exposed military males identified one significantly associated gene, phosphoribosyl transferase domain containing 1 (*PRTFDC1*; Nievergelt et al., 2015); yet, a meta-analysis of non-Hispanic EA and AA Iraq–Afghanistan veterans suggested two genes, protein kinase, cyclic guanosine monophosphate-dependent, type I (*PRKG1),* and DEAD-box helicase 60-like (*DDX60L)*, were associated with PTSD (Ashley-Koch et al., 2015). Finally, variants in zinc fin-

ger protein 626 *(ZNF626)* and ankyrin repeat domain 55 *(ANKRD55)* were associated with PTSD in EA and AA army members, respectively, although no findings surpassed genome-wide significance (GWS) thresholds in a Hispanic sample or trans-ethnic meta-analysis (Stein et al., 2016).

While Hispanics and AIs are clearly high-risk populations for trauma and/or PTSD, they comprise a conspicuously understudied group with respect to genetic influences contributing to the disorder. This study utilized two samples: a Hispanic sample of young adults who predominantly self-identify as Mexican American (MA cohort), in which previous work has shown similar rates of trauma exposure but higher rates of PTSD (Ehlers et al., 2016); and a family-based AI sample with a 94% rate of trauma exposure (Ehlers et al., 2013). The goals of this study were to examine the genetic basis of PTSD in each of these high-risk samples.

## Methods

### Samples

The first cohort was comprised of 619 MA young adults. Recruitment and exclusionary criteria of this sample have been previously described (Ehlers et al., 2016). Briefly, these subjects are primarily second-generation MAs recruited using a commercial mailing list. All subjects were required to be of MA heritage, between the ages of 18 and 30, residing in the United States legally, and able to read and write in English; subjects who were pregnant, nursing, or currently had a major medical or neurological disorder were excluded. Each subject was asked to assess their Hispanic heritage based on the origin (Caribbean or West Indian, Chicano, Cuban, Mexican, Mexican-American, Puerto Rican, South American, other Spanish, or Mexican Indian) of each of their eight grandparents; 83.8% of the sample self-identified as having 50% or more Mexican heritage alone.

The second sample was a family-based sample of AI participants recruited from eight geographically continuous reservations where roughly 3,000 individuals reside, as previously described (Ehlers et al., 2013). To be included in the study, each participant had to be of AI heritage, between the ages of 18 and 70, and be mobile enough to be transported from his or her home to The Scripps Research Institute (TSRI).

Phenotypic information was obtained through interviews using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994), which has been shown to be reliable and valid for diagnosing substance use behaviors, major depression, anxiety disorders, and antisocial personality disorder (Bucholz et al., 1994; Hesselbrock et al., 1999). There are 17 items from which the PTSD diagnosis is made. In the current study, the phenotypic measure tested was the sum score of these 17 items. Only subjects who had experienced trauma in their lifetime

were included in the analyses. In some cases, subjects have experienced trauma but had not been greatly upset or anxious about the event for a significant period of time and thus skipped out of the 17 PTSD items; these subjects were considered to have a sum symptom count of zero. All other subjects who had experienced trauma had numeric symptom counts. The Stressful Life Events and Response to Stressful Life-Events Scale (Hooper et al., 2011) was supplemented to the SSAGA and used to assess trauma exposure.

This work has been carried out in accordance with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Written consent was obtained for all participants and the Institutional Review Board (IRB) at TSRI approved the protocol for this study. Additionally, the Indian Health Council, a tribal review group overseeing health issues for the reservations in which recruitment took place, approved the AI study protocol.

