Genetic Epidemiology of Cigarette Smoke–Induced Lung Disease

Ann G. Schwartz[1]

[1]Population Studies and Disparities Research Program, Karmanos Cancer Institute, Department of Oncology, Wayne State University School of Medicine, Detroit, Michigan

Chronic obstructive pulmonary disease (COPD) and lung cancer represent two diseases that share a strong risk factor in smoking, and COPD increases risk of lung cancer even after adjusting for the effects of smoking. These diseases not only occur jointly within an individual but also there is evidence of shared occurrence within families. Understanding the genetic contributions to these diseases, both individually and jointly, is needed to identify the highest risk group for screening and targeted prevention, as well as aiding in the development of targeted treatments. The chromosomal regions that have been identified as being associated either jointly or independently with lung cancer, COPD, nicotine addiction, and lung function are presented. Studies jointly measuring genetic variation in lung cancer and COPD have been limited by the lack of detailed COPD diagnosis and severity data in lung cancer populations, the lack of lung cancer–specific phenotypes (histology and tumor markers) in COPD populations, and the lack of inclusion of minorities. African Americans, who smoke fewer cigarettes per day and have different linkage disequilibrium and disease patterns than whites, and Asians, also with different patterns of exposure to lung carcinogens and linkage patterns, will provide invaluable information to better understand shared and independent genetic contributions to lung cancer and COPD to more fully define the highest risk group of individuals who will most benefit from screening and to develop molecular signatures to aid in targeted treatment and prevention efforts.

Keywords: lung cancer; COPD; smoking; genetics

Tobacco exposure, primarily in the form of cigarette smoking, is responsible for more deaths than any other preventable exposure, accounting for one in every five deaths (~450,000) annually in the United States (1). Containing at least 250 chemicals that cause cancer or are toxic, tobacco use is associated with cancers of the lung, oral cavity, larynx, pancreas, bladder, and kidney, as well as cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and a number of other diseases. Eighty to 90% of all lung cancer and COPD is attributable to smoking (2, 3). Lung cancer is the second leading form of cancer diagnosed in the United States, with an estimated 222,520 new cases and 157,300 deaths in 2010 (4). Likewise, COPD causes substantial morbidity and mortality; it is the fourth leading cause of mortality in adults in the United States and by 2030 is expected to be the third leading cause of death worldwide (5). Neither lung cancer, with a 5-year survival rate of just 15%, nor COPD is particularly responsive to treatment; therefore, both represent a major public health challenge. Although efforts to prevent initiation of smoking and promote smoking cessation have resulted in a substantial decline in the rate of smoking among adults, there remain almost 50 million former smokers and another 45 million current smokers who continue to be at risk of lung cancer and COPD (6), reinforcing the need to better understand the disease processes. Given that only 15% of smokers will develop lung cancer and/or COPD, understanding the genetic contributions to individual differences in susceptibility to these diseases is essential.

COPD HISTORY AND RISK OF LUNG CANCER

Cigarette smoking contributes to lung cancer and COPD, but COPD itself is a risk factor for lung cancer. Once COPD is diagnosed, risk of developing lung cancer increases two- to threefold (7–12), even among never smokers (13). Lung cancer occurrence is also linked differentially to specific COPD phenotypes (i.e., emphysema and chronic bronchitis) (9, 14–19). In a metaanalysis, lung cancer was associated with a previous history of COPD (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.7–3.0), chronic bronchitis (OR, 1.5; 95% CI, 1.3–1.8), and emphysema (OR, 2.0; 95% CI, 1.7–2.4) (12). In a large, population-based case-control study in women in Detroit, COPD was associated with a significantly increased risk of non–small cell lung cancer (NSCLC) (OR, 1.67; 95% CI, 1.15–2.41; in whites, OR, 1.85; 95% CI, 1.21–2.81) (19). No increase in risk was seen in African American women. A history of emphysema was associated with a threefold increased risk of lung cancer (OR, 3.21; 95% CI, 1.60–6.45). A history of chronic bronchitis was associated with a 1.7-fold increased risk of lung cancer (95% CI, 1.13–2.59). Lung cancer cases with a chronic obstructive lung disease history were more likely to be white, be heavy smokers, be exposed to environmental tobacco smoke, have childhood asthma, and have a history of asbestos exposure. Each of these exposures is a risk factor for both COPD and lung cancer. The question remains as to whether COPD is in the causal pathway in the development of lung cancer or a variation in manifestation from the same exposures.

