Genetics of Smoking Behaviors in American Indians

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ABSTRACT

Background: The smoking behavior of American Indians (AI) differs from that of non-Hispanic whites (NHW). Typically light smokers, cessation interventions in AIs are generally less effective. To develop more effective cessation programs for AIs, clinicians, researchers, and public health workers need a better understanding of the genetic factors involved in their smoking behavior. Our aim was to assess whether SNPs associated with smoking behavior in NHWs are also associated with smoking in AIs.

Methods: We collected questionnaire data on smoking behaviors and analyzed blood and saliva samples from two Tribal populations with dramatically different cultures and smoking prevalence, one in the Northern Plains ($n = 323$) and the other in the Southwest ($n = 176$). A total of 384 SNPs were genotyped using an Illumina custom GoldenGate platform. Samples were also assessed for cotinine and 3-hydroxycotinine as markers of nicotine intake and nicotine metabolite ratio.

Results: Among 499 participants, we identified, in the Northern Plains sample only, a variant of the gamma-aminobutyric acid receptor subunit alpha-2 (*GABRA2*) (rs2119767) on chromosome 4p that was associated with many of the intake biomarkers of smoking we examined, suggesting a role for this gene in modifying smoking behavior in this population. We also identified three SNPs, in the Southwest sample only, as significant correlates of only cigarettes per day: rs4274224, rs4245147 (both dopamine receptor D2 gene), and rs1386493 (tryptophan hydroxylase 2 gene).

Conclusions: The contribution of many genes known to underlie smoking behaviors in NHWs may differ in AIs.

Impact: Once validated, these variants could be useful in developing more effective cessation strategies.

Introduction

Racial and ethnic differences in lifestyle, exposure, and genetics may contribute to health disparities (1, 2). Smoking is a well-known risk factor for lung cancer, respiratory disease, and cardiovascular disease (3), and its prevalence varies widely across the United States. American Indians have the highest prevalence of cigarette smoking of any U.S. racial or ethnic group, approximately 2.5 times that of the U.S. all-races population (4, 5). Although the overall proportion of current smokers in the United States declined from 42% in 1960 to 17% in 2014 (5), smoking prevalence in many American Indian communities has either not declined so significantly or has actually increased (4–6), with concomitant increases in lung cancer, respiratory disease, and cardiovascular disease (7–9).

The topography of smoking among American Indians is known to differ from those of other racial and ethnic groups (4, 10–13). For example, relative to non-Hispanic whites (NHW), American Indian smokers consume fewer cigarettes per day (14, 15), and many exhibit sporadic smoking patterns characterized by multiple unsuccessful cessation attempts, despite acute interest in quitting (16, 17). In addition, the age of smoking initiation has declined in recent American Indian birth cohorts (18). Finally, the use of cigarettes and commercial tobacco in ritualized and ceremonial settings in many Tribal populations further complicates the study of smoking behaviors (19, 20).

Considerable progress has been made in characterizing the behavioral, demographic, socioeconomic, and genetic factors that influence smoking behavior in NHWs and Blacks (21, 22). Several SNPs have been associated with smoking behavior (23–28), and shown to predict response to smoking cessation therapy (29–35). Nevertheless, studies suggest that these SNPs may have differential predictive value in different racial groups (30). Among American Indians in particular, little research has addressed the genetic correlates of smoking behavior.

A better understanding of these correlates is needed to inform interventions, programs, and policies that can effectively address the high prevalence of smoking among many American Indian Tribal populations. This article reports the results of an analysis of dopaminergic and serotonergic candidate gene determinants of smoking and nicotine dependence in two Tribal populations: one in the Northern Plains (NP), the other in the Southwest (SW).

Materials and Methods

Study design, setting, and recruitment

The purpose of this study was to examine SNPs in candidate genes previously associated with smoking and nicotine dependence in other racial/ethnic populations, to determine whether similar associations appear in American Indians.

To protect the confidentiality of the study communities, geographic descriptors are used instead of Tribal names. Participating Tribal

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populations in each region (NP vs. SW) are culturally and linguistically unrelated to each other, and their historic experiences differ substantially. The NP group resides predominantly on rural reservations, whereas the SW group is largely urban. NP Tribal members also smoke considerably more than their SW counterparts (18).

NP participants were recruited from a random subset of participants in an earlier study of risk factors for cancer and other chronic diseases (36). SW participants were recruited by using respondent-driven sampling among American Indian friends and family members of Tribal participants in a previous randomized clinical trial in the greater Phoenix metropolitan area (37). Both subsamples were stratified by sex and smoking status.

