# *SERPINA1* and *ELA2* Polymorphisms Are Not Associated with COPD or Lung Cancer

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**Abstract**. *Background: Through their roles in tissue remodeling, variants in the genes that encode alpha1-antitrypsin (AAT) and neutrophil elastase (NE) were hypothesized to be associated with the risk of both chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer (NSCLC). Materials and Methods: Cases with prevalent COPD (n=145), incident NSCLC (n=203) or prevalent COPD plus NSCLC (n=118) were compared to disease-free controls (n=317), to assess two functional polymorphisms in serpin peptidase inhibitor, clade A, member 1 (SERPINA1), which encodes AAT, and eleven tagging polymorphisms in and around elastase 2 (ELA2), which encodes NE. All analyses were stratified by race. Results: Among African-Americans, the less efficient SERPINA1 variant appeared to be associated with increased risk of prevalent COPD but only in the presence of NSCLC (odds ratio=7.39; 95% confidence interval=1.03-53.21) and not after correcting for multiple comparisons. Conclusion: Variations in SERPINA1 and ELA2 were not consistently or strongly associated with the risk of either COPD or NSCLC in either race.*

Chronic obstructive pulmonary disease (COPD) is a recognized clinical risk indicator for lung cancer (1) but it has been challenging to determine whether there are also shared susceptibility factors, because cigarette smoking is such a strong risk factor for both diseases. Variations in genes that encode proteins that either degrade or protect against lung tissue degradation may contribute to both diseases. Single-nucleotide polymorphisms (SNPs) in the promoter region of elastase 2 (*ELA2*) have been associated with increased transcription of neutrophil elastase (NE) and lung cancer susceptibility (2-4). Deficiencies in alpha1-antitrypsin (AAT), which covalently binds to NE (5) and is encoded by serpin peptidase inhibitor, clade A, member 1 (*SERPINA1*), has also been associated with the risk of COPD (6, 7) and lung cancer (8, 9). Only one previous study has simultaneously studied these two genes in relation to lung cancer risk (4) and to our knowledge, none have assessed COPD risk.

This study was carried out to characterize the potential contribution of variants in these two genes and the susceptibility to both COPD and lung cancer among both African-Americans and Caucasians, in order to determine if genetic variation could also explain racial differences in the incidence of these two diseases (10).

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## Materials and Methods

*Study population*. Histologically-confirmed non-small cell lung cancer (NSCLC) cases and two sets of controls (hospital and population) were enrolled, as previously described (11). For the current analyses, participants were further stratified according to self-report COPD diagnosis, which was ascertained during a structured detailed interview that all participants underwent after providing informed consent, to form four study groups: i) controls without either disease (n=317) and cases with ii) prevalent COPD-only (n=145), iii) incident NSCLC-only (n=203), and iv) prevalent COPD plus incident NSCLC (n=118).

*Genotyping*. DNA from lymphocytes was extracted using Flexigene DNA extraction kits (Qiagen, Valencia, CA, USA). Two SNPs in *SERPINA1* (S variant: rs17580 and Z variant: rs28929474), which

are associated with deficiencies in AAT and account for more than 95% of the variations in the gene (12, 13) were genotyped. The previously identified and purported functional *ELA2* polymorphisms (2-4) are located in a repetitive element of the promoter region, which made it technically difficult to develop precise genotype assays. As an alternative, we identified and genotyped eleven tagging SNPs in the region of *ELA2*, using the Caucasian HapMap data ($r^2$=0.8, minor allele frequency ≥5%). Rs17580 was determined using a Taqman assay at the National Cancer Institute's Core Genotyping Facility (Gaithersburg, MD, USA); assay details are available on their website (http://variantgps.nci.nih.gov/cgfseq/pages/home.do). All the other polymorphisms were determined using the MassARRAY iPlex™ platform by BioServe Biotechnologies, Ltd (Laurel, MD, USA); assay details are provided in Table I. All genotype completion rates were ≥93%, except for rs2240305 (88%). There was a 100% genotype concordance rate between duplicates for each test among 10% random, blinded samples.

