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Original Contribution

Genetic variation in antioxidant enzymes and lung function

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ABSTRACT

Not all cigarette smokers develop chronic obstructive pulmonary disease, and discovering susceptibility factors is an important research priority. The oxidative burden of smoking may overwhelm antioxidant defenses, and vulnerabilities may exist as a result of sequence variants in genes encoding antioxidant enzymes. This study explored the association between genetic variation in a network of antioxidant enzymes and lung phenotypes. Linear models evaluated single-locus marker associations in 2387 European American and African American participants in the Health, Aging, and Body Composition Study. After corrections were made for multiple comparisons, 15 statistically significant associations were identified, all of which were for SNP by smoking interactions. The most statistically significant findings were for genes encoding members of the isocitrate dehydrogenase gene family (*IDH3A, IDH3B, IDH2*). For rs6107100 (*IDH3B*) the variant genotype was associated with a difference of 6% in the FEV_1/FVC ratio in African American current smokers, but the SNP had little or no association with FEV_1/FVC in former and never smokers (nominal $p_{\text{interaction}} = 5 \times 10^{-6}$). A variant of the peroxiredoxin gene (rs9787810, *PRDX5*) was associated with lower percentage predicted FEV_1 and a lower ratio in European American current smokers, with little or no association in other smoking groups (nominal $p_{\text{interaction}} = 0.0001$ and 0.0003, respectively). The studied genes have not been reported in previous candidate gene association studies, and thus the findings suggest novel mechanisms and targets for future research and provide evidence for a contribution of sequence variation in genes encoding antioxidant enzymes to susceptibility in smokers.

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Chronic obstructive pulmonary disease (COPD) is characterized by the development of airflow obstruction that is not fully reversible, a phenotype that is characteristic of chronic bronchitis and emphysema. At advanced stages, COPD progresses to respiratory failure and death and is a significant cause of morbidity as well as the fourth leading cause of mortality in the United States [1]. Spirometry is a reliable and valid means of identifying airflow obstruction; clinical definitions of COPD [2] are based on the ratio of air exhaled in the first second of effort/total air exhaled (forced expiratory volume in the first second/forced vital capacity: FEV_1/FVC) and the absolute level of FEV_1 compared to what would be predicted given age, height, race, and gender (percentage predicted FEV_1: ppFEV_1). A decline in FEV_1 occurs naturally with aging, but a steeper rate of decline, as observed in susceptible cigarette smokers, is a harbinger of the debilitating low lung function that characterizes COPD.

Current theories of the pathogenesis of COPD posit that an imbalance between oxidant burden and antioxidant protection leads to oxidative damage that contributes to disease pathogenesis. Diminished antioxidant defenses, especially among cigarette smokers, who are exposed to a high level of oxidants, are hypothesized to contribute to tissue changes underlying disease development [3]. A minority of smokers develop obstructive lung disease [4], consistent with the hypothesis that in some smokers compromised antioxidant protection,

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; ppFEV_1, percentage of the FEV_1 value predicted; GGT1, γ-glutamyl transferase 1; GCLC, glutamate–cysteine ligase (catalytic subunit); GLRX, glutaredoxin; GSR, glutathione reductase; GST, glutathione *S*-transferase; IDH, isocitrate dehydrogenase; mGST, microsomal glutathione *S*-transferase; PRDX, peroxiredoxin; SEP, selenoprotein; SOD, superoxide dismutase; TXNRD, thioredoxin reductase.

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as a result of genetic variation in antioxidant enzymes, diets low in antioxidants, and/or inflammation, contributes to susceptibility. Whereas observational studies mainly report positive associations between nutrients with antioxidant properties and lung function, with stronger effects in cigarette smokers, studies of genes that play a role in antioxidant defenses provide an important and unique test of the susceptibility hypothesis.

Lung function is a heritable trait, and heritability estimates of FEV_1 and the ratio of FEV_1/FVC range from 40 to 90% [5–7]. A single gene disorder that increases COPD risk, α1-antitrypsin deficiency, accounts for only about 1 to 2% of cases [8], confirming the importance of additional genes and gene–environment interactions in lung function variability. Recently completed genome-wide association studies of lung function phenotypes [9–11] have identified 14 genomic regions for further investigation. Well-designed studies of candidate genes, specifically of genes encoding antioxidant enzymes, are important to the evidence base, but published studies have several limitations (as reviewed in [12]). The majority of studies considered only a few markers and/or genes and thus do not capture the related and redundant functions within the network of antioxidant-related genes. Published studies focus on a limited subset of genes (most prominently, glutathione *S*-transferases); thus many genes related to antioxidant defense are unstudied at the population level (for example, genes of the thioredoxin system: thioredoxin, thioredoxin reductase, and peroxiredoxin). Studies of the heritability of lung function provide compelling evidence for a gene–environment interaction [13–15], specifically a gene by smoking interaction, and a recent genome-wide assessment of gene expression in the small airway epithelium and genotype in smokers and nonsmokers indicates that smoking modifies the relation between genotype and gene expression (J. Mezey, personal communication). Despite this evidence, most studies do not consider gene–environment interactions and/or do not appropriately account for cigarette smoking in study design and analysis. Finally, data on African Americans are limited, and most studies with African American participants are underpowered to investigate any differences in the effects of genotype on lung phenotype by race.