We attempted to enroll equal numbers of never, former, and current smokers to facilitate analysis. Therefore, the prevalence of these three smoking categories among study participants does not reflect the population prevalence of smoking in their Tribes. No other categories of smoking behavior (e.g., cigarettes per day nor degree of dependence) contributed to our participant selection.

Informed consent and data collection

Ethical approval for all study procedures was obtained from the institutional review boards of the Great Plains Indian Health Service; the Phoenix Area Indian Health Service; the MD Anderson Cancer Center; the University of Washington; the University of Toronto, Ontario, Canada; the MedStar Health Research Institute; and appropriate Tribal entities. All participants provided written informed consent before commencing any study activities, and the study was conducted in accordance with the ethical guidelines recognized in the Belmont Report (38).

Individual interviews were conducted with all participants in 2012 to 2014 by trained American Indian research staff. All participants completed a questionnaire assessing demographics, cultural identity, language use, health, tobacco use (both ceremonial and commercial), nicotine dependence, recent feelings and emotional state, social influences on smoking, normative beliefs, and socioeconomic status. Samples of blood or saliva were also collected from all participants.

Measures

Tribal affiliation, smoking status and behaviors, nicotine intake biomarkers, estimates of secondhand smoke (SHS) exposure, and measures of nicotine dependence were assessed. Never smokers were defined as those who reported smoking less than 100 cigarettes in their lifetime, and current smokers as those who reported having smoked at least one cigarette in the last month and at least 100 cigarettes in their lifetime. For analytic purposes, we defined smoking status in two different ways: (1) never smokers versus ever smokers (current and former smokers combined) and (2) currently not smoking (former and never smokers combined) versus current smokers.

We examined several measures of smoking behavior in this study, including status, intensity, intake biomarkers, and nicotine dependence. Intensity was operationalized as the self-reported number of cigarettes smoked per day (CPD), either currently or in the past. Other measures, used in this study for current smokers only, were plasma concentrations of cotinine (COT, nicotine's primary metabolite) and of 3′-hydroxycotinine (3HC, COT's primary metabolite), the molar sum of COT+3HC, and the ratios of COT to CPD, and of the molar sum of cotinine+3HC to CPD, as more accurately reflecting nicotine intake and intensity of intake than the self-reported CPD. These biomarkers were analyzed by LC/MS-MS as described previously (14, 39).

In a previous study (14), we noted nontrivial concentrations of the plasma nicotine metabolites in self-reported former and never smokers in these populations, most likely from their SHS exposure. Therefore, assuming that SHS exposure may have affected the levels of the metabolite variables in current smokers as well, we adjusted our analyses of the metabolite variables for two self-reported proxy measures of SHS exposure. They were derived from the answers to the following two questions: "Are your home's residents or visitors allowed to smoke in your home (y/n)?", and "Of your closest three friends, how many of them smoke (0/1/2/3)?". We also evaluated the nicotine metabolite ratio (NMR, 3HC/COT).

We analyzed degree of nicotine dependence measured by the Fagerström Test for Nicotine Dependence (FTND; ref. 40), and the Hooked on Nicotine Checklist (HONC; ref. 41). These two measures were obtained from current smokers only.

We used a targeted candidate gene approach for genotyping, as the available sample size was insufficient for a well-powered genome-wide association study. A SNP was included in the analysis if two conditions were met: (i) it was linked to a gene previously reported to be associated with smoking behavior; and (ii) the minor allele frequency (MAF) of the SNP was at least 5% in Asians, the racial group purported to be the closest ancestral lineage to American Indians (42), owing to a paucity of frequency data for American Indians. A total of 310 candidate SNPs were identified and included in an Illumina custom GoldenGate genotyping platform (Illumina, Inc.). We supplemented the list with 74 markers informative of American Indian ancestry (43), to control for possible population stratification and reduce the chance of false-positive findings (44, 45). Participants with sample call rates below 90% were excluded, and markers with sample call rates of 90% or lower were also excluded. We applied these relatively permissive criteria to avoid losing too many participants from the analysis. The resulting genotyping rate was 99.64% in the SW population and 99.71% in the NP population. In addition, markers with allele distributions that deviated from Hardy–Weinberg equilibrium in either population ($P < 1 \times 10^{-5}$) or with a MAF below 5% in either population were excluded from the analysis of that population. After implementing these quality control procedures, 323 participants and 276 SNPs were available for the NP population, and 176 participants and 269 SNPs for the SW population (Supplementary Table S1A). However, SNPs with low MAFs were still used to compare allele frequencies between the two populations (337 SNPs in all; Supplementary Table S1B).

