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A Genome-Wide Association Study in Hispanics/Latinos Identifies Novel Signals for Lung Function. The Hispanic Community Health Study/Study of Latinos

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Lung function and chronic obstructive pulmonary disease (COPD) are heritable traits. Prior genome-wide association studies (GWAS) of lung function have identified numerous genetic variants associated with COPD risk; however, much of the individual variance in lung function remains unexplained. Furthermore, most of these studies have been limited to participants of European ancestry. Including multi-ethnic populations in GWAS research may identify novel variants that contribute to the etiology of lung function.

What this Study Adds to the Field

This study, the largest GWAS of lung function and COPD to exclusively include Hispanic/Latino participants, identified eight novel signals of which three replicated in independent populations. A novel locus for FEV_1 (rs4791658; *ZSWIM7*) replicated in a cohort of European ancestry. A locus for FEV_1/FVC (rs145174011; *HAL*); in a previously identified region for FEV_1/FVC in individuals of European ancestry and for percent emphysema in a Hispanic population remained independent in conditional analyses but did not replicate. Admixture mapping identified a novel region associated with Amerindian ancestry and FEV_1 which included a candidate variant (rs4133185) in the *AGMO* gene that replicated. Additionally, we identified a SNP (rs7709630) for COPD, which replicated in individuals of European ancestry. Several loci previously identified in European samples were also associated with lung function traits among Hispanic/Latino participants in HCHS/SOL at the genome-wide significance level. These results emphasize the importance of including admixed populations when performing genetic

studies to identify variants that may contribute to the genetic etiology of pulmonary function and COPD.

ABSTRACT

Rationale: Lung function and chronic obstructive pulmonary disease (COPD) are heritable traits. Genome-wide association studies (GWAS) have identified numerous pulmonary function and COPD loci, primarily in cohorts of European ancestry.

Objectives: Perform a GWAS of COPD-phenotypes in Hispanic/Latino populations to identify loci not previously detected in European populations.

Methods: GWAS of lung function and COPD in Hispanic/Latino participants from a population-based cohort. We performed replication studies of novel loci in independent studies.

Measurements and Main Results: Among 11,822 Hispanic/Latino participants, we identified eight novel signals; three replicated in independent populations of European Ancestry. A novel locus for forced expiratory volume in one second (FEV_1) in *ZSWIM7* (rs4791658; $p=4.99\times10^{-9}$) replicated. A rare variant (MAF=0.002) in *HAL* (rs145174011) was associated with FEV_1 to forced vital capacity (FEV_1/FVC) ($p=9.59\times10^{-9}$) in a region previously identified for COPD-related phenotypes; it remained significant in conditional analyses but did not replicate. Admixture mapping identified a novel region, with a variant in *AGMO* (rs41331850), associated with Amerindian ancestry and FEV_1, which replicated. A novel locus for FEV_1 identified among ever smokers (rs291231; $p=1.92\times10^{-8}$) approached statistical significance for replication in admixed populations of African ancestry and a novel SNP for COPD in *PDZD2* (rs7709630; $p=1.56\times10^{-8}$) regionally replicated. Additionally, loci previously identified for lung function in European samples were associated in Hispanic/Latino participants in HCHS/SOL at the genome-wide significance level.

Conclusions: We identified novel signals for lung function and COPD in a Hispanic/Latino cohort. Including admixed populations when performing genetic studies may identify variants contributing to genetic etiologies of COPD.

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Key Words: Hispanic/Latino, genome-wide association study, single nucleotide polymorphisms, lung function, airflow limitation, chronic obstructive pulmonary disease

INTRODUCTION

The Hispanic/Latino population is the largest and fastest-growing minority population in the United States (U.S.), accounting for 17% of the U.S. population currently and an estimated 33% by 2060(1). The Hispanic/Latino population in the U.S. is genetically diverse, with a mixture of European, African and Amerindian genetic ancestries(2-4).

Chronic obstructive pulmonary disease (COPD), characterized by persistent airflow obstruction(5, 6), is the third-leading cause of death in the U.S.(7). The prevalence of COPD in some Hispanic groups is lower than in non-Hispanic whites and African-Americans in the U.S.(8-10). In the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), the largest and best characterized cohort of Hispanics/Latinos in the US, the prevalence of COPD varied substantially by Hispanic/Latino heritage with Puerto Ricans and Cubans having a much higher prevalence of COPD than other Hispanic/Latino groups(10). This difference in HCHS/SOL was explained by smoking and asthma history; however, other investigators have noted that Hispanic ethnicity is inversely associated with COPD-phenotypes compared to whites(11, 12) and have hypothesized that genetic differences may lower risk of COPD in some Hispanic groups(11, 13).