There are some limitations to this work that need to be considered. The biggest limitation to the case-control studies, and all studies that rely on self-report, is the possibility of misclassification and lack of specificity of history of lung disease. The diagnosis of COPD includes a combination of two diseases that are frequently codiagnosed, chronic bronchitis and emphysema, making COPD a heterogeneous clinical phenotype. Disease presentation has been reported to vary by race, with COPD often diagnosed at an earlier age and at lower pack-years of exposure in African Americans than in whites (20, 21). One study also reports a different emphysema disease pattern seen on computed

(*Received in original form June 14, 2011; accepted in final form September 21, 2011*)

Supported in part by National Institutes of Health grants R01CA060691, R01CA87895, N01PC35145, and P30CA22453.

Correspondence and requests for reprints should be addressed to Ann G. Schwartz, Ph.D., M.P.H., Karmanos Cancer Institute, 4100 John R, Detroit, MI 48201. E-mail: schwarta@karmanos.org

Proc Am Thorac Soc Vol 9, Iss. 2, pp 22–26, May 1, 2012

DOI: 10.1513/pats.201106-037MS
Internet address: www.atsjournals.org

tomography (CT) between African Americans and whites (22). Given the clinical complexities, the COPD phenotype in these studies is unlikely to be uniformly accurate.

Three prospective studies have evaluated the association between CT evidence of emphysema and risk of lung cancer, reducing the potential for disease misclassification. de Torres and colleagues (23) report a 2.5-fold increased risk of lung cancer in the presence of emphysema, but no significant increased risk associated with airway obstruction. Risk was highest (relative risk, 4.3; 95% CI, 1.04–18.2) in the subset of participants with emphysema and no airway obstruction. Wilson and colleagues (11) report a 3.6-fold increased risk of lung cancer in smokers with CT-diagnosed emphysema and a 2.1-fold increased risk associated with airflow obstruction. In contrast, Maldonado and colleagues (24) reported no increased lung cancer risk among patients with CT-diagnosed emphysema. Risk of lung cancer has also been shown to increase with decreasing FEV_1; this was reported even in smokers with only minimal (10%) decreases in FEV_1 (18). Together these findings suggest that lung cancer occurrence is linked differentially to specific features of COPD; however, the pathologic mechanisms underlying this association are unknown.

FAMILIAL AGGREGATION OF LUNG CANCER AND COPD

Not only do COPD and lung cancer exist jointly within individuals, these diseases aggregate individually and jointly within families. Familial aggregation of lung cancer was first described almost 60 years ago (25), and several studies since have shown that a first-degree family history of lung cancer confers an approximately twofold increased risk of lung cancer (26). Likewise, familial aggregation of COPD has been reported. FEV_1 and FEV_1/FVC values were shown to be significantly lower in first-degree relatives of probands with early-onset COPD as compared with controls (27). Probands were also 3.6 times more likely to have a parent who smoked and had a diagnosis of COPD. In addition to disease-specific aggregation, lung cancer and COPD jointly aggregate in families. First-degree relatives of patients with lung cancer and patients with COPD show impaired FEV_1 (28), and a family history of COPD increases risk of lung cancer development (29), suggesting a common underlying genetic contribution to these diseases.

GENETIC SUSCEPTIBILITY TO LUNG CANCER AND COPD

Several analytic approaches have been used to identify genes associated with lung cancer and/or COPD. Family linkage studies require large pedigrees including several affected relatives. This approach is focused on finding rare, highly penetrant genes demonstrating Mendelian inheritance. Under a model assuming common diseases are caused by common variants, different strategies are needed. Until recently, a candidate gene approach was used to focus on those genes most likely involved in disease pathogenesis. With technological advances, such as high-throughput genotyping, investigators have taken an agnostic approach to variant identification using whole genome association studies (GWAS) or admixture mapping. GWAS involves genotyping 1 million or more variants in very large numbers of individuals to identify regions containing more common (minor allele frequencies$c > 5\%$), low-penetrant variants associated with disease risk, whereas admixture mapping typically involves genotyping fewer ancestry informative markers in an admixed population. Most recently, whole genome or whole exome sequencing is being used to identify a third class of genetic variants, namely rare variants (minor allele frequencies$c < 5\%$) with low to moderate penetrance under a model assuming that common diseases are caused by rare variants. All of these approaches have been used in the search for disease susceptibility genes.