Statistical analyses

We analyzed the two Tribal populations separately for several reasons, including their marked differences in SNP allele frequencies (Supplementary Table S1B), smoking prevalence, and cultural and socioeconomic factors.

To adjust for multiple testing, we first estimated the total number of independent SNPs. Two SNPs were considered to be independent when their pairwise linkage disequilibrium was below 0.8 as measured by R^2. We identified 102 independent SNPs (SNP clusters), so we considered the number of independent statistical tests to be 102. A P value of $\sim 5 \times 10^{-4}$ was considered statistically significant. We used logistic regression to analyze dichotomous outcomes (smoking status) and linear regression for continuous outcomes (smoking intensity, nicotine metabolism biomarkers, and nicotine dependence), controlling for age and gender and, in the analyses of nicotine biomarker variables, for the two indirect measures of SHS exposure as described above.

For linked SNPs showing study-wide significance, we first identified the most significant SNP in the region and then adjusted the

Table 1. A comparison of characteristics of the NP and SW populations.

Categorical characteristic	NP		SW		*P* value
	n	%	*n*	%	
Gender					0.256
Men	159	49.2	96	54.50	
Women	164	50.8	80	45.50	
Smoking status					0.008
Never smoker	119	36.8	67	38.1	
Former smoker	105	32.5	36	20.5	
Current smoker	99	30.7	73	41.5	

Quantitative characteristic	NP			NP			*P* value[a]
	N	Mean	SD	*N*	Mean	SD	
Age	323	51.3	14.6	176	43.8	12.8	5.19×10^{-9}
FTND score[b]	93	1.85	2.05	70	1.69	2.18	0.3523
HONC score[b]	94	4.54	3.06	70	3.21	3.04	0.0022
CPD[c], former smokers	96	8.44	9.34	36	5.20	5.83	0.0285
CPD[c], current smokers	91	6.78	6.52	73	2.94	5.16	7.40×10^{-7}

[a]Presented for the log-transformed FTND and CPD for current smokers and square root-transformed HONC and CPD for former smokers.
[b]Current smokers only.
[c]CPD, cigarettes per day.

effects of the remaining linked SNPs for the effects of the most significant one.

Results

The final study sample comprised 499 American Indians ages 20 to 88 years, with 323 in the NP and 176 in the SW. **Table 1** includes basic demographic data by region. The two Tribal populations show significant differences in demographic and smoking characteristics. Although gender distribution was similar in both samples, the mean age of NP participants was significantly higher than that of SW participants (51.3 years vs. 43.8 years). **Table 1** reveals that mean FTND scores were also similar in both populations, but mean HONC scores were lower in SW participants than in NP participants (3.21 vs. 4.54, $P = 0.0022$), indicating lower levels of nicotine dependence. The discrepancy between the two measures of nicotine dependence is likely owing to the fact that HONC is more sensitive to low-level smoking (46), as exemplified by the majority of the participants from both of our Tribal populations. Moreover, SW participants reported smoking fewer CPD than NP participants, both among current smokers (2.94 CPD vs. 6.78 CPD, $P = 7.4 \times 10^{-7}$) and among former smokers (5.20 vs. 8.44, $P = 0.0285$). The characteristics of variables related to NMR and smoking intake biomarkers for these populations have been reported previously (14, 39).

Analysis of smoking status

Table 2 shows the results of the analysis of smoking status. No SNPs were significant after adjustment for multiple testing.

Analysis of CPD

Table 3 shows that the CPD was more strongly associated than smoking status with SNPs. Former and current smokers were analyzed separately. We identified 24 nominally significant SNPs, among which three (rs1386493, rs4274224, and rs4245147), only in the Southwest,

Table 2. SNPs nominally significantly associated with smoking status in the logistic regression model, adjusted for age and gender, with additive mode of inheritance.

