CHEST

Original Research

COPD

Native American Ancestry, Lung Function, and COPD in Costa Ricans

Wei Chen, PhD; John M. Brehm, MD; Nadia Boutaoui, PhD; Manuel Soto-Quiros, MD; Lydiana Avila, MD; Bartolome R. Celli, MD, FCCP; Shannon Bruse, PhD; Yohannes Tesfaigzi, PhD; and Juan C. Celedón, MD, DrPH, FCCP

Background: **Whether Native American ancestry (NAA) is associated with COPD or lung function in a racially admixed Hispanic population is unknown.**

Methods: **We recruited 578 Costa Ricans with and without COPD into a hybrid case-control/family-based cohort, including 316 members of families of index case subjects. All participants completed questionnaires and spirometry and gave a blood sample for DNA extraction. Genome-wide genotyping was conducted with the Illumina Human610-Quad and HumanOmniExpress BeadChip kits (Illumina Inc), and individual ancestral proportions were estimated from these genotypic data and reference panels. For unrelated individuals, linear or logistic regression was used for the analysis of NAA and COPD (GOLD [Global Initiative for Chronic Obstructive Lung Disease] stage II or greater) or lung function. For extended families, linear mixed models and generalized estimating equations were used for the analysis. All models were adjusted for age, sex, educational level, and smoking behavior; models for FEV_1 were also adjusted for height.**

Results: **The average proportion of European, Native American, and African ancestry among participants was 62%, 35%, and 3%, respectively. After adjustment for current smoking and other covariates, NAA was inversely associated with COPD (OR per 10% increment, 0.55; 95% CI, 0.41-0.75) but positively associated with FEV_1, FVC, and FEV_1/FVC. After additional adjustment for pack-years of smoking, the association between NAA and COPD or lung function measures was slightly attenuated. We found that about 31% of the estimated effect of NAA on COPD is mediated by pack-years of smoking.**

Conclusions: **NAA is inversely associated with COPD but positively associated with FEV_1 or FVC in Costa Ricans. Ancestral effects on smoking behavior partly explain the findings for COPD but not for FEV_1 or FVC.**

CHEST 2014; 145(4):704–710

Abbreviations: BD = bronchodilator; HGDP = Human Genome Diversity Project; LAMP = Local Ancestry in Admixed Populations; SNP = single-nucleotide polymorphism

COPD is a common respiratory disease and a leading cause of morbidity and mortality worldwide.[1] Cigarette smoking is a major risk factor for COPD, but other lifestyle (eg, exposure to wood smoke) or genetic factors influence disease pathogenesis or severity.[2]

COPD is an important public health problem in Latin America. Among adults aged ≥ 40 years living in five large Latin American cities (Mexico City, Mexico; Caracas, Venezuela; São Paulo, Brazil; Santiago, Chile; and Montevideo, Uruguay), the prevalence of COPD (defined using GOLD [Global Initiative for Chronic Obstructive Lung Disease] criteria following spirometry) was highest in Montevideo and lowest in Mexico City.[3,4] Given that the average Native American ancestry of Mexicans living in Mexico City (about 56%)[4] is markedly higher than that of Uruguayans living in Montevideo (about 1%),[5] these findings could be partly explained by protective effects of Native American ancestry against nicotine addiction (eg, reduced intensity of smoking) and the detrimental effects of cigarette smoking on lung function or COPD. Because no Costa Rican cities were included in the study, estimates of a relatively low prevalence of COPD in Costa Rica (by self-report) may be a result of underdiagnosis.[6]

A study of adult smokers living in New Mexico found that Hispanic ethnicity or Native American ancestry (estimated with genetic markers) was positively associated with lung function measures (FEV_1 and FEV_1/FVC) but inversely associated with COPD.[7]

Most of the participants in the study (as well as their parents and grandparents) were born in the United States; thus, a "healthy migrant effect" is an unlikely explanation for the findings.[8] However, a key limitation of the study was an inability to adequately examine the relation between Native American ancestry and COPD or lung function only in racially admixed (Hispanic) subjects because of insufficient statistical power due to small sample size.[7] Thus, Native American ancestry was largely a surrogate marker of Hispanic ethnicity.

To our knowledge, there has been no study to date of Native American ancestry and lung function or COPD in an exclusively Hispanic subgroup. In addition, there has been no published study of Native American ancestry and lung function or COPD in adults living in a Latin American country. We hypothesized that Native American ancestry would be inversely associated with COPD but positively associated with lung function in Costa Ricans, who are known to have predominantly European (about 60%-65%) and Native American (about 30%-35%) racial ancestry. We examined this hypothesis in our ongoing study of COPD in 578 Costa Ricans.