Family Linkage Studies

Family linkage studies have been used to identify genes for lung cancer, lung function, and COPD (30–32). The only linkage study in lung cancer successfully identified a region on 6q24 linked to familial lung cancer (30, 33). With fine mapping, the *RGS17* gene was identified as a putative lung cancer susceptibility gene (34). Statistical modeling of the risk for lung cancer among those carrying a putative risk haplotype showed evidence for an interaction between exposure to smoking and inherited susceptibility to lung cancer (33). In addition to linkage on 6q, some evidence for linkage on chromosome 12 was also reported. For COPD, a region on 6q was most strongly linked to FEV_1 (31, 32). The region of tightest linkage was at the 6q terminus, just beyond the lung cancer linkage region and extending to the end of the chromosome. Evidence for linkage of lung function to moderate obstructive lung disease in smokers was reported on chromosome 12p (35, 36), and quantitative measures of FEV_1 and FVC have been linked to a region on 2q36 (37). The phenotype of postbronchodilator FEV_1 in these families was linked to a region on 8p23. These data provide some regions of potential overlap in areas linked to lung function, COPD, and lung cancer on chromosomes 6q and 12p.

Candidate Gene Studies

Pathways involved in the pathogenesis of COPD and lung cancer include inflammation, extracellular matrix proteolysis, and oxidative stress (38–40). A number of candidate gene single-nucleotide polymorphisms (SNPs) have been associated with susceptibility to lung cancer and COPD, including those coding for epoxide hydrolase 1 (EPHX1), matrix metalloproteinases, and IL-1β (41–45). Inflammatory pathway genes have been targeted for study because of the chronic inflammation caused by cigarette smoke exposure. *IL1*, *IL1B*, *IL1RN*, *TNFA*, *IL8*, *COX2*, and *IL10* SNPs have been associated with risk of lung cancer (43, 46–53). In the Detroit lung cancer case-control study, associations between lung cancer risk and SNPs varied by race and by history of COPD (54). SNPs in *IL7R*, *IL15*, *TNF*, *TNFRSF10A*, *IL1RN*, and *IL1A* were associated with lung cancer risk in women with self-reported COPD but not among women without COPD. Engles and colleagues reported that *IL1A* SNPs were more strongly associated with lung cancer risk in those with emphysema (43). COPD is also characterized by chronic inflammation and has been associated with IL-1β, PGE-2, and transforming growth factor-β (55). *TNFA* and *CXCR2* have been associated with spirometry measures of lung function (56), whereas *IFNG* has been associated with FEV_1% predicted in a series of smokers (57). Sadeghnejad and colleagues report that the association between pack-years of smoking and decline in mean percent predicted FEV_1 is modified by genotype at *IL13* (58).

GWAS

Several GWAS have identified a region of 15q25.1, containing nicotinic acetylcholine receptor subunit genes *CHRNA3* and *CHRNA5*, associated with lung cancer, nicotine addiction, cigarettes smoked per day, COPD, FEV_1, and emphysema (59–68). Additional regions of interest identified in lung cancer GWAS are on 3q29, 5p15, 6p21, 10q25, and 15q15 (69–71). The 5p15.33 region includes human telomerase reverse transcriptase

(*hTERT*) and *CLPTMIL*, and the 6p21.33 region contains *BAT3* and *MSH5* genes involved in apoptosis and DNA repair, respectively (64). GWAS of lung function measures in the Framingham Heart Study showed *IL-6R* to be associated with forced expiratory flow midexpiratory phase, and *GSTO2* was closely associated with mean FEV_1 and FVC measures (72). More recent GWAS report FEV_1 or FEV_1/FVC associated with regions on 4q31 (*HHIP*), 2q35 (*TNS1*), 4q24 (*GSTCD*), 4q22 (*FAM13A*), 5q33 (*HTR4, ADAM19*), 6p21 (*AGER*), 6q24 (*GPR126*), and 15q23 (*THSD4*) (73–76). A GWAS based on CT-diagnosed emphysema in patients with COPD reported an additional locus including *BICD1* on chromosome 12p11.2, with potential functional significance in telomere shortening (77). Evaluating lung cancer and COPD jointly, Young and colleagues report that the 15q25 locus is associated with risk of both diseases, variants on 4q31 and 4q22 are associated with reduced risk of both diseases, loci on 6p21 are most strongly associated with lung cancer risk in smokers with COPD, and variants on 5p15 and 1q23 alter lung cancer risk when COPD is not present (78). The findings presented illustrate the complexities in teasing apart the genetic contributions to lung cancer and COPD jointly and separately.

Admixture Mapping

Admixture mapping has been used as an alternative approach for the identification of disease susceptibility regions in African Americans. This approach benefits from the linkage disequilibrium characteristics of admixed populations. In the only admixture study in lung cancer, regions on chromosomes 1q42, 3q25, 6p24, 10q23, and 15q12–13 were identified that need to be followed up with fine mapping. These regions contain potential candidate genes, including *EPHX1*, *PTEN*, *GABA* receptors, and *CHRNA7*. The 10q23 region has been reported to be associated with lung function (31). Redefining the outcome as self-reported COPD, several regions common to lung cancer and COPD were identified on chromosomes 1, 3, and 10 (Schwartz AG, unpublished data), where there is also evidence for association with lung function (72).