Population	Comparison	SNP	CHR	A1	A2	OR	95% CI		*P* value[a]	Gene(s)
							Lower	Upper		
Southwest	Ever vs. Never	rs2630351	3	A	G	0.258	0.110	0.605	0.00182	*DRD3*
		rs3773678	3	A	G	0.302	0.134	0.683	0.00405	*DRD3*
		rs10819700	9	G	A	2.043	1.237	3.376	0.00529	*NR4A3/LOC441461*
		rs569207	15	G	A	2.991	1.214	7.370	0.01723	*CHRNA5*
		rs518596	6	G	A	2.422	1.178	4.977	0.01611	*OPRM1/IPCEF1*
	Current vs. Not	rs2280075	4	G	A	4.023	1.254	12.907	0.01924	*GABRA4*
		rs790260	6	G	A	1.881	1.076	3.286	0.02652	*IPCEF1*
Northern Plains	Ever vs. Never	rs4565946	12	A	G	0.562	0.397	0.796	0.00115	*TPH2*
		rs2225251	1	A	G	0.696	0.498	0.973	0.03388	*SLC2A1/FAM183A*
	Current vs. Not	rs1799978	11	G	A	1.922	1.072	3.446	0.02822	*TMPRSS5/DRD2*
		rs6495309	18	G	A	1.538	1.060	2.224	0.02234	*CHRNA3/CHRNB4*

[a]A *P* value $< 5 \times 10^{-4}$ was considered study-wide significant.

Table 3. Analysis of smoking as a quantitative trait: SNPs associated with the number of cigarettes smoked per day.

Site	Smoking status	SNP	Chr	BP	β	*P* value[a]	Gene
SW	Current[b]	**rs1386493**	**12**	**72355179**	**0.500**	**1.50E−05**	***TPH2***
		rs6582072	12	72354477	0.408	5.47E−04	*TPH2*
		rs10506645	12	72385500	−0.385	0.0011	*TPH2*
		rs10833	4	142654547	0.337	0.0054	*IL15*
		rs3762607	4	46996338	0.295	0.0161	*GABRA4/GABRB1*
		rs6841454	4	142635042	0.259	0.0348	*IL15*
		rs1487276	12	72405059	0.253	0.0372	*TPH2*
		rs6850492	4	142637305	0.254	0.0415	*IL15*
	Former[c]	**rs4274224**	**11**	**113319452**	**0.662**	**1.37E−04**	***DRD2***
		rs4245147	**11**	**113318007**	**0.631**	**2.94E−04**	***DRD2***
		rs1893829	18	74954315	0.484	0.0072	*GALR1/MBP*
		rs10891552	11	113333671	−0.480	0.0100	*DRD2*
		rs2797853	9	136512515	0.477	0.0130	*DBH*
		rs7131056	11	113329774	0.467	0.0136	*DRD2*
NP	Current[b]	rs6537064	4	142658406	0.232	0.0171	*INPP4B/IL15*
	Former[c]	rs725667	1	68488650	0.249	0.0069	*GNG12/LOC100133029*
		rs1042602	11	88911696	0.229	0.0138	*TYR*
		rs11133762	5	1391161	0.220	0.0187	*SLC6A3/CLPTM1L*
		rs1800498	11	113291588	0.196	0.0428	*DRD2*

[a]*P* values $< 5 \times 10^{-4}$ were considered study-wide significant (shown in bold); adjusted for age and gender.
[b]The statistics are presented for the log-transformed variable.
[c]The statistics are presented for the square root-transformed variable.

remained significant after adjustment for multiple testing. Rs4274224 and rs4245147 are intronic variants in the dopamine receptor D2 (*DRD2*) gene on chromosome 11. However, the effect of rs4245147 was no longer significant after adjustment for rs4274224. The rs1386493 variant is an intronic SNP in the tryptophan hydroxylase-2 (*TPH2*) gene on chromosome 12. Its effect remained significant in current smokers.

Analysis of the variables reflecting biomarkers of intake and nicotine metabolism

There were several findings at the study-wide level of significance for the nicotine intake biomarkers (**Table 4**). In the NP Tribal population, COT, 3HC, their molar sum (COT+3HC), and the ratio of COT to CPD all showed an association with rs2119767, an intronic SNP in the *GABRA2* gene. In addition, several other SNPs in that gene showed nominally significant associations with the same traits, albeit not reaching the study-wide significance (Supplementary Table S2). Rs7685396, an intergenic SNP between *DRD5* and *SLC2A9*, was associated with the COT level, and an intergenic SNP rs10840491 (*TH/ASCL2*) was associated with the ratio of COT+3HC to CPD. No study-wide significant association was detected among the SW Tribal participants (Supplementary Table S3). Of note, no associations were found with chromosome 15 or 19 and the nicotine intake biomarkers, nor for the NMR and chromosome 19, in either Tribal population. We also observed that the adjustment for SHS exposure did not make any material difference, as the results were virtually identical with and without this adjustment.