Examination of genetic risk among non-European populations may reveal novel variants that yield new pathways to treatments, such as *PCSK9*(14). We are aware of only two genome-wide association studies (GWAS) of lung function or COPD-related phenotypes that analyzed Hispanics separately(13, 15). One identified a novel variant near *MAN2B1* that was associated with percent emphysema on computed tomography (CT)(16) and the other identified two loci that approached genome wide statistical

significance for COPD(13). This literature contrasts with that among persons of European ancestry, in whom GWAS have identified multiple loci in genes for lung function and COPD(17-31)

To improve our current understanding of the genetic architecture of lung function-related traits in Hispanics/Latinos, we performed a meta-analysis for FEV_1, FEV_1/FVC, airflow limitation and COPD among six Hispanic/Latino groups in the HCHS/SOL cohort(10, 32). Findings were replicated in European, Hispanic and African populations. Some of the results have been previously reported in abstract form(33).

METHODS

Study Sample

HCHS/SOL is a community-based cohort study of 16,415 self-identified Hispanic/Latino persons aged 18-74 years recruited from four U.S. communities. The study design, cohort recruitment(10, 32), and baseline clinical examination(34) have been previously described. Institutional Review Boards at each field center approved study protocols and written informed consent was obtained from all participants.

For genetic analyses, HCHS/SOL participants were classified in six genetic analysis groups: Central American, Cuban, Dominican, Mexican, Puerto Rican, and South American. The genetic ancestry structure of these groups, including principal components (PCs) plots for all individuals, have been previously reported(35). Henceforward we will refer to the six genetic analysis groups as Hispanic/Latino ancestry groups.

Exclusion criteria were lack of valid spirometric or genetic data, missing covariates, near exclusive Asian ancestry and participants who were not classified in the Hispanic/Latino ancestry groups. Details are provided in the online supplement.

Phenotypic and Outcome Measures

Spirometry was conducted in accordance with American Thoracic Society/European Respiratory Society guidelines(36) using a dry rolling sealed spirometer as previously described(10). Participants with pre-bronchodilator FEV_1/FVC ratios less than 70% or the lower limit of normal were selected for post-bronchodilator spirometry, the former defined by NHANES reference equations(37) since those from HCHS/SOL(38) were not available during data collection.

Airflow limitation was defined as a pre-bronchodilator FEV_1/FVC ratio < 70% and COPD as a post-bronchodilator FEV_1/FVC ratio < 70%(5). Controls had normal lung function defined as a pre-bronchodilator FEV_1/FVC ratio > 70% and FVC > 80 percent predicted.

Genotyping, Quality Control and Imputation

Consenting HCHS/SOL subjects were genotyped at Illumina on the HCHS/SOL custom 15041502 B3 array. We applied standard quality-assurance and quality-control methods(39) as previously described(35). Genome-wide imputation was carried out with the full, cosmopolitan 1000 Genomes Project phase 1 reference panel(40); associations for novel loci were confirmed with 1000 Genome phase 3 imputation panel. Details are

provided in the online supplement.

Statistical Analyses

See the online supplement for details.

Quantitative Lung Function Analyses

Analyses of FEV_1 and FEV_1/FVC ratio employed linear mixed models, stratified by Hispanic/Latino ancestry group, and adjusted for age, age^2, sex, height, height^2, study center, smoking status, pack-years, sampling weights, and the first 5 PCs, as fixed effects. We used random effects for genetic relatedness (kinship), and household and community (block unit) to account for environmental correlation. Results from each Hispanic/Latino ancestry group were then meta-analyzed using the MetaCor method(41). Genome-wide significance threshold was defined as $p<5x10^{-8}$, the Bonferroni adjustment for 1 million independent tests (42). *A priori,* we planned additional meta-analyses stratified by never vs ever smoking.

Analyses for Airflow Limitation and COPD

We analyzed airflow limitation and COPD in pooled analyses implementing the GMMAT software(43) to fit a logistic mixed model adjusting for age, sex, study center, smoking status, pack-years, sampling weights, the first 5 PCs and Hispanic/Latino ancestry groups, as fixed effects and with random effects for kinship and block unit. Participants younger than 45 years were excluded.

Admixture Mapping and Analyses

Local ancestry estimates were previously inferred in the HCHS/SOL(44). A genome-wide admixture mapping scan was performed using a linear mixed model, as described above, testing European, African, and Amerindian ancestries at each available local ancestry interval (LAI). Statistical significance for admixture mapping was set at $p<5.68x10^{-5}$ based on previous simulation results for HCHS/SOL(45). After discovering a genome-wide significant LAI association (at the admixture mapping level), we identified a candidate variant and performed conditional admixture mapping analysis(46).

Replication of Lung Function SNPs

We pursued replication of novel loci associated with FEV_1 and FEV_1/FVC in populations with Hispanics(13, 47-51), African-American(47, 48), and European representation(17). We performed a look-up in each individual study then meta-analyzed across studies. For airflow limitation and COPD, we performed regional replication in publically available GWAS results of airflow obstruction in participants of European ancestry(23). For admixture mapping signals, we performed a look-up in the UK Biobank results for individuals of European ancestry (https://sites.google.com/broadinstitute.org/ukbbgwasresults).