NextGen Sequencing

GWAS are designed to discover variation under a common disease–common variant hypothesis. To date, however, GWAS results explain only about 5% of the genetic variation in disease risk. Rare variants are not captured in GWAS studies. Whole genome or whole exome sequencing is a novel approach that has only recently become possible on a large scale at lower cost allowing the study of genetic variation to extend beyond common variants in the search for rare, moderately penetrant variants that confer greater risk than seen so far in GWAS. This approach results in the identification of novel SNPs, copy number variants, rearrangements, and insertions and deletions, and has been used successfully to follow up GWAS regions identified in prostate cancer (79). The most powerful way to conduct these studies is by enriching the sample for extreme phenotypes, such as individuals with a family history (80), as has been done successfully for other familial cancers, such as hereditary pancreatic (81) and breast (82) cancers. In addition, the approach is strengthened by the inclusion of sequencing in both germline and tumor DNA to identify novel causal tumor suppressor genes. These types of studies are just getting underway for lung cancer.

SUMMARY

Lung cancer and COPD are responsible for hundreds of thousands of deaths each year in the United States. These diseases share a strong risk factor in smoking, and COPD increases risk of lung cancer even after adjusting for the effects of smoking. Uncoupling shared risk factors from causal pathways will be difficult. Although some of the biologic responses to tobacco smoke that underlie both COPD and lung cancer may be shared, genetic susceptibility underlying COPD and lung cancer may also be distinct. Which pathways are activated and/or suppressed is likely to determine the course of disease development. A number of chromosomal regions have been identified that are associated either jointly or independently with lung cancer, COPD, nicotine addiction, and lung function. Studies jointly measuring genetic variation in lung cancer and COPD have been limited by the lack of detailed COPD diagnosis and severity data in lung cancer populations, the lack of lung cancer–specific phenotypes (histology and tumor markers) in COPD populations, and the lack of inclusion of minorities. African Americans, who smoke fewer cigarettes per day and have different linkage disequilibrium and disease patterns than whites, and Asians, also with different patterns of exposure to lung carcinogens and linkage patterns, will provide invaluable information to better understand shared and independent genetic contributions to lung cancer and COPD. With the promise of new screening approaches for the early detection of lung cancer, defining the highest-risk group of individuals who will most benefit from screening will require a better understanding of the interactions between cigarette smoking, family history, genotype, lung function, and history of COPD. In addition, the development of molecular signatures for these diseases is needed to determine the common and disparate mechanisms in their pathogenesis to aid in targeted treatment and prevention efforts.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. Giovino GA. The tobacco epidemic in the United States. *Am J Prev Med* 2007;33:S318–S326.
2. Mattson ME, Pollack ES, Cullen JW. What are the odds that smoking will kill you? *Am J Public Health* 1987;77:425–431.
3. Sethi JM, Rochester CL. Smoking and chronic obstructive pulmonary disease. *Clin Chest Med* 2000;21:67–86, viii.
4. American Cancer Society. Cancer Facts & Figures. Atlanta; 2010 [updated 2010; accessed 2011 May 31]. Available from: http://www.cancer.org/Research/CancerFactsFigures/CancerFactsFigures/index.
5. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006;3:e442.
6. Centers for Disease Control and Prevention (CDC). Cigarette smoking among adults–United States, 2002. *MMWR Morb Mortal Wkly Rep* 2004;53:428–431.
7. Mannino DM, Aguayo SM, Petty TL, Redd SC. Low lung function and incident lung cancer in the United States: data From the First National Health and Nutrition Examination Survey follow-up. *Arch Intern Med* 2003;163:1475–1480.
8. Purdue MP, Gold L, Jarvholm B, Alavanja MC, Ward MH, Vermeulen R. Impaired lung function and lung cancer incidence in a cohort of Swedish construction workers. *Thorax* 2007;62:51–56.
9. Schabath MB, Delclos GL, Martynowicz MM, Greisinger AJ, Lu C, Wu X, Spitz MR. Opposing effects of emphysema, hay fever, and select genetic variants on lung cancer risk. *Am J Epidemiol* 2005;161:412–422.
10. Littman AJ, Thornquist MD, White E, Jackson LA, Goodman GE, Vaughan TL. Prior lung disease and risk of lung cancer in a large prospective study. *Cancer Causes Control* 2004;15:819–827.
11. Wilson DO, Weissfeld JL, Balkan A, Schragin JG, Fuhrman CR, Fisher SN, Wilson J, Leader JK, Siegfried JM, Shapiro SD, *et al*. Association of radiographic emphysema and airflow obstruction with lung cancer. *Am J Respir Crit Care Med* 2008;178:738–744.
12. Brenner DR, McLaughlin JR, Hung RJ. Previous lung diseases and lung cancer risk: a systematic review and meta-analysis. *PLoS ONE* 2011;6:e17479.