*Statistical analyses*. The COPD patients were prevalent cases. Therefore, to maintain case–control comparability, time-dependent characteristics (age, pack-years smoked) were truncated. For the COPD cases, truncation was at the time of COPD diagnosis. For the disease-free controls, a truncation age was randomly assigned based on the distribution of age at COPD diagnosis among cases within the same birth year (±5 years) group. To estimate the association between genotypes and the risk of COPD and lung cancer within each race group, odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression in SAS (version 8; Statistical Analysis Systems, Cary, NC, USA). In addition to the three case groups being compared to the disease-free controls, cases with both diseases were compared to the cases with COPD-only; these latter comparisons were conducted to test association robustness. The Bonferroni correction was applied to account for the multiple comparisons. The genotype distributions for all SNPs were in Hardy-Weinberg equilibrium, except for rs17684161in African-Americans ($p$=0.03) and rs12985692 in Caucasians ($p$<0.01).

## Results

Characteristics of the study population are summarized in Table II. Among African-Americans, having at least one *SERPINA1* S or Z variant, cases appeared to be associated with NSCLC but only in the presence of COPD and only before correcting for multiple comparisons (OR=7.39, 95% CI=1.03-53.21; Table III). There were no African-American NSCLC-only cases with either the S or Z variant. No other associations were observed among African-Americans or Caucasians.

## Discussion

We carried out a candidate gene association study in Caucasian and African-American participants to test the hypotheses that variants in genes that encode AAT (*SERPINA1*) and NE (*ELA2*) were associated with susceptibility to both COPD and lung cancer, two leading causes of death that have long been observed to co-occur in patients.

Among African-Americans, carriers of *SERPINA1* S or Z variants appeared to have a higher risk of COPD plus lung cancer (OR=7.39), but not after adjusting for multiple comparisons. Among Caucasians these variants were non-significantly inversely associated with lung cancer only (OR=0.40). An increased risk of COPD among African-Americans would corroborate findings of meta-analyses of the Z (7) and S (6) variants. These variants have also been associated with increased lung cancer risk (4, 8), without consideration of COPD status. In the current study, inferences were limited because these variants were absent from African-Americans with lung cancer-only.

The results of the present study do not provide convincing evidence that the *ELA2* tagging SNPs were associated with risk of COPD or lung cancer. To our knowledge, no studies have investigated genetic variation in and around *ELA2* with the risk of COPD, and previous lung cancer studies have focused on different SNPs. Of the SNPs we investigated, rs3826946 was in closest proximity to the previously studied SNPs. *ELA2* is only 5 kb long (14), hence the other tagging SNPs were located in and around other genes, including proteinase-3 and D component of complement, which are functionally similar to *ELA2* (15-18). Therefore, studying SNPs in this region still adds relevant evidence to the overall hypothesis.

Several aspects of our study warrant discussion. Firstly, the COPD cases were prevalent cases; however, time-dependent variables such as age and pack-years for both the COPD cases and controls were truncated to make them as comparable as possible. Conformational changes in the structure of the *SERPINA1* S and Z variants result in their accumulation in the endoplasmic reticulum of hepatocytes, which leads to lower circulating concentrations of AAT, liver damage and shortened lifespan (19, 20). The COPD cases had to survive long enough to be included in the study, introducing the potential for survival bias for these polymorphisms. The study findings should thus be viewed as preliminary. Secondly, our method of ascertaining COPD may have resulted in misclassification due to lack of sensitivity (symptoms severe enough to seek medical attention and a diagnosis), specificity (chronic bronchitis, emphysema and unspecified COPD were combined) and/or incorrect self-reported information. Our method of ascertainment could also be partially responsible for the inconsistent findings both within our study by race and with previous studies if the distribution of subcategory COPD differed and if any of the studied SNPs was specifically associated only with chronic bronchitis or emphysema. Thirdly, the *ELA2* tagging SNPs were selected using the HapMap Caucasian population, which is composed of Utah residents; therefore, these tagging SNPs may not reflect the

true haplotype blocks for either of our race groups. Finally, although the racially diverse study population provides a start to exploring the potential racial differences in susceptibility to these important lung diseases, the need to stratify analyses by race reduced the statistical precision of our study. This highlights the challenges of disparities in research, as carrying-out a study of racial comparisons of genetic markers of two diseases, introduces formidable sample size requirements.

In spite of these limitations, this study had notable strengths in that it simultaneously investigated variations in two candidate genes in the same pathway that might underlie both COPD and lung cancer. Research examining the potential links between COPD and lung cancer extends back approximately 40 years (21). This research has historically been based on case–control studies that have assessed the association between previous lung disease (*i.e.*, COPD) and subsequent lung cancer risk (22). Very few studies have investigated variations in candidate genes that are potentially involved in the development of both diseases within the same study population, as was done in the current study (23-27). Furthermore, although a previous study found AAT deficiency and variations in *ELA2* to be independently associated with lung cancer risk (4), to our knowledge, the current study is the first simultaneous assessment of these genetic variations in regard to COPD risk. Additionally, although COPD and lung cancer are important public health issues among African-Americans, previous research in this field has been conducted exclusively or predominately among Caucasians (22). Therefore, by including both African-Americans and Caucasians, this study provided further insight into potential racial differences.