Generalization analyses of previously reported SNPs

We looked-up previously reported SNPs, their effects, standard errors and p-value in HCHS/SOL(52).

RESULTS

The mean age of the 11,822 HCHS/SOL participants with valid lung function and genetic data was 46±14 years. Thirty-nine percent had ever smoked cigarettes with median pack-years of 7.5. The COPD analysis included 363 and 5,253 individuals with and without COPD, respectively. Characteristics of the participants are shown in **table 1**. Manhattan and Quantile-Quantile (Q-Q) plots for FEV_1, FEV_1/FVC, airflow limitation and COPD are shown in **figures E1, E2, E3 and E4**. Genomic inflation factors ranged from 1.020–1.026 in quantitative lung function analyses and 0.988–1.011 in analyses of COPD.

GWAS of Lung Function across all Hispanic/Latino ancestry groups

Across all Hispanic/Latino ancestry groups, seven signals achieved genome-wide statistical significance, of which two were novel for lung function (**table 2**). The lead novel SNP, rs4791658, in the locus associated with FEV_1 (**figure 1a**) was an intron variant in the gene *ZSWIM7* on chromosome 17 (Beta=33.4, $p=4.99\times10^{-9}$). Its minor allele frequency (MAF) ranges from 0.39–0.49 across Hispanic/Latino ancestry groups (**figure 1b**). SNP, rs4791658 neared genome-wide significance for FEV_1 among ever smokers (Beta=46.8, $p=1.53\times10^{-6}$). Effect size and p-values for rs4791658 across all lung function and COPD-related traits are shown in **Table E1**.

The lead novel SNP, rs145174011, in the locus associated with FEV_1/FVC (**figure 1c**) was an intronic variant in the gene *HAL* on chromosome 12 (Beta=4.86, $p=9.59\times10^{-9}$). The SNP is rare with a MAF that ranges from 0.001–0.008 across Hispanic/Latino ancestry groups (**figure 1d**). The minor allele does not exhibit an outlier

effect **(figure E5).** Sensitivity analysis using rank-normalized residuals is shown in supplement. This locus is near the gene *CCDC38*, which was previously identified for FEV_1/FVC in individuals of European Ancestry (17) and the gene *SNRPF*, which was previously identified for percent emphysema on CT in racially/ethnically diverse participants (16). In conditional analysis adjusting for rs1036429 (*CCDC38*) and rs7957346 (*SNRPF*) in HCHS/SOL, rs145174011 (*HAL* SNP) remained associated with FEV_1/FVC (Beta=4.92 $p=6.4\times10^{-9}$), suggesting its association with FEV_1/FVC is independent of previously identified variants. The findings for rs145174011 among ever and never smokers are concordant and trended towards significance (**table E1)**. Regional association plots and forest plots of previously reported genome wide significant associations for FEV_1 and FEV_1/FVC meta-analyzed across all Hispanic/Latino ancestry groups are shown in **figure E6**.

Stratification by Smoking Status

In the meta-analysis across all Hispanic/Latino ancestry groups stratified by smoking status, we identified one novel locus among ever smokers for FEV_1 and one novel locus among never smokers for FEV_1/FVC (**table 3**). The lead variant in the locus associated with FEV_1 in ever smokers was an Indel variant ($p=1.66\times10^{-8}$) on chromosome 11. The top SNP, rs291231 (Beta=57.28, $p=1.92\times10^{-8}$), in this locus has a MAF that ranges from 0.28 – 0.42 across Hispanic/Latino ancestry groups. This SNP lies between the genes *EED* and *CCDC81* (**figure 2a and 2b**). The SNP-by-pack-years interaction trended towards significance (p-interaction=0.06) and the genotype effect became greater at higher pack-years (**figure E7**).

The top SNP (rs7228593) in the locus associated with FEV_1/FVC in never smokers (Beta=1.34, $p=3.47\times10^{-8}$) is located between the genes *SMIM21* and *LCOC339298* (**figure 2c**) on chromosome 18. The findings in never smokers for airflow limitation (OR=0.46, $p=2.63\times10^{-4}$) and COPD (OR=0.36, p=0.005) were directionally concordant and trended towards significance (**table E1**). Its MAF varies significantly across different Hispanic/Latino ancestry groups (**figure 2d**) with the highest in participants from the Dominican ancestry group (MAF=0.16) and lowest in Mexican ancestry group (MAF=0.02). Forest plots and regional association plot of remaining genome-wide significant associations for FEV_1 and FEV_1/FVC stratified by smoking status are shown in **figure E8**.

GWAS of COPD

We identified two previously unreported SNPs for COPD (**table E2 and figure E9**). SNP rs7709630 is an intron in the *PDZD2* gene on chromosome 5 ($p=1.56\times10^{-8}$; MAF=0.11) and SNP rs2286351 is a noncoding transcript variant in *CDRT15P1* on chromosome 17 ($p=1.97\times10^{-8}$, MAF=0.09). Lung function association analyses of these COPD SNPs are reported in **table E3**.