### Genotyping

DNA was extracted from consenting subjects from blood samples. In the MA cohort, DNA was prepared and genotyping performed using the Affymetrix Exome1A chip according to the Affymetrix Axiom 2.0 Assay Manual Workflow documentation. Quality control on the markers was initially performed according to Affymetrix best practices, as described previously (Norden-Krichmar et al., 2014). Additionally, PLINK (Purcell et al., 2007) was used to calculate Hardy–Weinberg equilibrium (HWE) $p$ values on a set of maximally unrelated subjects and SNPs out of HWE ($p < 1E{-}10$) were subsequently removed. SNPs with bad genotype clusters were removed using a Java program called snpChecker, which enables the investigator to visually check and compare the clustering characteristics for each variant; snpChecker has a graphical interface that allows for the reclustering of bad calls or removal of variants with ascertainment bias or poor overall genotype calls. Genome-wide complex trait analysis (GCTA; Yang et al., 2011) was used to remove related subjects with a genetic relationship matrix (GRM) cut-off of 0.125. A second GRM was calculated after removing subjects with high hidden relatedness and pruning for minor allele frequency (MAF < 1%) and linkage disequilibrium (LD), and used to compute principal components (PCs) on autosomal SNPs. Variants with MAF < 1% were then excluded and imputation was performed using the Michigan Imputation Server (https://imputationserver.sph.umich.edu/index.html#!pages/home); the 1,000 Genomes (1,000G) Phase 3 v5 American (AMR) population was used as a reference panel and the ShapeIT software to phase the data. Post-imputation quality control included removing duplicates, variants with low imputation accuracy (Rsq < 0.9), variants with low MAF (<1%), and variants out of HWE ($p < .001$). 301,019 variants remained for analysis.

DNA from the AI cohort was extracted from blood samples and both sequenced using Illumina low-coverage whole-genome sequencing (WGS) and genotyped using an Affymetrix Exome1A chip, as previously described (Bizon et al., 2014). Paired-end sequencing was performed using the HiSeq2000 sequencers. Coverage was approximately evenly distributed at 3–12x for roughly 80% of samples. WGS reads were aligned using BWA (Li & Durbin, 2009), and subsequently realigned around indels using GATK (DePristo et al., 2011). Variants were called using two pipelines: the GATK Unified Genotyper, following best practices for low-coverage samples (Van der Auwera et al., 2013); and Thunder (Li et al., 2011), an LD aware variant caller. As described previously, the sequencing calls and exome genotypes were in good agreement (Bizon et al., 2014). Variant calls for the 301,019 variants imputed in the MA sample were extracted from the sequencing data to create a replication sample; 269,453 total variants were selected based on base pair location. Quality control steps for the variant calls included: removing variants with low MAF (<1%), and variants out of HWE ($p < .001$). This left 258,441 variants to be included in the analysis. GCTA (Yang et al., 2011) was used to calculate a GRM and PCs for this sample, after variants were pruned for LD.

### Association Analysis

In the MA cohort, a linear regression was run in PLINK2 (https://www.cog-genomics.org/plink2; Chang et al., 2015) using an additive model to test for genome-wide association with sum PTSD symptoms. Gender, age, and 20 PCs were included as covariates. Adaptive permutation testing was run to account for skewed phenotypic distribution. MAF for SNPs in the sample was evaluated using PLINK (Purcell et al., 2007). Power calculations for the MA sample were performed in R (R Development Core Team, 2012) using the commands outlined in the Genome Analysis Wiki (http://genome.sph.umich.edu/wiki/Power_Calculations:_Quantitative_Traits).

A mixed linear model association (MLMA; Yang et al., 2014) was run in the AI cohort using GCTA (Yang et al., 2011), in which the additive effect of the SNP is tested for association with the phenotype, given the relationship matrix between subjects (e.g., the GRM calculated in GCTA). Gender and age were included as covariates (analyses were run including PCs as additional covariates with similar results). Allele frequencies were calculated within GCTA. Power calculations were performed using the Genetic Power Calculator (Purcell et al., 2003). Specifically, the variance components quantitative trait locus (QTL) association for sibships and singletons module was used; these calculations are based upon a formula derived in (Sham et al., 2000).

Quantile–quantile (QQ) and Manhattan plots was generated using the Manhattan package (Turner, 2014) in R

**TABLE 1**

**Sample Characteristics**

|  | Mexican American | American Indian |
|---|---|---|
| N | 254 | 258 |
| % Female | 53.15% | 56.59% |
| Age: mean ± *SD*, (range) | 23.78 ± 3.71, (18–30) | 31.84 ± 14.47, (18–82) |
| Self-reported respective heritage ≥ 50% | 83.46% | 33.33% |
| BMI: mean ± *SD*, (range) | 27.05 ± 6.54, (16.92–64.40) | 32.27 ± 7.99, (18.25–66.45) |
| Education (years): mean ± *SD*, (range) | 13.34 ± 1.78, (7–17) | 11.61 ± 1.59, (6–17) |
| Income: % < $20,000/year | 19.92% | 39.24% |
| PTSD symptoms: mean ± *SD*, (range) | 4.70 ± 5.71, (0–17) | 6.71 ± 5.98, (0–17) |

Note: *SD* = standard deviation; BMI = body mass index.