In conclusion, the observed pattern of associations were not consistent or strong enough to support the hypothesis that the less efficient *SERPINA1* S or Z variants or any of the *ELA2* tagging SNPs were associated with risk of COPD or lung cancer.

## Conflicts of Interest

The Authors have no conflicts of interest to disclose.

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Table I. *Primers and methods used for genotyping polymorphisms with the MassARRAY iPLEX™ platform.*

| Polymorphism | PCR Primer 1 | PCR Primer 2 | Extension Primer |
|---|---|---|---|
| rs28929474 | ACGTTGGATGATAGACATGGTATGGCCTC | ACGTTGGATGACAACGTGTCTCTGCTTCTC | CCGCTTCAGTCCCTTTCT |
| rs2240305 | ACGTTGGATGATGTGTTGCTCTGAGGGCTG | ACGTTGGATGGCTTTGGGCTCAAGGTCC | CGTCTGTGGCCATGTTGC |
| rs2074639 | ACGTTGGATGTGGCATTGGGCTATAAGAGG | ACGTTGGATGACTCACCGCTCAGCAGCAAG | GGCTATAAGAGGAGCTTGA |
| rs351111 | ACGTTGGATGACGACGCGGAGAACAAACTG | ACGTTGGATGAATGCTGGCTGCAGGAATGG | GCGGAGAACAAACTGAACGAC |
| rs629631 | ACGTTGGATGCACACCCACCACCTCAAAA | ACGTTGGATGGTGACAAATGGGACAAAGGG | ACCTCAAAACGCCGC |
| rs3826946 | ACGTTGGATGGAGCACCAGCTGTATACTAC | ACGTTGGATGCCAGAACCAGGATATGAACC | TCCATTCTCACGTGCAGTC |
| rs1683564 | ACGTTGGATGGTAGGAAGGTCACTTGACAC | ACGTTGGATGCCTTGGCCTTTCCAACTTTC | TGTCTCTGTCCCTGTG |
| rs3826945 | ACGTTGGATGAACACGTGGTGAGGTTGAGG | ACGTTGGATGCCTATCGCCTAGGCCACAA | CCTAGAGGGGCGTGG |
| rs12985692 | ACGTTGGATGCACAGAAGACGCTCACATTC | ACGTTGGATGCTCCTGGTCTGGCTCATAC | TCCCCTTCCCCTTGGTAAGCA |
| rs17684161 | ACGTTGGATGTGGTGACCACCACGAAGTTG | ACGTTGGATGAGAGACTCCGTCTCAAAAAC | ACGAAGTTGGAGCTCAC |
| rs10424211 | ACGTTGGATGTGAACTCCCAGGCTCAAGTG | ACGTTGGATGGACCAAAGGATGCAAGATG | TACGGGATCCTCCTGCCTGG |
| rs1651895 | ACGTTGGATGACAGATGAGGAAACAGAGGC | ACGTTGGATGCCACATAGTCCTCTGAGTTG | GGCCATATATATGGCAGTG |

Methods: 10 ng of sample DNA are used to perform a MassARRAY iPLEX™ platform (http://www.bioserve.com/preclinical-molecular-services/maldi-tof-massarray-iplex.cfm) at BioServe Biotechnologies, Ltd. (Laurel, MD, USA). Reactions are set up using the above listed primers. The cycling parameters for polymerase chain reaction (PCR) are as follows: 95˚C for 15 min (activation of Taq enzyme); 45 cycles of 95˚C for 20 sec (denaturation); 56˚C for 30 sec (annealing); 72˚C for 1 min (extension); a final extension temperature of 72˚C for 3 min before cooling at 4˚C. This is followed by a Shrimp Alkaline Phosphatase (SAP) Treatment as follows: SAP is added to the PCR product at 37˚C for 20 min followed by a hold at 85˚C for 5 min and a final cooling step of 4˚C. This process helps remove the unincorporated nucleotides. The single-base extension protocol used was as follows: 94˚C for a 30 sec hold; 40 cycles of 94˚C for 5 sec; 52˚C for 5 sec; 80˚C for 5 sec; followed by a nested 5 cycles from 52˚C for 5 sec, and 80˚C for 5 sec in each of the 40 cycles; a final extension is performed at 72˚C for 3 min and then cooled to 4˚C.