Admixture Mapping:

Manhattan plots from admixture mapping analyses for FEV_1, and FEV_1/FVC testing Amerindian, African, and European ancestry counts individually in LAIs are shown in **figures E10 and E11**. We identified one novel significant local ancestry association

region of Amerindian ancestry for FEV_1 **(figure E10a)** on chromosome 7 (Beta =-37.51, $p=2.86x10^{-6}$). There were no significant associations in the European versus others or African versus others analyses.

We identified a candidate variant (rs4133185) within this novel LAI region (Beta = -31.44, $p= 7.43x10^{-7}$; **table E4 and figure 3**) with considerable differences in ancestry-specific allele frequencies (**figure 4**). The lead SNP, rs4133185, in this candidate variant was an intron variant in the gene *AGMO*. The admixture mapping signal is less significant after conditional analyses adjusting for rs4133185 (**table E5, figures 4 and E**12).

Replication

Characteristics of the participants in the replication cohorts are shown in **table E4.** Of the two novel loci identified for lung function, only the FEV_1 locus on chromosome 17 successfully replicated (replication $p=3.37x10^{-5}$; adjusted threshold for statistical significance was $p<9.2x10^{-4}$) but only in the SpiroMeta consortium look-up (n=94,612)(17). The candidate variant (rs4133185), identified through admixture mapping, associated with Amerindian ancestry and FEV_1 replicated in UK Biobank (Beta = -8.3, p=0.004). SNP rs291239, a genotyped SNP in the novel locus on chromosome 11 identified for FEV_1 among ever smokers, approached statistical significance for replication in the meta-analysis across all cohorts with admixed populations of African ancestry (replication p=0.007); however, the direction of effect was discordant in the individual replication cohorts (**table E7**).

The novel SNP (rs7709630; *PDZD2*) associated with COPD regionally replicated in publically available results from the SpiroMeta-CHARGE GWAS meta-analysis of airflow obstruction among participants of European ancestry(23). The smallest p-value in the replication region was for rs409839 ($p=8.9x10^{-4}$) and the adjusted threshold for statistical significance was $p< 4.2x10^{-3}$. The other loci were not successfully replicated.

Generalization Analyses of Previously Identified Lung Function Loci

Using the FDR adjusted look-up threshold, several of the previously reported SNPs for FEV_1, FEV_1/FVC and COPD identified in European populations were generalized to Hispanic/Latino populations (**tables E8, E9, E10 and Figure E13**). See online supplement for details.

DISCUSSION

In this GWAS of 11,822 Hispanic/Latino HCHS/SOL participants, we identified eight novel signals, of which three replicated in independent cohorts of European ancestry. Three novel signals were associated with lung function. A novel locus in *ZSWIM7* (rs4791658) was associated with FEV_1 replicated and a rare variant in *HAL* (rs145174011) was associated with FEV_1/FVC did not replicate; it is in a previously identified region but remained significant in conditional analyses, suggesting an independent effect. Admixture mapping identified a novel LAI region, with a candidate variant in the *AGMO* gene (rs4133185), associated with Amerindian ancestry and FEV_1, which replicated. In smoking stratified analyses, a novel locus (rs291231) associated with FEV_1 among 4,595 ever smokers approached statistical significance for replication

in cohorts with admixed populations of African ancestry and a novel SNP for COPD in *PDZD2* (rs7709630) regionally replicated in individuals of European ancestry. In addition, we confirmed loci previously identified in European samples [*KCNE2*(17) and *GPR126*(27)] for FEV_1/FVC in this Hispanic/Latino sample.

Several SNPs in *ZSWIM7* were associated with FEV_1 at genome-wide significance and replicated in independent cohorts of European ancestry. *ZSWIM7* mutations were associated colorectal adenomatous polyposis(53) and in a GWAS of SNP-by-smoking interaction, *ZSWIM7* neared significance for systolic blood pressure(54). *ZSWIM7* is a highly conserved eukaryotic regulator of homologous recombination and plays an important role in error-free DNA repair processes for DNA double-strand breaks (DSBs)(55-57). Unrepaired DSBs trigger cell senescence, apoptosis, and pro-inflammatory responses, all of which are established mechanisms in the pathogenesis of COPD(58-60). Oxidative stress and cigarette smoke cause DSBs(61, 62) and DSBs have been implicated in the pathogenesis of COPD(62). Furthermore, COPD patients have a greater number of unrepaired DSBs which are associated with a higher expression of markers for senescence, apoptosis, and pro-inflammatory phenotypes compared to asymptomatic smokers and nonsmokers(62). In our study, the effect size of *ZSWIM7* for FEV_1 was of greater magnitude among ever smokers which is consistent with known effects of cigarette smoke causing DSBs. Thus, *ZSWIM7* through its regulation of homologous recombination and role in error-free DNA repair processes for DSBs is relevant to the pathogenesis of COPD.