(R Development Core Team, 2012). The genomic inflation factor (lambda, λ) was calculated in R using the commands outlined in http://genometoolbox.blogspot.com/2014/08/how-to-calculate-genomic-inflation.html. Locus zoom plots were generated with the LocusZoom software (http://locuszoom.sph.umich.edu/locuszoom/) from the University of Michigan (Pruim et al., 2010) using the 1,000G AMR population as a reference population and the hg19 build. Variants were annotated using ANNOVAR (Wang et al., 2010).

GWAS typically test a million or more variants and thus use the standard Bonferroni multiple testing correction of $p < 5\text{E-}08$. Because a much smaller number of variants were assessed in this study (~300,000), this correction is too stringent. Thus, suggestive and GWS thresholds were calculated in each cohort based on the effective number of independent tests using the Genetic Type 1 Error Calculator (GEC) software (Li et al., 2012).

### Meta-Analysis

A meta-analysis of the MA and AI cohorts was run in PLINK (Purcell et al., 2007), which performs both a fixed and random effects meta-analysis. Variants were annotated with ANNOVAR (Wang et al., 2010). Manhattan and QQ plots were generated, as described above.

### Pathway Analysis

SNPs with $p < .0025$ for either the fixed or random effects meta-analysis and $I^2 < 50$ (a measure of heterogeneity ranging from 0 to 100) were annotated to genes using ANNOVAR (Wang et al., 2010). These genes underwent pathway analysis using the functional annotation tools in DAVID (Database for Annotation, Visualization, and Integrated Discovery) version 6.8 (Huang et al., 2009a, 2009b). In cases where a SNP was annotated to more than one gene both genes were included in the DAVID analysis. This $p$ value threshold was chosen in order to obtain a set of genes greater than 100, as the DAVID documentation recommends a reasonable number of genes (e.g., 100–2,000) for functional analysis (Huang et al., 2009b).

## Results

### Association Analyses

Of the 548 MA subjects, who consented to give DNA and passed quality control procedures, 254 had experienced trauma according to the stressful life events criteria and were available for analysis. While 720 AI subjects were genotyped, the PTSD segment of the SSAGA was administered after the study collection began; thus, of the 309 subjects with phenotypic data, only 258 had both been genotyped and experienced trauma and were included in the analysis (Table 1). Only a very small proportion of the MA and AI samples had rated their most traumatic event as military combat related (2.75% and 0.392%, respectively). In the MAs, the most commonly endorsed disturbing events were witnessing trauma to others (51.83%), injury or assault to self (21.10%), and sexual abuse (12.84%). Conversely, the most commonly endorsed disturbing events in the AIs were death of others due to natural causes or illness (34.12%), injury or assault to self (20.00%), and crime without self-injury (14.90%). Generally, the AI cohort was older, had more PTSD symptoms, fewer years of education, and a higher proportion of the sample earning less than $20,000 per year as compared to the MA sample.

In the MA GWAS, no variants survived correction for GWS at $p < 9.22\text{E-}07$, but six variants were suggestively associated with PTSD at $p < 1.84\text{E-}05$ (Figure 1), as given by GEC, and this association remained after permutation (Table 2). The genomic inflation factor was λ = 0.989, indicating no inflation of test scores (Figure S1). The suggestively significant variants were in high LD (Figure S2). All six suggestively significant variants were exonic variants in olfactory receptor family 11 subfamily L member 1 (*OR11L1*), of which four (rs10888255, rs10888257, rs10888256, rs4607924) were non-synonymous variants. The minor alleles were associated with increased risk for PTSD in this sample (see Table S1 for a list of the top 50 hits.) Power calculations indicated this cohort of 254 unrelated subjects was 23.6% powered to identify a marker explaining 5% of the phenotypic variance at $p < 1.84\text{E-}05$. In order for a study to be 80% powered to detect a marker explaining just 1% of the phenotypic variance at $p < 1.84\text{E-}05$