Table II. *Demographic information by chronic obstructive pulmonary disease (COPD) and non-small cell lung cancer (NSCLC) status and race, Maryland Lung Cancer Study, 1998-2004.*

| Race | Characteristic | Controls | COPD cases | $p^1$ | NSCLC cases | $p^1$ | COPD plus NSCLC cases | $p^1$ | $p^2$ |
|---|---|---|---|---|---|---|---|---|---|
| African-American, n | | 144 | 39 | | 55 | | 25 | | |
| | Mean age±s.d. (years) | 65.3±10.3 | 66.3±10.1 | 0.58 | 63.0±9.5 | 0.16 | 66.3±7.5 | 0.65 | 0.98 |
| | Gender, % | | | | | | | | |
| | Male | 53 | 36 | | 53 | | 28 | | |
| | Female | 47 | 64 | 0.06 | 47 | 0.99 | 72 | 0.02 | 0.51 |
| | Smoking Status, %[3] | | | | | | | | |
| | Never | 35 | 28 | | 9 | | 0 | | |
| | Former | 44 | 62 | | 40 | | 52 | | |
| | Current | 20 | 10 | 0.14 | 51 | <0.01 | 48 | <0.01[+] | <0.01[+] |
| | Mean pack-years ±s.d.[4] | 23.2±18.8 | 34.3±26.6 | 0.01 | 34.5±21.0 | <0.01 | 50.1±29.9 | <0.01 | 0.05 |
| | Mean age at first COPD diagnosis ±s.d. (years)[§] | 46.8±20.4 | 50.1±19.8 | 0.37 | | | 44.8±19.6 | | 0.32 |
| | Mean years since first COPD diagnosis±s.d.[§] | 16.2±17.9 | 16.3±15.4 | 0.97 | | | 21.4±21.0 | | 0.28 |
| | Smoking Status at first COPD diagnosis, %[§] | | | | | | | | |
| | Never | 42 | 33 | | | | 4 | | |
| | Former | 26 | 23 | | | | 13 | | |
| | Current | 32 | 44 | 0.38 | | | 83 | | <0.01 |
| | Mean pack-years at first COPD diagnosis±s.d[§4] | 18.8±17.0 | 31.7±24.8 | <0.01 | | | 30.7±29.2 | | 0.89 |
| Caucasian, n | | 173 | 106 | | 148 | | 93 | | |
| | Mean age±s.d. (years) | 65.8±10.3 | 66.7±8.8 | 0.50 | 66.4±11.2 | 0.66 | 66.3±9.1 | 0.69 | 0.80 |
| | Gender, % | | | | | | | | |
| | Male | 57 | 56 | | 59 | | 44 | | |
| | Female | 43 | 44 | 0.80 | 41 | 0.69 | 56 | 0.04 | 0.10 |
| | Smoking Status, %[3] | | | | | | | | |
| | Never | 38 | 2 | | 6 | | 4 | | |
| | Former | 50 | 58 | | 49 | | 34 | | |
| | Current | 12 | 41 | <0.01 | 45 | <0.01 | 61 | <0.01 | 0.02[+] |
| | Mean pack-years±s.d.[4] | 29.9±25.0 | 52.6±29.4 | <0.01 | 43.3±26.4 | <0.01 | 52.2±25.9 | <0.01 | 0.92 |
| | Mean age at first COPD diagnosis±s.d. (years)[§] | 50.65±18.0 | 51.3±18.1 | 0.73 | | | 52.5±18.4 | | 0.65 |
| | Mean years since first COPD diagnosis±s.d.[§] | 14.2±15.4 | 15.3±15.0 | 0.58 | | | 14.3±16.2 | | 0.64 |
| | Smoking Status at first COPD diagnosis, %[§] | | | | | | | | |
| | Never | 42 | 7 | | | | 9 | | |
| | Former | 25 | 22 | | | | 20 | | |
| | Current | 32 | 77 | <0.01 | | | 71 | | 0.79 |
| | Mean pack-years at first COPD diagnosis±s.d.[§4] | 24.6±20.3 | 41.0±28.2 | <0.01 | | | 40.2±25.7 | | 0.85 |

[1]Compared to controls using the t-test for continuous variables and chi-square test for categorical variables. [2]Compared to COPD cases using the t-test for continuous variables and chi-square test for categorical variables. [3]At the time of lung cancer diagnosis or study enrollment for those without lung cancer. [4]Among ever smokers at that time. [§]Values among the controls group were imputed in order to be comparable to the prevalent COPD cases. [+]Fisher's exact test, s.d.: standard deviation.