A rare variant in *HAL* (rs145174011) was associated with FEV_1/FVC among all participants. The minor allele was associated with decreases in FEV_1/FVC of 4.9% and

6.3% (all participants and ever smokers, respectively), and with decreases in FEV_1 of 100 mL and 173 mL (all participants and ever smokers, respectively). It is possible that this variant was not successfully replicated due to lack of power, given that it is a rare variant in African and Hispanic populations and is not polymorphic in European populations(63).

The *HAL* SNP (rs145174011) is near two previously identified loci for pulmonary traits (*CCDC38* and *SNRPF)*. *CCDC38* has been associated with FEV_1/FVC in European ancestry individuals(17), and *SNRPF* has been associated with percent emphysema on CT in racially/ethnically diverse participants in the Multi-Ethnic Study of Atherosclerosis (MESA) Lung Study (16). In the MESA Lung Study, linkage disequilibrium (LD) between *SNRPF* and *CCDC38* accounted for much of the effect seen in Whites, and less so in African Americans and Chinese; however, the observed effect of *SNRF* on percent emphysema on CT in Hispanics appeared to be independent from *CCDC38*(16). In our study, the association of SNP rs145174011 (*HAL* locus) with FEV_1/FVC was maintained in analyses conditioning on previously reported loci. Collectively, these data suggest there are three independent loci associated with COPD-related phenotypes in this region.

Although the *HAL* locus contained numerous SNPs, they were all imputed rare variants and did not replicate; therefore, further investigation, such as whole-genome sequencing of this region and functional studies, is required to refine these loci, confirm association, and understand their biological implications for COPD.

The *HAL* gene encodes the enzyme histidine ammonia-lyase(64, 65) - the first step in histidine catabolism(66). Low levels of histidine have been associated with

increased inflammation and oxidative stress(67)(68) and decreased concentrations of histidine were associated with advanced COPD and emphysema(69). Recently, whole-exome sequencing in African-Americans identified three rare loss-of-function variants in *HAL* that were associated with increased histidine levels and were inversely related to coronary heart disease risk in African-American and European-American populations. Thus, a functional *HAL* variant may decrease histidine levels and increase susceptibility to COPD and emphysema through its effects on oxidative stress.

The region associated with Amerindian ancestry and FEV_1 on chromosome 7 contained a candidate variant (rs4133185) within the *AGMO* gene. This SNP, rs4133185, has large differences in ancestry-specific allele frequencies (~0.8 for Amerindian and ≤0.2 for European and African) and is associated with obstructive physiology, as measured by FEV_1 ($p=7.43x10^{-7}$). In the conditional analysis, rs4133185 explains part but not all of the admixture signal. SNP rs4133185 may not be the causal variant and the presence of multiple SNPs within the LAI region may explain the residual signal. A prior report showed an association of AGMO with FVC in a multi-ethnic population(70). Future whole-genome sequencing studies are needed for better fine mapping of this region.

The chromosome 11 locus (rs291231) associated with FEV_1 among ever smokers nominally replicated in the meta-analysis across all cohorts with admixed populations of African ancestry. However, the direction of effect was discordant in some replication cohorts. Different directions of associations may be due different patterns of LD with the causal variant between populations. The minor allele in rs291231 might be

protective in ever smokers as demonstrated by a per-allele increase in FEV_1 of 57.28 mL.

The chromosome 18 locus associated with FEV_1/FVC among never smokers contained multiple SNPs. The lead SNP (rs7228593) varies in MAF across different Hispanic/Latino ancestry groups in HCHS/SOL (0.02-0.16), is common in African populations (MAF=0.39) and is not polymorphic in European populations (MAF=0)(71) These variable allele frequencies and small sample size for replication may have contributed to lack of replication. Differing environmental exposures and LD may explain the observed genetic association of FEV_1/FVC among never smokers in HCHS/SOL and lack of replication in independent cohorts of different ancestry backgrounds.

In the COPD analysis, SNP rs7709630, a genotyped intron variant in *PDZD2*, was a single SNP association with COPD. This genomic region replicated for airflow obstruction in an independent population of European ancestry(23) suggesting a true association. Whereas the *CDRT15P1* locus only contained imputed SNPs and did not replicate, thus reducing the probability that this is a true association with COPD.