**TABLE 2**

Suggestively Significant Hits for PTSD in the Mexican American Sample

| Chromosome | BP[a] | dbSNP 138 | Minor allele | Beta[b] | SE | Statistic | p | Empirical p[c] | # Permutations | MAF[d] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 248,004,296 | rs6681483 | G | 4.183 | 0.854 | 4.898 | 1.83E-06 | 3.00E-06 | 1,000,000 | 0.08394 |
| 1 | 248,004,614 | rs6667389 | G | 4.183 | 0.854 | 4.898 | 1.83E-06 | 3.00E-06 | 1,000,000 | 0.08394 |
| 1 | 248,004,687 | rs10888255 | C | 4.183 | 0.854 | 4.898 | 1.83E-06 | 3.00E-06 | 1,000,000 | 0.08394 |
| 1 | 248,004,877 | rs10888257 | C | 4.183 | 0.854 | 4.898 | 1.83E-06 | 3.00E-06 | 1,000,000 | 0.08394 |
| 1 | 248,004,775 | rs10888256 | C | 4.147 | 0.851 | 4.872 | 2.05E-06 | 3.00E-06 | 1,000,000 | 0.08029 |
| 1 | 248,004,848 | rs4607924 | G | 4.147 | 0.851 | 4.872 | 2.05E-06 | 3.00E-06 | 1,000,000 | 0.08029 |

Note: Additional details available in Table S1. SE = Standard error.
[a]From the Human Genome 19 (hg19) build.
[b]The direction of the regression coefficient represents the effect of each extra minor allele whereby a positive regression coefficient means that the minor allele increases risk.
[c]Derived from phenotype permutations.
[d]Minor allele frequency for the entire genotyped sample ($N = 548$).
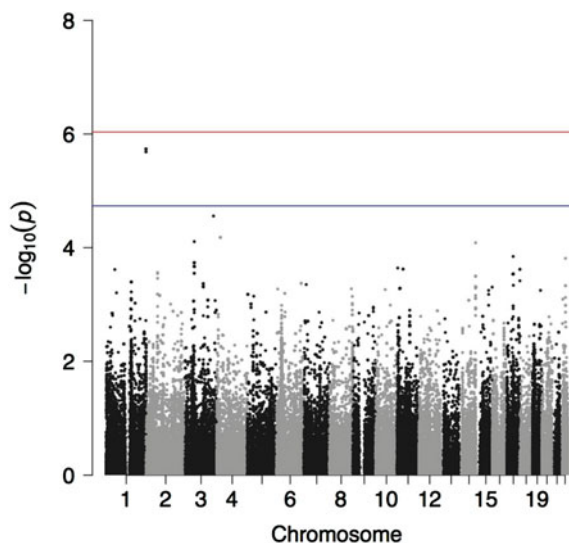


**FIGURE 1**

(Colour online) Manhattan plot showing the *p* value for sum PTSD symptoms in the Mexican American cohort. Suggestive (blue line) and genome-wide (red line) significance thresholds are $p < 1.84E-05$ and $p < 9.22E-07$, respectively, calculated using the Genetic Type 1 Error Calculator (GEC) software.
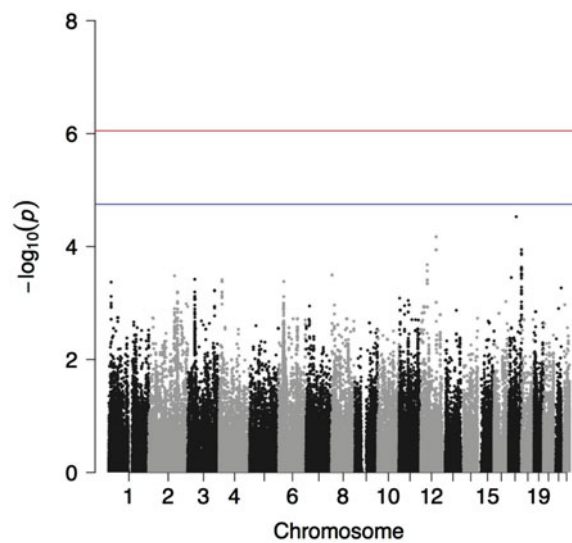


**FIGURE 2**

(Colour online) Manhattan plot showing the *p* value for sum PTSD symptoms in the American Indian sample. Suggestive (blue line) and genome-wide (red line) significance thresholds are $p < 1.78E-05$ and $p < 8.91E-07$, respectively, calculated using the Genetic Type 1 Error Calculator (GEC) software.

or $p < 9.22E-07$, 2,630 or 3,310 subjects would be required, respectively.