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Table III. *Association between SERPINA1 and ELA2 polymorphisms with chronic obstructive pulmonary disease (COPD) and/or non-small cell lung cancer (NSCLC), Maryland Lung Cancer Study, 1998-2004.*

| | | | | Controls | COPD cases | | NSCLC cases | | COPD plus NSCLC cases | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Race | Gene | Polymorphism | Exposed/Unexposed | N | N | OR (95% CI)[1,3] | N | OR (95% CI)[1,4] | N | OR (95% CI)[1,4] | OR (95% CI)[2,4] |
| African-American | *SERPINA1* | rs17580 and rs28929474 | S+V/M | 3/141 | 4/35 | 4.35 (0.89, 21.29) | 0/55 | -- | 3/22 | 7.39 (1.03, 53.21) | 0.82 (0.13, 5.05) |
| | *ELA2* | rs2240305 | CT+TT/CC | 26/118 | 6/33 | 0.84 (0.31, 2.26) | 15/40 | 2.07 (0.93, 4.62) | 6/16 | 1.22 (0.35, 4.26) | 1.22 (0.26, 5.66) |
| | | rs2074639 | CT+TT/CC | 19/125 | 2/37 | 0.38 (0.08, 1.72) | 7/48 | 0.94 (0.34, 2.59) | 2/23 | 0.18 (0.02, 1.35) | 0.51 (0.05, 5.44) |
| | | rs351111 | AG/AA | 81/33 | 23/9 | 1.06 (0.43, 2.60) | 29/16 | 0.71 (0.32, 1.61) | 12/4 | 2.28 (0.51, 10.24) | 1.41 (0.26, 7.59) |
| | | | GG/AA | 30/33 | 7/9 | 0.79 (0.25, 2.46) | 10/16 | 0.68 (0.25, 1.86) | 9/4 | 4.48 (0.91, 22.17) | 6.35 (0.87, 46.22) |
| | | rs629631 | CT/CC | 78/45 | 18/10 | 2.78 (0.97, 7.99) | 26/20 | 0.83 (0.39, 1.75) | 10/11 | 0.98 (0.21, 4.68) | 0.46 (0.11, 1.99) |
| | | | TT/CC | 21/45 | 11/10 | 1.12 (0.46, 2.72) | 9/20 | 1.02 (0.37, 2.87) | 4/11 | 0.89 (0.29, 2.80) | 0.37 (0.06, 2.10) |
| | | rs3826946 | AT+AA/TT | 49/95 | 10/29 | 0.66 (0.29, 1.50) | 21/34 | 1.24 (0.61, 2.51) | 12/13 | 2.34 (0.83, 6.63) | 3.77 (0.96, 14.78) |
| | | rs1683564 | AC+AA/CC | 42/102 | 14/25 | 1.30 (0.61, 2.81) | 17/38 | 0.88 (0.42, 1.83) | 10/15 | 0.78 (0.26, 2.36) | 1.05 (0.29, 3.82) |
| | | rs3826945 | CT+CC/TT | 44/100 | 11/28 | 0.96 (0.43, 2.16) | 14/41 | 0.98 (0.46, 2.10) | 8/17 | 0.76 (0.24, 2.44) | 0.62 (0.15, 2.53) |
| | | rs17684161 | CT+CC/TT | 56/88 | 12/27 | 0.73 (0.33, 1.60) | 19/36 | 0.88 (0.44, 1.78) | 13/12 | 2.47 (0.86, 7.14) | 1.32 (0.37, 4.68) |
| | | rs10424211 | CG+CC/GG | 29/115 | 9/30 | 1.10 (0.46, 2.64) | 11/44 | 0.82 (0.35, 1.89) | 4/21 | 0.73 (0.21, 2.61) | 0.88 (0.18, 4.29) |
| | | rs1651895 | AG+AA/GG | 42/102 | 14/25 | 1.25 (0.58, 2.70) | 16/39 | 0.92 (0.44, 1.94) | 6/19 | 0.98 (0.32, 2.99) | 0.82 (0.21, 3.22) |
| Caucasian | *SERPINA1* | rs17580 and rs28929474 | S+V/M | 17/156 | 14/92 | 1.40 (0.59, 3.30) | 9/139 | 0.40 (0.15, 1.02) | 10/83 | 0.77 (0.29, 2.03) | 0.86 (0.36, 2.07) |