13. Turner MC, Chen Y, Krewski D, Calle EE, Thun MJ. Chronic obstructive pulmonary disease is associated with lung cancer mortality in a prospective study of never smokers. *Am J Respir Crit Care Med* 2007;176:285–290.
14. Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA, Jr., Enright PL, Kanner RE, O'Hara P, *et al*. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. *JAMA* 1994;272:1497–1505.
15. McGarvey LP, John M, Anderson JA, Zvarich M, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007;62:411–415.
16. Brownson RC, Alavanja MC, Caporaso N, Berger E, Chang JC. Family history of cancer and risk of lung cancer in lifetime non-smokers and long-term ex-smokers. *Int J Epidemiol* 1997;26:256–263.
17. Mayne ST, Buenconsejo J, Janerich DT. Familial cancer history and lung cancer risk in United States nonsmoking men and women. *Cancer Epidemiol Biomarkers Prev* 1999;8:1065–1069.
18. Wasswa-Kintu S, Gan WQ, Man SF, Pare PD, Sin DD. Relationship between reduced forced expiratory volume in one second and the risk of lung cancer: a systematic review and meta-analysis. *Thorax* 2005; 60:570–575.
19. Schwartz AG, Cote ML, Wenzlaff AS, Van Dyke A, Chen W, Ruckdeschel JC, Gadgeel S, Soubani AO. Chronic obstructive lung diseases and risk of non-small cell lung cancer in women. *J Thorac Oncol* 2009;4:291–299.
20. Dransfield MT, Bailey WC. COPD: racial disparities in susceptibility, treatment, and outcomes. *Clin Chest Med* 2006;27:463–471, vii.
21. Dransfield MT, Davis JJ, Gerald LB, Bailey WC. Racial and gender differences in susceptibility to tobacco smoke among patients with chronic obstructive pulmonary disease. *Respir Med* 2006;100:1110–1116.
22. Chatila WM, Hoffman EA, Gaughan J, Robinswood GB, Criner GJ. Advanced emphysema in African-American and white patients: do differences exist? *Chest* 2006;130:108–118.
23. de Torres JP, Bastarrika G, Wisnivesky JP, Alcaide AB, Campo A, Seijo LM, Pueyo JC, Villanueva A, Lozano MD, Montes U, *et al*. Assessing the relationship between lung cancer risk and emphysema detected on low-dose CT of the chest. *Chest* 2007;132:1932–1938.
24. Maldonado F, Bartholmai BJ, Swensen SJ, Midthun DE, Decker PA, Jett JR. Are airflow obstruction and radiographic emphysema risk factors for lung cancer? A nested case-control study using quantitative emphysema analysis. *Chest*. 2010;138:1295–1302.
25. Tokuhata GK, Lilienfeld AM. Familial aggregation of lung cancer in humans. *J Natl Cancer Inst* 1963;30:289–312.
26. Matakidou A, Eisen T, Houlston RS. Systematic review of the relationship between family history and lung cancer risk. *Br J Cancer* 2005;93:825–833.
27. Silverman EK, Chapman HA, Drazen JM, Weiss ST, Rosner B, Campbell EJ, O'Donnell WJ, Reilly JJ, Ginns L, Mentzer S, *et al*. Genetic epidemiology of severe, early-onset chronic obstructive pulmonary disease. Risk to relatives for airflow obstruction and chronic bronchitis. *Am J Respir Crit Care Med* 1998;157:1770–1778.
28. Cohen BH, Diamond EL, Graves CG, Kreiss P, Levy DA, Menkes HA, Permutt S, Quaskey S, Tockman MS. A common familial component in lung cancer and chronic obstructive pulmonary disease. *Lancet* 1977;2:523–526.
29. Wu AH, Yu MC, Thomas DC, Pike MC, Henderson BE. Personal and family history of lung disease as risk factors for adenocarcinoma of the lung. *Cancer Res* 1988;48:7279–7284.
30. Bailey-Wilson JE, Amos CI, Pinney SM, Petersen GM, de Andrade M, Wiest JS, Fain P, Schwartz AG, You M, Franklin W, *et al*. A major lung cancer susceptibility locus maps to chromosome 6q23–25. *Am J Hum Genet* 2004;75:460–474.
31. Joost O, Wilk JB, Cupples LA, Harmon M, Shearman AM, Baldwin CT, O'Connor GT, Myers RH, Gottlieb DJ. Genetic loci influencing lung function: a genome-wide scan in the Framingham Study. *Am J Respir Crit Care Med* 2002;165:795–799.
32. Wilk JB, DeStefano AL, Joost O, Myers RH, Cupples LA, Slater K, Atwood LD, Heard-Costa NL, Herbert A, O'Connor GT, *et al*. Linkage and association with pulmonary function measures on chromosome 6q27 in the Framingham Heart Study. *Hum Mol Genet* 2003; 12:2745–2751.