No variants were associated with PTSD at suggestive or GWS thresholds at $p < 1.78E-05$ and $p < 8.91E-07$, respectively, in the AI MLMA (Figure 2). A $λ = 0.9995$ indicated no inflation of test scores (Figure S3). The *OR11L1* hits on chromosome 1 in the MA sample did not replicate in this sample; however, a signal in a nearby olfactory receptor on chromosome 1, olfactory receptor family 2 subfamily L member 13 (*OR2L13*), tagged by rs151319968, was nominally associated with PTSD (Figure S4). This association did not survive correction for suggestive or GWS. A list of the top 50 results is shown in Table S2. Given no dominance effects and a sample size of 258, this study was 25.7% powered to detect a QTL explaining 5% of the phenotypic variance at $p < 1.78E-05$. The samples were assumed unrelated (e.g., sibling correlation of 0 and 'singletons' for sibship size) due to the large extended pedigree structure. However, relatedness in samples will generally lead to slightly higher power estimates (Sham & Purcell, 2014). A sample size of 2,621 subjects would be needed to detect a QTL explaining 1% of the variance at $p < 1.78E-05$ with 80% power; a sample size of 3,296 would be needed to detect a QTL explaining 1% of the variance at $p < 8.91E-07$ with 80% power.

**Meta-Analysis**

In the meta-analysis of 238,631 variants, no variants survived correction for suggestive or GWS, using the more stringent significance thresholds obtained in the MA cohort (Figure 3). A list of the top 50 results is shown in Table S3. The QQ plot and genomic inflation factor ($λ = 1.047$) for

**TABLE 3**

Enriched Terms With Benjamini Corrected $p < .05$ From the Functional Annotation Chart Analysis in DAVID v6.8

| Category | Term | Count[a] | %[b] | Modified Fisher exact $p$ value | Benjamini corrected $p$ value |
|---|---|---|---|---|---|
| UP_KEYWORDS | Polymorphism | 105 | 65.63 | 1.84E-04 | .0135 |
| UP_KEYWORDS | Glycoprotein | 52 | 32.5 | 1.24E-04 | .0137 |
| UP_KEYWORDS | Sensory transduction | 15 | 9.38 | 8.61E-05 | .0189 |
| UP_KEYWORDS | G-protein coupled receptor | 16 | 10.00 | 7.47E-04 | .0234 |
| UP_KEYWORDS | Transmembrane | 58 | 36.25 | 6.72E-04 | .0246 |
| UP_KEYWORDS | Transmembrane helix | 58 | 36.25 | 6.17E-04 | .0270 |
| UP_KEYWORDS | Transducer | 17 | 10.63 | 5.00E-04 | .0274 |
| UP_KEYWORDS | Olfaction | 11 | 6.88 | 1.03E-03 | .0282 |
| KEGG_PATHWAY | hsa04612:Antigen processing and presentation | 6 | 3.75 | 2.93E-04 | .0342 |
| UP_SEQ_FEATURE | glycosylation site:N-linked (GlcNAc...) | 50 | 31.25 | 5.28E-05 | .0343 |
| KEGG_PATHWAY | hsa04915:Estrogen signaling pathway | 6 | 3.75 | 9.89E-04 | .0385 |