We investigated the association of variants of genes encoding antioxidant enzymes with the lung function phenotypes $ppFEV_1$ and FEV_1/FVC. As the elderly are at the greatest risk for reduced lung function associated with both aging and smoking, these analyses were conducted in the Health, Aging, and Body Composition (Health ABC) Study. Although the Health ABC Study is a prospective cohort study, this analysis is cross-sectional, evaluating study data collected at baseline. The analysis explored the relation of all genotypes with the two phenotypes, stratified by race and allowing for differential effects of genotype by cigarette smoke exposure and dose.

Methods

Population

The Health ABC cohort study enrolled 3075 men and women ages 70–79 at the study baseline in 1997. Health ABC is a random sample of European Americans and African American Medicare-eligible persons residing in ZIP codes from the metropolitan areas surrounding Pittsburgh, Pennsylvania, and Memphis, Tennessee. Eligibility criteria included self-report of no difficulty in walking one-quarter of a mile or climbing 10 steps without resting; no difficulty in performing basic activities of daily living; no use of a cane, walker, crutches, or other special equipment to ambulate; no history of active treatment for cancer in the prior 3 years; and no plan to move out of the area in the subsequent 3 years.

Exclusion criteria included a low call rate for genotypes (i.e., if the classification of genotype was unsuccessful in $>5\%$ of samples), missing outcome measurements, or prevalent chronic obstructive pulmonary disease, defined as *both* FEV_1 and FEV_1/FVC below the population-defined lower limits of normal. Prevalent COPD cases were excluded as our interest was on genetic susceptibility to low lung function, not to disease progression. Exclusions were also made based on quality of spirometry testing for FEV_1; participants with low-quality FVC measurements were further excluded from the FEV_1/FVC analysis.

Lung function outcome

Spirometry was performed during the clinical visit at study entry using a horizontal dry rolling seal HF6 spirometer (Sensor Medics Corp., Yorba Linda, CA, USA) connected to a personal computer. Tests were conducted in accordance with ATS standardized guidelines, as previously reported [16]. $PpFEV_1$ values were calculated using race-specific prediction equations generated from the Third National Health and Nutrition Examination Survey data [17]. If baseline pulmonary function measurements were missing (or did not meet quality control standards), a measurement from a subsequent clinical visit was substituted, if available, provided that the age of the participant at the available measurement was between 70 and 79 years (the age range of the sample at baseline). The majority (95%) of data used in these analyses were from the first clinic visit.

Selection of single nucleotide polymorphisms (SNPs)

Fifty-six genes were identified that are known to affect the balance of antioxidants/oxidants and are expressed in lung tissue (Supplementary Table 1); briefly, selected genes encoded the following: glutathione synthesis proteins, glutathione *S*-transferases, peroxidases, heme-oxygenases, disulfide reductases, selenoproteins, proteins affecting supply of reducing equivalents, superoxide dismutases, and catalase. Three hundred eighty-four SNPs were selected with the goal of capturing sequence variation across each gene and its regulatory region (2 kb upstream and downstream). SNP selection was conducted according to the following order of priority: (1) nonsynonymous SNPs, which alter the sequence of the encoded protein (and have an increased probability of functional effects); (2) SNPs to cover variation across the gene by evaluating the degree of correlation (linkage disequilibrium: LD) between SNPs (a maximum of 0.9 LD units between SNPs was allowed); (3) if genetic variation was limited across the gene, SNPs to cover large physical distance; and (4) SNPs that were highly correlated with SNPs of particular interest to provide redundancy in case of assay failure. When possible, a minimum of 5 SNPs were selected per gene. Separate consideration was given to European Americans and African Americans in SNP selection to maximize coverage in both populations, given differences in LD structure and allele frequencies. Further details of analyzed SNPs are presented separately (Supplementary Table 2).

Genotyping

DNA for the Health ABC participants was extracted using the Gentra Puregene DNA purification kit (Qiagen, Valencia, CA, USA) from stored, frozen buffy coat originally extracted from 10 ml whole blood. SNPs were assayed using the Illumina Goldengate platform; genotyping services were provided by Johns Hopkins University under U.S. Federal Government Contract N01-HV-48195 from the National Heart, Lung, and Blood Institute. Genotyping quality was excellent as determined through the use of blind duplicates and HapMap controls with known genotypes (99.99 and 99.83% reproducibility rates, respectively).

Statistical analysis

Linear models were used to evaluate the association between single-locus markers and lung function phenotype. Given the probability of confounding by race, as both genotype frequencies and lung

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