Table 5 reflects our use of both FTND and HONC to analyze nicotine dependence phenotypes. Although some SNPs showed suggestive effects, none was statistically significant after correction for multiple testing. Notably, these two measures show a moderate correlation (Pearson $\rho = 0.598$ in NP, 0.635 in SW), and their nominally significant SNPs overlap but are not identical.

Discussion

In a sample of 499 American Indian participants from two distinct Tribal populations, we identified in the NP sample only a GABRA2 variant rs2119767 (Chromosome 4p) significantly associated with many of the nicotine intake and metabolism biomarkers we examined, suggesting a role for this gene in modifying smoking behavior in this population. While associations with other GABRA2 variants have been

Table 4. SNPs associated with the variables related to nicotine metabolism in the NP Tribal Group.

Metabolite trait[a]	Chromosome	SNP rs ID	Base pair	β	*P* value[b]	Gene
Cotinine (COT)	4	rs2119767	46391573	−0.3732	**6.69E−05**	*GABRA2*
COT	4	rs7685396	9794724	−0.7933	**2.70E−04**	*DRD5/SLC2A9*
3′-Hydroxycotinine (3HC)	4	rs2119767	46391573	−0.3636	**1.52E−05**	*GABRA2*
Molar sum COT+3HC	4	rs2119767	46391573	−0.0822	**1.58E−05**	*GABRA2*
COT/CPD	4	rs2119767	46391573	−0.3156	**2.58E−04**	*GABRA2*
(COT+3HC)/CPD	11	rs10840491	2194390	0.1596	**1.09E−04**	*TH/ASCL2*

[a]The statistics are presented for the log-transformed variables.
[b]*P* values $< 5 \times 10^{-4}$ were considered study-wide significant (shown in bold); adjusted for age, gender, and measures of SHS exposure; the results were not materially different if SHS exposure was not adjusted for.

Table 5. SNPs nominally associated with two measures of nicotine addiction: the FTND and HONC.

Site	Addiction measure	SNP	Chr	BP	β	*P* value[a]	Gene
SW	FTND[b]	rs1386493	12	72355179	0.407	0.0008	*TPH2*
		rs6582072	12	72354477	0.362	0.0030	*TPH2*
		rs613355	6	154449850	−0.340	0.0054	*OPRM1/IPCEF1*
		rs6495309	15	78915245	0.311	0.0111	*CHRNA3/CHRNB4*
		rs2000841	18	74987007	0.296	0.0160	*GALR1/LOC100132713*
		rs1461227	5	153169594	−0.300	0.0187	*GRIA1*
	HONC[c]	rs1386493	12	72355179	0.380	0.0018	*TPH2*
		rs3735028	7	136558158	−0.356	0.0034	*CHRM2*
		rs1519551	4	142570472	0.363	0.0036	*LOC100286983*
		rs11179022	12	72370746	0.353	0.0043	*TPH2*
		rs172423	11	18056225	0.332	0.0070	*TPH1*
		rs717091	13	44685946	−0.320	0.0093	*LOC121838/LOC100287738*
NP	FTND[b]	rs285	8	19815189	0.239	0.0240	*LPL*
	HONC[c]	rs1948	15	78917399	0.305	0.0037	*CHRNB4*
		rs285	8	19815189	0.302	0.0040	*LPL*
		rs1159315	4	47003076	−0.247	0.0223	*GABRB1/GABRA4*

[a]*P* values $< 5 \times 10^{-4}$ were considered study-wide significant; adjusted for age and gender.
[b]The statistics are presented for the log-transformed variable.
[c]The statistics are presented for the square root-transformed variable.

reported (47–50), this appears to be the first time the rs2119767 variant has been associated with smoking behaviors, and needs further validation.

We also identified three SNPs (rs1386493 in *TPH2* and rs4274224 and rs4245147 in *DRD2*) that were significantly associated with CPD in the SW sample only after adjustment for multiple testing. However, no SNP in either population was significantly associated with any other self-reported smoking phenotype. This finding is consistent with previous research suggesting that smoking intensity has a stronger genetic component than smoking status, which is strongly influenced by behavioral, cultural, and socioeconomic factors (51).