Note: [a]Number of genes involved in the term from the imported gene list.
[b]Percentage of genes involved in the term from the list.
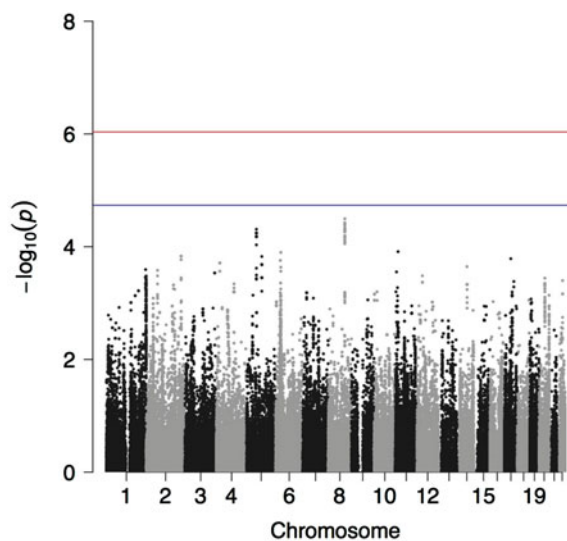


**FIGURE 3**

(Colour online) Manhattan plot showing the *p* value for the fixed effects meta-analysis of the Mexican American and American Indian cohorts; significance thresholds represent the more conservative estimate from the Mexican American cohort. The blue and red lines represent suggestive and genome-wide significance thresholds, respectively.

the fixed effects *p* value indicated no inflation of test scores (Figure S5).

**Pathway Analysis**

One hundred and sixty genes mapped to *Homo sapiens* and were used in the DAVID pathway analyses. Enrichment analysis using the functional annotation chart tool, which identifies enriched annotation terms from the gene list, identified 148 terms (using all but 20 genes), 11 of which survived correction for multiple testing at $p < .05$ (Table 3). Notably, olfaction and sensory transduction were among these terms. The functional annotation clustering

tool, which clusters similar pathway terms from the gene list into groups, identified 23 clusters, 5 with enrichment score >1.3 (the suggested cut-off in DAVID; Huang et al., 2009b). The most enriched cluster (with enrichment score 2.82; see Table 4) included terms related to sensory transduction, olfactory receptor activity, G-protein coupled receptors (GPCRs), and cell/plasma membrane. Information on the remaining four clusters with enrichment score >1.3 is available in Table S4. These analyses were repeated arbitrarily using only the first gene each SNP was annotated to (e.g., in cases where a SNP was annotated to more than one gene only the first gene was included, as opposed to using both genes as originally done, yielding 137 genes), with similar results: the most enriched cluster (enrichment score 2.01) contained the same terms as those shown in Table 4, with the exception of the 'topological domain:Cytoplasmic' term.

## Discussion

We present the first GWAS of PTSD in two high-risk minority samples. These populations are important to study as research has shown racial/ethnic differences in trauma exposure, risk for PTSD, and PTSD severity (Alcantara et al., 2013; Beals et al., 2002; Beals, Manson et al., 2005; Beals, Novins et al., 2005; Ehlers et al., 2013; Ehlers et al., 2016; Kulka, 1990; Manson et al., 2005; Marshall et al., 2009; Ortega & Rosenheck, 2000; Pole et al., 2008; Roberts et al., 2011; Robin et al., 1997; Santos et al., 2008; Schell & Marshall, 2008). This study included two samples: a sample of male and female MAs living in the United States who had primarily witnessed trauma to others, experienced injury or assault to self or been sexually abused, rather than exposed to combat trauma as in many previous studies; and a family-based sample of male and female AIs previously shown to have high trauma exposure rates due to unexpected death, injury or assault to self, and crime without injury (Ehlers

**TABLE 4**

Terms Included in the Most Enriched Annotation Cluster From the Functional Annotation Clustering Analysis in DAVID v6.8 (Enrichment Score 2.82)