33. Amos CI, Pinney SM, Li Y, Kupert E, Lee J, de Andrade MA, Yang P, Schwartz AG, Fain PR, Gazdar A, *et al*. A susceptibility locus on chromosome 6q greatly increases lung cancer risk among light and never smokers. *Cancer Res* 2010;70:2359–2367.
34. You M, Wang D, Liu P, Vikis H, James M, Lu Y, Wang Y, Wang M, Chen Q, Jia D, *et al*. Fine mapping of chromosome 6q23–25 region in familial lung cancer families reveals RGS17 as a likely candidate gene. *Clin Cancer Res* 2009;15:2666–2674.
35. DeMeo DL, Celedon JC, Lange C, Reilly JJ, Chapman HA, Sylvia JS, Speizer FE, Weiss ST, Silverman EK. Genome-wide linkage of forced mid-expiratory flow in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2004;170:1294–1301.
36. Silverman EK, Mosley JD, Palmer LJ, Barth M, Senter JM, Brown A, Drazen JM, Kwiatkowski DJ, Chapman HA, Campbell EJ, *et al*. Genome-wide linkage analysis of severe, early-onset chronic obstructive pulmonary disease: airflow obstruction and chronic bronchitis phenotypes. *Hum Mol Genet* 2002;11:623–632.
37. Palmer LJ, Celedon JC, Chapman HA, Speizer FE, Weiss ST, Silverman EK. Genome-wide linkage analysis of bronchodilator responsiveness and post-bronchodilator spirometric phenotypes in chronic obstructive pulmonary disease. *Hum Mol Genet* 2003;12:1199–1210.
38. Masri FA, Comhair SA, Koeck T, Xu W, Janocha A, Ghosh S, Dweik RA, Golish J, Kinter M, Stuehr DJ, *et al*. Abnormalities in nitric oxide and its derivatives in lung cancer. *Am J Respir Crit Care Med* 2005; 172:597–605.
39. Yoshida T, Tuder RM. Pathobiology of cigarette smoke-induced chronic obstructive pulmonary disease. *Physiol Rev* 2007;87:1047–1082.
40. Macnee W. Pathogenesis of chronic obstructive pulmonary disease. *Clin Chest Med* 2007;28:479–513, v.
41. Schwartz AG, Prysak GM, Bock CH, Cote ML. The molecular epidemiology of lung cancer. *Carcinogenesis* 2006;28:507–518.
42. Schwartz AG, Ruckdeschel JC. Familial lung cancer: genetic susceptibility and relationship to chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2006;173:16–22.
43. Engels EA, Wu X, Gu J, Dong Q, Liu J, Spitz MR. Systematic evaluation of genetic variants in the inflammation pathway and risk of lung cancer. *Cancer Res* 2007;67:6520–6527.
44. Molfino NA. Current thinking on genetics of chronic obstructive pulmonary disease. *Curr Opin Pulm Med* 2007;13:107–113.
45. Smolonska J, Wijmenga C, Postma DS, Boezen HM. Meta-analyses on suspected chronic obstructive pulmonary disease genes: a summary of 20 years' research. *Am J Respir Crit Care Med* 2009;180:618–631.
46. Vogel U, Christensen J, Wallin H, Friis S, Nexo BA, Raaschou-Nielsen O, Overvad K, Tjonneland A. Polymorphisms in genes involved in the inflammatory response and interaction with NSAID use or smoking in relation to lung cancer risk in a prospective study. *Mutat Res* 2008;639: 89–100.
47. Campa D, Zienolddiny S, Maggini V, Skaug V, Haugen A, Canzian F. Association of a common polymorphism in the cyclooxygenase 2 gene with risk of non-small cell lung cancer. *Carcinogenesis* 2004;25:229–235.
48. Zienolddiny S, Ryberg D, Maggini V, Skaug V, Canzian F, Haugen A. Polymorphisms of the interleukin-1 beta gene are associated with increased risk of non-small cell lung cancer. *Int J Cancer* 2004;109: 353–356.
49. Shih CM, Lee YL, Chiou HL, Chen W, Chang GC, Chou MC, Lin LY. Association of TNF-alpha polymorphism with susceptibility to and severity of non-small cell lung cancer. *Lung Cancer* 2006;52:15–20.
50. Shih CM, Lee YL, Chiou HL, Hsu WF, Chen WE, Chou MC, Lin LY. The involvement of genetic polymorphism of IL-10 promoter in non-small cell lung cancer. *Lung Cancer* 2005;50:291–297.
51. Lind H, Zienolddiny S, Ryberg D, Skaug V, Phillips DH, Haugen A. Interleukin 1 receptor antagonist gene polymorphism and risk of lung cancer: a possible interaction with polymorphisms in the interleukin 1 beta gene. *Lung Cancer* 2005;50:285–290.
52. Hu Z, Shao M, Chen Y, Zhou J, Qian J, Xu L, Ma H, Wang X, Xu Y, Lu D, *et al*. Allele 2 of the interleukin-1 receptor antagonist gene (IL1RN*2) is associated with a decreased risk of primary lung cancer. *Cancer Lett* 2006;236:269–275.
53. Landvik NE, Hart K, Skaug V, Stangeland LB, Haugen A, Zienolddiny S. A specific interleukin-1B haplotype correlates with high levels of