| | *ELA2* | rs2240305 | CT+TT/CC | 36/70 | 36/70 | 0.80 (0.45, 1.44) | 53/97 | 0.78 (0.46, 1.31) | 37/56 | 1.32 (0.70, 2.51) | 1.35 (0.75, 2.45) |
| | | rs2074639 | CT+TT/CC | 40/66 | 40/66 | 1.39 (0.77, 2.53) | 55/97 | 1.69 (0.99, 2.88) | 31/62 | 1.03 (0.53, 2.03) | 0.72 (0.39, 1.33) |
| | | rs351111 | AG/GG | 52/17 | 52/17 | 1.36 (0.73, 2.54) | 70/22 | 1.24 (0.71, 2.16) | 48/12 | 1.54 (0.77, 3.04) | 0.99 (0.53, 1.85) |
| | | | AA/GG | 37/17 | 37/17 | 0.81 (0.34, 1.91) | 56/22 | 0.92 (0.43, 1.94) | 33/12 | 0.72 (0.27, 1.92) | 0.69 (0.28, 1.70) |
| | | rs629631 | CT+TT/CC | 15/91 | 15/91 | 0.80 (0.37, 1.72) | 30/118 | 0.96 (0.50, 1.84) | 16/77 | 0.97 (0.42, 2.22) | 1.48 (0.67, 3.28) |
| | | rs3826946 | AT+AA/TT | 33/75 | 31/75 | 0.93 (0.51, 1.70) | 39/109 | 0.77 (0.44, 1.34) | 30/63 | 1.17 (0.60, 2.28) | 0.99 (0.53, 1.86) |
| | | rs1683564 | AC/CC | 54/40 | 54/40 | 1.18 (0.44, 3.12) | 60/71 | 0.66 (0.39, 1.13) | 45/38 | 0.91 (0.47, 1.76) | 0.87 (0.48, 1.60) |
| | | | AA/CC | 12/40 | 12/40 | 1.05 (0.58, 1.92) | 17/71 | 1.09 (0.46, 2.59) | 10/38 | 0.98 (0.32, 3.02) | 0.79 (0.30, 2.09) |
| | | rs3826945 | CT/TT | 48/45 | 48/45 | 1.42 (0.77, 2.62) | 60/77 | 0.95 (0.55, 1.61) | 43/41 | 1.33 (0.68, 2.58) | 0.97 (0.53, 1.77) |
| | | | CC/TT | 13/45 | 13/45 | 0.88 (0.35, 2.20) | 11/77 | 0.41 (0.16, 1.06) | 9/41 | 0.46 (0.16, 1.32) | 0.66 (0.25, 1.76) |
| | | rs12985692* | CT+CC/TT | 3/103 | 3/103 | 0.91 (0.18, 4.54) | 6/142 | 1.10 (0.27, 4.44) | 2/91 | 0.58 (0.09, 3.78) | 0.99 (0.16, 6.28) |
| | | rs17684161 | CT+CC/TT | 18/88 | 18/88 | 0.73 (0.36, 1.48) | 47/101 | 1.63 (0.93, 2.85) | 25/68 | 1.28 (0.63, 2.60) | 1.73 (0.86, 3.46) |
| | | rs10424211 | CG+CC/GG | 34/72 | 34/72 | 0.63 (0.35, 1.14) | 48/100 | 0.64 (0.38, 1.09) | 39/54 | 1.01 (0.54, 1.89) | 1.66 (0.91, 3.01) |
| | | rs1651895 | AG/GG | 42/58 | 42/58 | 0.98 (0.54, 1.77) | 50/88 | 0.68 (0.40, 1.16) | 47/41 | 1.45 (0.76, 2.77) | 1.68 (0.93, 3.03) |
| | | | AA/GG | 6/58 | 6/58 | 0.41 (0.13, 1.33) | 10/88 | 0.57 (0.21, 1.52) | 5/41 | 0.41 (0.10, 1.66) | 1.24 (0.34, 4.52) |

[1]Compared to controls or [2]COPD-only cases [3]adjusted for smoking status (never, former, current) and pack-years (continuous) truncated at COPD diagnosis or [4]adjusted for smoking status (never, former, current) and pack-years (continuous) at enrollment, all *SERPINA1* and *ELA2* variables were included in the same model. *Rs12985692 among African-Americans was monomorphic and thus not reported.

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