| Category | Term | Count[a] | %[b] | Modified Fisher exact *p* value | Benjamini corrected *p* value |
|---|---|---|---|---|---|
| UP_KEYWORDS | Sensory transduction | 15 | 9.38 | 8.61E-05 | .0189 |
| UP_SEQ_FEATURE | topological domain:Cytoplasmic | 41 | 25.62 | 3.55E-04 | .0753 |
| UP_SEQ_FEATURE | topological domain:Extracellular | 35 | 21.88 | 4.42E-04 | .0704 |
| UP_KEYWORDS | Transducer | 17 | 10.63 | 5.00E-04 | .0274 |
| UP_KEYWORDS | G-protein coupled receptor | 16 | 10.00 | 7.47E-04 | .0234 |
| INTERPRO | IPR017452:GPCR, rhodopsin-like, 7TM | 15 | 9.38 | 8.29E-04 | .2119 |
| KEGG_PATHWAY | hsa04740:Olfactory transduction | 11 | 6.88 | 8.92E-04 | .0517 |
| GOTERM_BP_DIRECT | GO:0050911~detection of chemical stimulus involved in sensory perception of smell | 11 | 6.88 | 9.48E-04 | .4292 |
| UP_KEYWORDS | Olfaction | 11 | 6.88 | 1.03E-03 | .0282 |
| INTERPRO | IPR000725:Olfactory receptor | 11 | 6.88 | 1.06E-03 | .1414 |
| GOTERM_MF_DIRECT | GO:0004984~olfactory receptor activity | 11 | 6.88 | 1.22E-03 | .2269 |
| INTERPRO | IPR000276:G protein-coupled receptor, rhodopsin-like | 14 | 8.75 | 2.00E-03 | .1745 |
| GOTERM_MF_DIRECT | GO:0004930~G-protein coupled receptor activity | 14 | 8.75 | 2.09E-03 | .1975 |
| UP_KEYWORDS | Receptor | 23 | 14.37 | 2.17E-03 | .0521 |
| GOTERM_BP_DIRECT | GO:0007186~G-protein coupled receptor signaling pathway | 14 | 8.75 | 1.20E-02 | .8322 |
| GOTERM_CC_DIRECT | GO:0005886~plasma membrane | 39 | 24.38 | 3.94E-02 | .6169 |
| UP_KEYWORDS | Cell membrane | 30 | 18.75 | 5.37E-02 | .5585 |

Note: Additional clusters with enrichment score >1.3 are shown in Table S4.
[a]Number of genes involved in the term from the imported gene list.
[b]Percentage of genes involved in the term from the list.

et al., 2013). Information regarding trauma exposure and PTSD in our MA sample has been previously published. In short, this work showed a higher prevalence of PTSD in this sample compared to other Hispanic groups (Ehlers et al., 2016). The present study identified a genetic signal in *OR11L1* associated with PTSD in the MA sample. A signal in the nearby olfactory receptor *OR2L13* on chromosome 1, tagged by rs151319968, was nominally associated with PTSD in the AI cohort, although this association did not survive correction for suggestive or GWS. Results from a meta-analysis of the two cohorts showed an enrichment cluster that included terms related to sensory transduction and olfaction from a pathway analysis in DAVID.

Although this is the first association of *OR11L1* in a human genetic study with a psychiatric disorder, a functional interaction network constructed from GWAS findings on PTSD by Guffanti et al. (2013) revealed nine modules, in one of which the top pathways were olfactory transduction and olfactory signaling pathway. While these pathways did not survive correction for multiple testing, our results support this finding; pathway analyses identified an enriched cluster with terms such as 'olfaction' and 'sensory transduction'. Together, these data support a role for genetic variants that are involved in, or perturb, olfaction in PTSD.

Clinical studies have previously implicated olfaction in triggering traumatic memories. Trauma-associated smells (e.g., napalm and diesel) have been shown to trigger emotional memories and induce traumatic recall in combat veterans with PTSD (Kline & Rausch, 1985; Vermetten

& Bremner, 2003). Positron emission tomographic (PET) measurements have shown changes in cerebral blood flow in response to various olfactory stimuli in subjects with PTSD compared to controls, suggesting that PTSD patients are more sensitive to smell than control subjects without PTSD (Vermetten et al., 2007). A recent study comparing combat-exposed veterans with and without PTSD to controls found that combat veterans show decreased distress and relaxation in response to both negative and positive hedonic odors; however, compared to controls, combat veterans with PTSD reported higher distress with specific negative hedonic odors, including fuel, blood, gunpowder, and burning hair, but not all negative hedonic odors (Cortese et al., 2015). Patients with PTSD have also shown differences in olfactory identification compared to controls; studies of male combat veterans with PTSD have exhibited deficits in odor identification (Dileo et al., 2008; Vasterling et al., 2000), although a study in women exposed to non-combat trauma with PTSD showed higher odor identification than controls (Croy et al., 2010). Thus, odor sensitivity may afford more opportunity to be triggered by memories and to form associations with traumatic triggers via the release of catecholamines.