We hypothesize that novel loci did not replicate due to small sample size of the Hispanic/Latino replication cohorts along with differing environmental exposures, differing LD, and the complex racial admixture(2) that varies by different Hispanic/Latino ancestry groups. Furthermore, the novel locus for FEV_1/FVC in *HAL* and the chromosome 18 locus for FEV_1/FVC among never smokers have marked differences in MAF between race and ethnic populations suggesting genetic diversity between races in these loci. The highest MAF for the lead SNPs in the *HAL* and in the chromosome 18 locus were observed in African populations (MAF = 0.005 and 0.38, respectively)

compared with virtually no variability in European populations for these loci (MAF=0)(63). The lack of variance of these loci in European populations limits the ability to replicate these loci as the vast majority of GWAS of lung function have been performed in studies of European ancestry. Evidence for replication of the novel locus on chromosome 11 for FEV_1 in ever smokers was stronger in the meta-analysis of cohorts with admixed populations that include African ancestry compared with the meta-analysis of all cohorts (p=0.007 and p=0.04, respectively) supporting the need for additional studies on admixed populations to identify possible ethnicity- or race-specific variants that may elucidate novel pathways in the pathogenesis of COPD.

The study has several potential limitations. This population-based cohort of diverse Hispanic/Latino participants is subject to population stratification. Multiple loci demonstrated varying MAF across Hispanic/Latino groups highlighting the complex racial admixture of Hispanic/Latino populations and raises the possibility of residual population stratification. However, we adjusted our analysis for PCs and our inflation factors ranged from 0.988 to 1.026 which indicates good control of population stratification with small inflation. The COPD analysis consisted of 363 and 5,253 participants with and without COPD (respectively), which is a relatively small sample size for a GWAS. We optimized COPD phenotype by limiting the analysis to age greater than or equal to 45 and used post-bronchodilator spirometry measurements to define COPD.

In conclusion, we identified novel biologically plausible signals associated with clinically important pulmonary measures with evidence for replication in *ZSWIM7, AGMO,* and *PDZD2*; confirmed previous reports of association with FEV_1/FVC in

KCNE2 and *GPR126,* and established that loci previously identified in European populations are generalizable in Hispanic/Latino populations. There is a paucity of genetic studies for lung function that include under-represented minority populations, such as Hispanic/Latino(2, 72) and African populations(14, 26, 73-75). Our findings emphasize the importance of including admixed and multi-racial populations when performing genetic studies of complex diseases and have the potential to advance our understanding of genetic risks for lung disease affecting Hispanic/Latino populations.

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Figure 1 Regional Association Plots and Forest Plots of genome wide significant loci associated with FEV_1 and FEV_1/FVC meta-analyzed across all Hispanic/Latino ancestry groups.

For each locus, we provide regional association plots with correlations between the reference SNP (the SNP with the lowest p-value) and other SNPs in the region. The reference SNPs a purple diamond (genotyped SNP) or upside down triangle (imputed SNP). Other SNPs in the region are depicted as circles (genotyped SNPs) and "X"s (imputed SNPs) . The correlations (r^2) are calculated from the group of interest and are indicated by the colors shown on the plot. For each locus, we also provide a forest plot comparing the SNP-trait association testing results across the Hispanic/Latino ancestry groups. (a) Regional association plot for the FEV_1 locus (lead SNP rs4791658) on chromosome 17. (b) Forrest Plot for the FEV_1 locus (lead SNP rs4791658) on chromosome 17. (c) Regional association plot for the FEV_1/FVC locus (lead SNP rs145174011) on chromosome 12. (d) Forrest Plot for the FEV_1/FVC locus (lead SNP rs192375903) on chromosome 12.

Figure 2 Regional Association Plots and Forest Plots of genome wide significant loci associated with FEV_1 and FEV_1/FVC stratified by smoking status and meta-analyzed across all Hispanic/Latino Ancestry groups.

For each locus, we provide regional association plots with correlations between the reference SNP (the SNP with the lowest p-value) and other SNPs in the region. The reference SNPs a purple diamond (genotyped SNP) or upside down triangle (imputed SNP). Other SNPs in the region are depicted as circles (genotyped SNPs) and "X"s (imputed SNPs). The correlations (r^2) are calculated from the group of interest and are indicated by the colors shown on the plot. For each locus, we also provide a forest plot comparing the SNP-trait association testing results across the Hispanic/Latino ancestry in smoking stratified group of interest. (a) Regional association plot for the FEV_1/FVC locus among never smokers (lead SNP rs7228593) on chromosome 18. (b) Forrest Plot for the FEV_1/FVC locus among never smokers (lead SNP rs7228593) on chromosome 18. (c) Regional association plot for the FEV_1 locus among ever smokers (lead SNP rs291231) on chromosome 11. (d) Forrest Plot for the FEV_1 locus among ever smokers (lead SNP rs291231) on chromosome 11.

Figure 3 Regional Association Plot and Forest Plot of candidate variant identified in local ancestry interval region associated with Amerindian ancestry and FEV_1 meta-analyzed across all Hispanic/Latino ancestry groups.