Numerous genome-wide association studies on genetic control of smoking behavior have been conducted among NHWs. However, according to the Catalog of Published Genome-Wide Association Studies (52), the genetic architecture underlying smoking behavior in American Indians remains poorly characterized. In a recent publication (39), we showed that the NP and SW populations are genetically distinct at the *CYP2A6* locus, which is responsible for roughly 80% of the nicotine metabolism. Specifically, the NP population included a lower frequency of *CYP2A6* reduced-function variants than the SW Tribal population, resulting in distinctive allele frequencies. Consequently, the rate of nicotine metabolism is markedly faster among the NP smokers. Our recent paper discusses the nicotine metabolite ratio and *CYP2A6* genetic variation in relation to the smoking dose in these populations (39), however it is notable that no chromosome 19 (i.e., CYP2A6) SNPs were study-wide significant here, which may be due to (i) the low frequency of the variant alleles in these populations, and/or (ii) that the variants prevalent in some populations (i.e., Asians) are copy number variants, which are not easily assessed on the platforms used here (53).

Previous research has demonstrated that the effects of SNPs on smoking behavior differ between NHWs and African Americans (54, 55), and between NHWs and Asians (56, 57). In our study, SNPs in the *CHRNA3/B4/A5* region, associated with nicotine dependence and smoking quantity traits in NHWs (28, 58), did not show a significant association with any of the smoking-related phenotypes including intake biomarkers. However, MAFs for the SNPs genotyped in the region in our study were relatively low, varying from 6% to 27%. In particular, the frequencies of the minor A allele at rs16969968, a known risk variant in populations of European descent (59), were 7.6% in NP and 5% in SW participants, as compared with 35% in European-Americans. These frequencies are so low that we would not expect this SNP to show an association in a study sample as small as ours.

Besides the limited power, another possible reason for not observing the same genetic effects among American Indians as among NHWs is that these effects may depend on environment, culture, and lifestyle, which are different between American Indians and NHWs. For example, it is well-established that SHS exposure influences smoking initiation and behavior (60–63). Our cross-sectional study design and the indirect way of assessing SHS exposure precludes a meaningful analysis of the influence of SHS on smoking behaviors in these populations. However, for the same two American Indian populations, we recently reported relatively high levels of serum COT among participants who had not smoked (14), indicating very high levels of SHS exposure, especially in the NP sample. It is to be noted that we did not observe an association between the indirect measures of SHS exposure and the nicotine biomarker variables for the active smokers in this study, nor any effect of the SHS measures on the associations between the nicotine biomarkers and SNPs.

This is the first study with American Indians to evaluate the effects of SNPs in previously established candidate genes involved in dopamine and serotonin synthesis and metabolism. One strength of our study is that we collected a comprehensive array of data on smoking history, nicotine biomarkers, and nicotine dependence. Limitations of our study include our modest sample size, a cross-sectional design that precludes causal inference, and the candidate gene approach. Further research, preferably including genome-wide association studies, is needed to further elucidate the genetic architecture of smoking among American Indians. The genetic heterogeneity we've shown between our NP and SW Tribal populations in this study leads us to think that the contributions of genes known to underlie smoking behaviors in NHWs may well differ widely across different Tribal populations.

The results of this study add to accumulating data suggesting that the genetic correlates of smoking behavior in American Indians may

differ from those described in NHWs. Additional work is needed to more fully characterize and confirm the genetic architecture of smoking and nicotine dependence in these and other Tribal populations. Such further confirmatory characterizations would facilitate future culturally tailored approaches to smoking prevention and cessation treatment in American Indian communities, which would in turn help to improve population health by reducing tobacco-related morbidity and mortality.

Disclosure of Potential Conflicts of Interest

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Authors' Contributions

J.A. Henderson: Conceptualization, resources, data curation, supervision, funding acquisition, investigation, methodology, project administration, writing–review and editing. **D.S. Buchwald:** Resources, funding acquisition, project administration, writing–review and editing. **B.V. Howard:** Data curation, supervision and project administration. **P.N. Henderson:** Investigation, methodology, writing–review and editing. **Y. Li:** Software, formal analysis, investigation and methodology. **R.F. Tyndale:** Resources, software, formal analysis, supervision, investigation, writing–review and editing. **C.I. Amos:** Software, formal analysis, supervision, investigation. **O.Y. Gorlova:** Software, formal analysis, validation, investigation, writing–original draft.

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