Previously identified genes for PTSD, including *RORA, COBL, TLL1, AC068718.1, PRKG1, DDX60L, ZNF626,* and *ANKRD55* (Ashley-Koch et al., 2015; Guffanti et al., 2013; Logue et al., 2013; Stein et al., 2016; Xie et al., 2013), were not among the top hits in the current study. However, these findings pertain to primarily EA and AA samples. Only

one study found a SNP of GWS from a meta-analysis of a multi-ethnic sample; although the gene, *PRTFDC1*, was not among our top hits, SNPs in two genes, pogo transposable element with KRAB domain *(POGK)* and CUB and Sushi multiple domains 1 *(CSMD1)*, were trending toward association with PTSD and specifically driven by a combined MA and AI sample (Nievergelt et al., 2015). Two SNPs in *CSMD1,* rs3802303 and rs7833969, were associated with sum PTSD symptoms in our AI sample at $p = 3.19E\text{-}04$ (and were within the top 50 hits; see Table S2). In the MA sample and meta-analysis, however, these SNPs were not associated with PTSD at $p < .05$. While these SNPs do not survive correction for suggestive or GWS in our AI cohort and are different than the trending SNP in the study by Nievergelt and colleagues (2015), this suggests a role for *CSMD1* in PTSD among AIs specifically. It is increasingly important to consider differences between samples and how these relate to understanding the biological underpinning of PTSD. Different triggers may produce different PTSD symptoms among individuals and ethnicities and it is increasingly important to define these ethnically sensitive triggers. Furthermore, the cultural interpretation of one's symptoms could influence diagnosis. The identification of culturally specific genes influencing PTSD will enable researchers to accommodate for and better treat PTSD symptoms.

This study has both limitations and strengths. The small sample size resulted in low power to detect genetic signals of small effect. Our MA and AI samples had a mean age of 23.78 and 31.84 years, respectively; although this may have contributed to a relatively low trauma endorsement, the heritability of PTSD was previously estimated to be 72% in a sample of females between the ages of 18 and 29 (Sartor et al., 2011), suggesting genetic factors for PTSD may play a large role in this age group. While the AI data were sequenced, only common variants were analyzed here, as was the goal of the study; however, larger sample sizes can be used in the future to detect genetic effects in rare variants. Similarly, while imputation was used in the MA data, only variants in LD with exonic SNPs were imputed by the nature of the data and thus important signals may have been missed. However, our MA and AI cohorts are unique, high-risk samples, which in itself is both a strength and limitation of the current study; these samples are distinctive, comprised of a non-combat exposed, minority, primarily young adult population, who have a unique risk for PTSD.

In conclusion, the present study provides evidence that genetic variation in genes influencing olfaction may confer risk for PTSD in these minority populations. Although this study was underpowered to fully evaluate the phenotype given the limitation of small sample size, suggestive evidence for genetic association was nevertheless found in both cohorts. Specifically, variation in *OR11L1* was associated with PTSD in a young adult MA sample and a signal in the nearby olfactory receptor *OR2L13* on chromosome 1 was nominally associated with PTSD in the AI sample. Pathway analysis using both cohorts showed enrichment of functional terms related to the olfactory system, particularly signal transduction, olfactory receptor activity, GPCRs, and olfaction. This is in agreement with findings from a functional interaction network derived from GWAS findings on PTSD in which olfactory transduction and olfactory signaling pathway were top pathways in one of the associated modules identified (Guffanti et al., 2013), as well as numerous clinical studies supporting a role for olfaction in PTSD (Cortese et al., 2015; Croy et al., 2010; Dileo et al., 2008; Kline & Rausch, 1985; Vasterling et al., 2000; Vermetten & Bremner, 2003; Vermetten et al., 2007). These data suggest that olfaction may play a role in PTSD, but may not necessarily mean that variants in the same olfactory genes contribute risk for PTSD across populations.

## Disclosure of Interests

None.

## Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/thg.2017.12

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