For each locus, we provide regional association plots with correlations between the reference SNP (the SNP with the lowest p-value) and other SNPs in the region. The reference SNPs a purple diamond (genotyped SNP) or upside-down triangle (imputed SNP). Other SNPs in the region are depicted as circles (genotyped SNPs) and "X"s (imputed SNPs) . The correlations (r^2) are calculated from the group of interest and are indicated by the colors shown on the plot. We also provide a forest plot comparing the SNP-trait association testing results across the Hispanic/Latino ancestry groups. (a) Regional association plot for the FEV_1 locus (lead SNP rs4133185) on chromosome 7. (b) Forrest Plot for the FEV_1 locus (lead SNP rs4133185) on chromosome 7.

Figure 4 Amerindian Admixture Mapping Region on Chromosome 7 for FEV_1

The left panel provides the admixture mapping results as two lines with the blue line representing results from the primary analysis, the green line representing results from the conditional analysis and the association results in the same region are represented as circles. The genome-wide significant threshold for admixture mapping in HCHS/SOL data set is the horizontal grey dashed line. The blue and green lines and circles are given as –log(p-value,10) against genomic positions. The red-filled triangle corresponds to the SNP used in the conditional analysis (rs4133185). The right panel provides the ancestry-specific effect allele frequencies for the SNP used in the conditional analysis (rs4133185), as estimated by ASAFE applied on HCHS/SOL data set(46).

Table 1: Characteristics of Participants in HCHS/SOL Study

	Central American	Cuban	Dominican	Mexican	Puerto Rican	South American	Combined
Number of participants	1,315	2,138	1,063	4,438	2,000	868	11,822
Age (years)	44 ± 13	49 ± 13	45 ± 14	44 ± 14	48 ± 14	46 ± 13	46 ± 14
Male Sex (%)	40	47	35	39	43	40	41
Height (cm)	160 ± 9	164 ± 9	162 ± 9	161 ± 9	163 ± 9	161 ± 9	162 ± 9
BMI (kg/m^2)	30 ± 6	29 ± 6	29 ± 6	30 ± 6	31 ± 7	29 ± 5	30 ± 6
Smoking (never) %	68	52	77	65	48	66	61
Smoking (former) %	19	19	13	19	20	20	19
Smoking (current) %	13	29	10	16	32	14	20
Pack years of smoking*	4.5 (1.7 - 14)	18.5 (6 - 36)	8.2 (3.4 – 18.3)	4.0 (1.3 – 10.5)	11.0 (4 – 25.5)	4.9 (1.5 - 16)	7.5 (2.4 - 21)
Pre-bronchodilator FEV_1 (liters)	2.88 ± 0.74	2.80 ± 0.81	2.70±0.75	2.97 ± 0.78	2.70 ± 0.83	2.95 ± 0.79	2.86 ± 0.80
Pre-bronchodilator FEV_1/FVC (%)	81.5 ± 5.9	78.7 ± 8.3	81.8 ± 7.2	80.8 ± 6.1	79.3 ± 7.9	80.1 ± 6.5	80.3 ± 7
COPD n (%)†	24 (1.8)	124 (5.8)	24 (2.3)	85 (1.9)	86 (4.3)	20 (2.3)	363 (3.1)
Airflow Limitation n (%)‡	60 (4.6)	260 (12.2)	62 (5.8)	207 (4.7)	216 (10.8)	49 (5.7)	854 (7.2)

Data presented as mean ± standard deviation for continuous measures and percentage for binary measures

Definition of abbreviations: FEV_1 = forced expiratory volume in one second, FEV_1/FVC = ratio of forced expiratory volume in one second over forced vital capacity %

* Pack years of smoking presented as median ± Inter Quartile Range (IQR) in former or current smokers

† Chronic Obstructive Pulmonary Disease defined as post-bronchodilator FEV_1/FVC ratio < 0.70

‡ Defined as pre-bronchodilator FEV_1/FVC ratio < 0.70

Table 2: Genome wide significant loci associated with FEV_1 and FEV_1/FVC

SNP rsID	Trait	Position Build 37 Chr: basepair	Gene /nearest Gene(s) (function)	Effect allele	EAF	Genotyped or Imputed SNP	oevar*	N	Beta	SE	P Value
rs76656601	FEV_1/FVC	6: 168428548	*KIF25* (intron)	G	0.996	Imputed	0.7	11822	4.70	0.77	1.31×10^{-9}
rs4791658	**FEV_1**	**17:15884792**	***ZSWIM7*† (intron)**	**G**	**0.541**	**Imputed‡**	**0.996**	**11822**	**33.35**	**5.70**	**4.99×10^{-9}**
rs145174011	**FEV_1/FVC**	**12: 96378700**	***HAL*† (Intron)**	**T**	**0.997**	**Imputed**	**0.98**	**11822**	**4.85**	**0.85**	**9.59×10^{-9}**
rs28593428	FEV_1/FVC	21: 35632170	*KCNE2*	C	0.902	Imputed	0.996	11821	0.80	0.14	1.45×10^{-8}
rs262113	FEV_1/FVC	6: 142824950	*GPR126*	T	0.812	Imputed†	0.999	11822	- 0.57	0.10	2.83×10^{-8}
rs74444778	FEV_1/FVC	7: 42553708	*LOC105375250* (intron)	G	0.999	Imputed	0.914	11822	6.17	1.12	3.61×10^{-8}
rs115745680	FEV_1	5: 154407079	*GEMIN5 KIF4B*	A	0.997	Imputed	0.981	11822	313.24	57.32	4.63×10^{-8}