IL1B mRNA in the lung and increased risk of non-small cell lung cancer. *Carcinogenesis* 2009;30:1186–1192.
54. Van Dyke AL, Cote ML, Wenzlaff AS, Chen W, Abrams J, Land S, Giroux CN, Schwartz AG. Cytokine and cytokine receptor single-nucleotide polymorphisms predict risk for non-small cell lung cancer among women. *Cancer Epidemiol Biomarkers Prev* 2009;18:1829–1840.
55. Lee JM, Yanagawa J, Peebles KA, Sharma S, Mao JT, Dubinett SM. Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. *Crit Rev Oncol Hematol* 2008;66: 208–217.
56. Matheson MC, Ellis JA, Raven J, Walters EH, Abramson MJ. Association of IL8, CXCR2 and TNF-alpha polymorphisms and airway disease. *J Hum Genet* 2006;51:196–203.
57. He JQ, Burkett K, Connett JE, Anthonisen NR, Pare PD, Sandford AJ. Interferon gamma polymorphisms and their interaction with smoking are associated with lung function. *Hum Genet* 2006;119:365–375.
58. Sadeghnejad A, Meyers DA, Bottai M, Sterling DA, Bleecker ER, Ohar JA. IL13 promoter polymorphism 1112C/T modulates the adverse effect of tobacco smoking on lung function. *Am J Respir Crit Care Med* 2007;176:748–752.
59. Pillai SG, Ge D, Zhu G, Kong X, Shianna KV, Need AC, Feng S, Hersh CP, Bakke P, Gulsvik A, *et al*. A genome-wide association study in chronic obstructive pulmonary disease (COPD): identification of two major susceptibility loci. *PLoS Genet* 2009;5:e1000421.
60. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, Mukeria A, Szeszenia-Dabrowska N, Lissowska J, Rudnai P, *et al*. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. *Nature* 2008;452:633–637.
61. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, Manolescu A, Thorleifsson G, Stefansson H, Ingason A, *et al*. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. *Nature* 2008;452:638–642.
62. Liu P, Vikis HG, Wang D, Lu Y, Wang Y, Schwartz AG, Pinney SM, Yang P, de Andrade M, Petersen GM, *et al*. Familial aggregation of common sequence variants on 15q24–25.1 in lung cancer. *J Natl Cancer Inst* 2008;100:1326–1330.
63. Spitz MR, Amos CI, Dong Q, Lin J, Wu X. The CHRNA5–A3 region on chromosome 15q24–25.1 is a risk factor both for nicotine dependence and for lung cancer. *J Natl Cancer Inst* 2008;100:1552–1556.
64. Wang Y, Broderick P, Webb E, Wu X, Vijayakrishnan J, Matakidou A, Qureshi M, Dong Q, Gu X, Chen WV, *et al*. Common 5p15.33 and 6p21.33 variants influence lung cancer risk. *Nat Genet* 2008;40:1407–1409.
65. Amos CI, Wu X, Broderick P, Gorlov IP, Gu J, Eisen T, Dong Q, Zhang Q, Gu X, Vijayakrishnan J, *et al*. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. *Nat Genet* 2008;40:616–622.
66. Lambrechts D, Buysschaert I, Zanen P, Coolen J, Lays N, Cuppens H, Groen HJ, Dewever W, van Klaveren RJ, Verschakelen J, *et al*. The 15q24/25 susceptibility variant for lung cancer and chronic obstructive pulmonary disease is associated with emphysema. *Am J Respir Crit Care Med* 2010;181:486–493.
67. Saccone NL, Culverhouse RC, Schwantes-An TH, Cannon DS, Chen X, Cichon S, Giegling I, Han S, Han Y, Keskitalo-Vuokko K, *et al*. Multiple independent loci at chromosome 15q25.1 affect smoking quantity: a meta-analysis and comparison with lung cancer and COPD. *PLoS Genet* 2010;6.
68. Thorgeirsson TE, Gudbjartsson DF, Surakka I, Vink JM, Amin N, Geller F, Sulem P, Rafnar T, Esko T, Walter S, *et al*. Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. *Nat Genet* 2010;42:448–453.