Materials and Methods

Study Population

We recruited 578 subjects between April 2003 and November 2010, including 316 members of 13 families of probands (index case subjects [e-Table 1]) with COPD, 68 case subjects with COPD, 159 control subjects, and 35 individuals who could not be classified as either case or control subjects after review of their spirometric measures (see next). Probands and case subjects were recruited from four major public hospitals in San José, Costa Rica, and through newspaper ads. Control subjects were recruited from a smoking cessation clinic in San José and through newspaper ads. All study participants had to have at least six great-grandparents born in the Central Valley of Costa Rica (to ensure the subject's descent from the founder population comprising primarily Europeans and Native Americans). All probands and case and control subjects also had to be aged ≥ 21 years and have a history of at least 10 pack-years smoking. Members of families of probands had to be aged ≥ 12 years. Other inclusion criteria for case subjects or probands were physician-diagnosed COPD and a post-bronchodilator (BD) $FEV_1 \leq 65\%$ predicted and a post-BD FEV_1/FVC ratio $< 70\%$. Control subjects had no physician-diagnosed COPD and normal spirometry.

All study participants completed a protocol that included a questionnaire used to collect demographics, smoking history, and respiratory health data[9]; pulmonary function testing; and collection of blood samples for DNA extraction. Spirometry was conducted with a Collins Survey Tach spirometer (Collins Medical). All subjects had to be free of respiratory illnesses for ≥ 4 weeks before spirometry and were instructed (when possible) to avoid the use of inhaled short-acting BDs for ≥ 4 h before testing. Of the 578 study participants, 543 (about 94%) performed spirometry before and 15 min after the administration of 180 μg (two puffs) albuterol. Forced expiratory maneuvers were judged to be acceptable if they met or exceeded American Thoracic Society criteria.[10] For simplicity and to maximize statistical power, pre-BD values were used for the analysis of lung function measures (FEV_1, FVC, and FEV_1/FVC).

Written informed consent was obtained from all participants. The study was approved by the institutional review boards of the Hospital Nacional de Niños (UBIHNN-010-2003), Brigham and Women's Hospital (2001-P-001393/49), and the University of Pittsburgh (PRO10040165).

Genotyping

Whereas the first 115 participants (probands, unrelated case subjects, and unrelated control subjects) were genotyped with the Illumina Human610-Quad platform (Illumina Inc) (containing about 610,000 single-nucleotide polymorphisms [SNPs]), the remaining participants (n = 463) were genotyped at a later date with the Illumina HumanOmniExpress platform (containing about 730,000 SNPs). We applied stringent filters for quality control of each dataset by excluding SNPs with a minor allele frequency $< 1\%$, a completion rate $< 90\%$, or out of Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$ in unrelated control subjects). We then merged the two SNP datasets and implemented quality control measures similar to those previously conducted for each separate dataset while also examining potential batch effects by comparing allele frequencies and performing a clustering analysis. To assess for Mendelian inconsistencies in members of families of probands, the KING (Kinship-based Inference for Gwas) program[11] was used to determine relationships based on the genome scan marker data.

Estimation of Racial Ancestry

To select SNPs for ancestry estimation, we first merged about 300,000 SNPs that overlapped between the two genotyping platforms used in this study with reference panels from the Human Genome Diversity Project (HGDP).[12] Such reference panels included data from 88 Europeans, 159 Africans, and 31 Native Americans (seven Colombians, 13 Mayans, and 11 Pima). After applying an SNP-pruning algorithm,[13] we had 50,000 SNPs with $r^2 < 0.1$ for any pair within a window of 500 kb. Using this panel of SNPs, we applied a model-based program (STRUCTURE,[14] version 2.3.3) to estimate the percentage of racial ancestry from each founder population (African, European, and Native American) for each subject. To avoid introducing bias, we did not explicitly label the reference populations but instead allowed the program

Manuscript received June 5, 2013; revision accepted November 10, 2013.
Affiliations: From the Division of Pulmonary Medicine, Allergy and Immunology (Drs Chen, Brehm, Boutaoui, and Celedón), Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; Division of Pediatric Pulmonology (Drs Soto-Quiros and Avila), Hospital Nacional de Niños, San José, Costa Rica; Division of Pulmonary and Critical Care Medicine (Dr Celli), Brigham and Women's Hospital, Boston, MA; and Lovelace Respiratory Research Institute (Drs Bruse and Tesfaigzi), Albuquerque, NM.
Drs Chen and Brehm contributed equally to this article.
Funding/Support: This work was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health [Grant R01-HL073373] and by Children's Hospital of Pittsburgh of UPMC.
Correspondence to: Juan C. Celedón, MD, DrPH, FCCP, Division of Pulmonary Medicine, Allergy and Immunology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Ave, Pittsburgh, PA 15224; e-mail: juan.celedon@chp.edu

DOI: 10.1378/chest.13-1308