Definition of abbreviations: SNP= single nucleotide polymorphism, FEV_1/FVC= ratio of forced expiratory volume in one second over forced vital capacity,

Chr = chromosome, nearest gene = the nearest genes on each side of the intergenic marker, EAF = effect allele frequency, oevar = observed / expected variance, N = sample size used in testing the given variant, Beta (FEV_1) = per-allele change in FEV_1 (mL), Beta (FEV_1/FVC) = per-allele change in FEV_1/FVC %, SE = standard error

Gene abbreviations: *KIF25* = (kinesin family member 25), *ZSWIM7* = (zinc finger, SWIM-type containing 7), *HAL*= (histidine ammonia-lyase*), GPR126*= (G protein-coupled receptor 126), *KCNE2* = (potassium channel, voltage gated subfamily E regulatory beta subunit 2), *GEMNIN5*= gem nuclear organelle associated protein 5, *KIF4B*= kinesin family member 4B

Analyses were performed using data imputed to 1000 Genome phase 1 data and stratified by Hispanic/Latino ancestry group and were adjusted for age, age^2, sex, height, height^2, smoking status, pack-years, sampling weights, first 5 principal components, Hispanic/Latino ancestry groups, kinship and block unit. Within subgroup estimates were then meta-analyzed. Previously unreported associations are in bold. Retrospectively, association analyses using genetic data imputed to 1000 Genome phase 3 imputation panel were performed in novel loci.

* oevar is provided by MACH software as a measure of imputation quality;

† Results for analyses using genetic data imputed to 1000 Genome phase 3 imputation panel

‡ Genotyped SNP in locus

Table 3: Loci associated with FEV_1 and FEV_1/FVC ratio at genome-wide significance in analyses stratified by smoking status

Ever Smokers

SNP rsID	Trait	Position Build 37 Chr: basepair	Nearest Gene(s)	Effect allele	EAF	Genotyped or imputed SNP	oevar*	N	Beta	SE	P Value
Indel (no rs#)	**FEV_1**	**11: 86006803**	***EED CCDC81***	**GACA**		**Imputed†**	**1.017**		**56.95**	**10.09**	**1.66×10^{-8}**
rs291231	**FEV_1**	**11: 86007090**	***EED CCDC81***	**G**	**0.341**	**Imputed†**	**0.999**	**4595**	**57.28**	**10.19**	**1.92×10^{-8}**
rs9974878	FEV_1/FVC	21: 35642446	*KCNE2*	G	0.887	Imputed†	0.994	4594	1.28	0.23	3.58×10^{-8}

Never Smokers

SNP rsID	Trait		Nearest Gene(s)	Effect allele	EAF	Genotyped or imputed SNP	oevar*	N	Beta		P Value
rs116726860	FEV_1/FVC	2: 155486042	*KCNJ3 GALNT13*	T	0.992	Imputed	0.897	7227	3.49	0.60	6.04×10^{-9}
rs7228593	**FEV_1/FVC**	**18: 73575704**	***SMIM21 LOC339298***	**G**	**0.948**	**Imputed†**	**0.997**	**7227**	**1.34**	**0.24**	**3.47×10^{-8}**

Definition of abbreviations: SNP= single nucleotide polymorphism, FEV_1/FVC= ratio of forced expiratory volume in one second over forced vital capacity,

Chr = chromosome, nearest gene = the nearest genes on each side of the intergenic marker, EAF = effect allele frequency, oevar = observed / expected variance, N = sample size used in testing the given variant, Beta (FEV_1) = per-allele change in FEV_1 (mL), Beta (FEV_1/FVC) = per-allele change in FEV_1/FVC %, SE = standard error, Indel = Indel mutation

Gene abbreviations: *KCNJ3* = potassium voltage-gated channel subfamily J member 3*, GALNT13* = polypeptide N-acetylgalactosaminyltransferase 13, *SMIM21* = small integral membrane protein 21, *EED* = genes embryonic ectoderm development, *KCNE2* = (potassium channel, voltage gated subfamily E regulatory beta subunit 2), *MROH2A* = *(*maestro heat-like repeat family member 2A)

Analyses were stratified by Hispanic/Latino ancestry group and smoking status. Model adjusted for age, age^2, sex, height, height^2, smoking status, pack-years, sampling weights, first 5 principal components, Hispanic/Latino ancestry groups, kinship and block unit. Within subgroup estimates were then meta-analyzed. Previously unreported associations are in bold.

* oevar is provided by MACH software as a measure of imputation quality; it is a measure of imputation quality

† Genotyped SNP in locus