69. Broderick P, Wang Y, Vijayakrishnan J, Matakidou A, Spitz MR, Eisen T, Amos CI, Houlston RS. Deciphering the impact of common genetic variation on lung cancer risk: a genome-wide association study. *Cancer Res* 2009;69:6633–6641.
70. Yoon KA, Park JH, Han J, Park S, Lee GK, Han JY, Zo JI, Kim J, Lee JE, Takahashi A, *et al*. A genome-wide association study reveals susceptibility variants for non-small cell lung cancer in the Korean population. *Hum Mol Genet* 2010;19:4948–4954.
71. Rafnar T, Sulem P, Besenbacher S, Gudbjartsson DF, Zanon C, Gudmundsson J, Stacey SN, Kostic JP, Thorgeirsson TE, Thorleifsson G, *et al*. Genome-wide significant association between a sequence variant at 15q15.2 and lung cancer risk. *Cancer Res* 2011;71:1356–1361.
72. Wilk JB, Walter RE, Laramie JM, Gottlieb DJ, O'Connor GT. Framingham Heart Study genome-wide association: results for pulmonary function measures. *BMC Med Genet* 2007;8:S8.
73. Repapi E, Sayers I, Wain LV, Burton PR, Johnson T, Obeidat M, Zhao JH, Ramasamy A, Zhai G, Vitart V, *et al*. Genome-wide association study identifies five loci associated with lung function. *Nat Genet* 2010; 42:36–44.
74. Hancock DB, Eijgelsheim M, Wilk JB, Gharib SA, Loehr LR, Marciante KD, Franceschini N, van Durme YM, Chen TH, Barr RG, *et al*. Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function. *Nat Genet* 2010;42:45–52.
75. Wilk JB, Chen TH, Gottlieb DJ, Walter RE, Nagle MW, Brandler BJ, Myers RH, Borecki IB, Silverman EK, Weiss ST, *et al*. A genome-wide association study of pulmonary function measures in the Framingham Heart Study. *PLoS Genet* 2009;5:e1000429.
76. Young RP, Whittington CF, Hopkins RJ, Hay BA, Epton MJ, Black PN, Gamble GD. Chromosome 4q31 locus in COPD is also associated with lung cancer. *Eur Respir J* 2010;36:1375–1382.
77. Kong X, Cho MH, Anderson W, Coxson HO, Muller N, Washko G, Hoffman EA, Bakke P, Gulsvik A, Lomas DA, *et al*. Genome-wide association study identifies BICD1 as a susceptibility gene for emphysema. *Am J Respir Crit Care Med* 2011;183:43–49.
78. Young RP, Hopkins RJ, Whittington CF, Hay BA, Epton MJ, Gamble GD. Individual and cumulative effects of GWAS susceptibility loci in lung cancer: associations after sub-phenotyping for COPD. *PLoS ONE* 2011;6:e16476.
79. Chung CC, Ciampa J, Yeager M, Jacobs KB, Berndt SI, Hayes RB, Gonzalez-Bosquet J, Kraft P, Wacholder S, Orr N, *et al*. Fine mapping of a region of chromosome 11q13 reveals multiple independent loci associated with risk of prostate cancer. *Hum Mol Genet* 2011;20:2869–2878.
80. Manolio TA, Collins FS, Cox NJ, Goldstein DB, Hindorff LA, Hunter DJ, McCarthy MI, Ramos EM, Cardon LR, Chakravarti A, *et al*. Finding the missing heritability of complex diseases. *Nature* 2009;461: 747–753.
81. Jones S, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, Lin JC, Palmisano E, Brune K, Jaffee EM, *et al*. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009;324:217.
82. Wong MW, Nordfors C, Mossman D, Pecenpetelovska G, Avery-Kiejda KA, Talseth-Palmer B, Bowden NA, Scott RJ. BRIP1, PALB2, and RAD51C mutation analysis reveals their relative importance as genetic susceptibility factors for breast cancer. *Breast Cancer Res Treat* 2011;127:853–859.