# A *DRD1* Polymorphism Predisposes to Lung Cancer among those Exposed to Secondhand smoke during Childhood

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## Abstract

Lung cancer has a familial component which suggests a genetic contribution to its etiology. Given the strong evidence linking smoking with lung cancer, we studied miRNA-related loci in genes associated with smoking behavior. *CHRNA*, *CHRNB* gene families, *CYP2A6* and *DRD1* were mined for single nucleotide polymorphisms (SNPs) that fell within the seed region of miRNA binding sites and then tested for associations with risk in a three-stage validation approach. A 3'UTR SNP in *DRD1* (*Dopamine Receptor D1*) was associated with a lower risk of lung cancer among individuals exposed to secondhand smoke during childhood (OR: 0.69; 0.60, 0.79; *P*<0.0001). This relationship was evident in both ever (OR: 0.74; 0.62, 0.88; *P*=0.001) and never smokers (OR 0.61; 0.47, 0.79; *P*<0.0001), European American (OR: 0.65; 0.53, 0.80; *P*<0.0001) and African American (OR: 0.73; 0.62, 0.88; *P*=0.001) populations. While much remains undefined about the long-term risks associated with exposure to secondhand smoke and heterogeneity between individuals in regard to their susceptibility to the effects of secondhand smoke, our data show an interaction between a SNP in the 3'UTR of *DRD1* and exposure to secondhand smoke during childhood. Further work is needed to explore the mechanistic

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underpinnings of this SNP and the nature of the interaction between DRD1 and exposure to secondhand smoke during childhood.

## Introduction

Though lung cancer was once considered a rare disease it is now the leading cause of cancer-related deaths worldwide (1). Tobacco smoking is the main risk factor. The lifetime risk of developing lung cancer among smokers is approximately 16% in men, and 10% in women. These estimates are significantly lower for non-smokers; 0.2% and 0.4%, respectively. Exposure to environmental tobacco smoke is also a significant cause of lung cancer. The 2006 Report of the Surgeon General on *The Health Consequences of Involuntary Exposure to Tobacco Smoke* (2) concluded that there was sufficient evidence to infer a causal relationship between adult secondhand smoke (SHS) exposure and lung cancer incidence, while we and others have shown that exposure to SHS during childhood is associated with a higher risk of lung cancer in never smokers (3–5).

Apart from smoking, familial and segregation studies have shown that genetics also play a role in the etiology of lung cancer (6, 7). As not all smokers get lung cancer, it has been interesting to learn of several gene-environment interactions that modulate lung cancer risk. Among the most notable of these are a suite of polymorphisms in *CYP2A6*, the enzyme responsible for the metabolism of nicotine and other tobacco-specific carcinogens. *CYP2A6* single nucleotide polymorphisms (SNPs) that reduce the metabolism of nicotine have been associated with both smoking behavior and lung cancer incidence (8–10). In addition, several genome-wide association studies (GWAS) of lung cancer have identified a significant lung cancer susceptibility locus at cytoband 15q25, especially in early-onset smokers (9, 11, 12). SNPs in this region, which encodes subunits of the nicotinic acetylcholine receptors (nAChRs), have been shown to modulate the physiological response to nicotine, smoking behavior and lung carcinogenesis (13). nAChRs are activated both by endogenous neurotransmitters and exogenous agents such as nicotine, which stimulates acetylcholine receptors in the ventral tegmental area causing the release of dopamine into the nucleus accumbens. Dopamine then activates dopamine receptors to mediate reward, and thus reinforcing the effects of nicotine (14). Gene-environment interactions with indoor air pollution, exposure to SHS during adulthood and exposure to SHS during childhood have also been reported to modulate lung cancer risk (3, 15, 16). Since CYP2A6, nAChRs and dopamine mediate sensitivity to nicotine, we hypothesized that variants in these genes could modulate lung cancer susceptibility via primary or secondhand exposure. Specifically, we focused on the 3'UTR region of these genes as this area has not been extensively studied in the past, and SNPs in this region have strong potential to modulate miRNA binding and protein levels (17). In addition, global deregulation of miRNAs has been observed in lung cancer, while specific miRNAs have been demonstrated to function as both oncogenes and tumor suppressors (18). miR-21 and miR-155, for example, are key microRNAs associated with poor outcome in lung cancer (19). Our study included an initial test population and 2 validation cohorts. We found that the rs686 polymorphism in *DRD1*, is associated with risk of lung cancer in European Americans and African Americans and further identify a novel

gene-environment interaction between this variant with exposure to secondhand smoke during childhood.

## Materials and Methods

### Patients

**NCI-MD case-control study**—Patients with histologically confirmed non-small-cell lung cancer (NSCLC) were recruited from seven hospitals in the greater metropolitan area of Baltimore, MD. Population controls were identified from the Department of Motor Vehicles, MD, and frequency matched to cases by age, ethnicity and gender. Written informed consent was obtained from all participants and the study was approved by the Institutional Review Boards of the participating institutions. Inclusion criteria for this on-going case-control study have been previously described (20). Never smokers were defined as those who smoked <100 cigarettes over their lifetime. Former smokers were defined as those who reported quitting smoking 1 year before the date of interview. Ethnicity and exposure to secondhand smoke were self-reported. All participants included in this study, 665 cases and 774 population controls, self-reported their race to be either European American or African American; no individuals of Hispanic ancestry were included (Table 1 and Supplementary Table 1).

**Mayo Clinic Study**—Three hundred and twenty one controls and 323 cases were used, all of whom were never smokers (Table 1 and Supplementary Table 1). Written informed consent was obtained from all participants at each of the participating institutions. A detailed explanation of the recruitment process has been reported previously (21). The study included predominantly European American participants (623/625).

**EXHALE Study**—The Exploring Health, Ancestry, and Lung Epidemiology (EXHALE) study is a population-based case-control study. African American (AA) cases were identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS), a participant in the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program. AA controls were selected from volunteers, including friends of the cases, and through advertising. Controls were frequency matched to cases by 5-year age group, sex and self-reported ethnicity. This study has been described previously (22). In total, 442 AA controls and 394 AA cases were included (Table 1 and Supplementary Table 1).

### SNP Selection

SNPs in the 3' UTR of *CHRNA1, CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA8, CHRNA9, CHRNA10, CHRNB1, CHRNB2, CHRNB3, CHRNB5*, and *CYP2A6* were initially identified and then evaluated for potential positioning within the seed region of a miRNA binding site using three web-based tools; Patrocles (www.patrocles.org), PolymiRTS http://compbio.uthsc.edu/miRSNP/) and SNPInfo (http://snpinfo.niehs.nih.gov/) (Supplementary Figure 1). We excluded SNPs with a minor allele frequency <5% because of low statistical power. SNPs identified by 2 or more programs were included for further analysis. To increase the likelihood that we would select SNPs with biological function, i.e., SNPs that affect RNA structure and thus alter miRNA-mRNA binding, we used RNAHybrid

(http://bibiserv.techfak.uni-bielefeld.de/rnahybrid/) to compare thermodynamic models for ancestral and variant alleles (Supplementary Table 2). A SNP in *DRD1* (rs686) previously related to nicotine dependence and in the seed region of binding by miR-504 (23, 24) was also included and genotyped for this study. This filtering process resulted in 3 SNPs for downstream analysis; rs686, rs4809294, and rs2292975. A flowchart detailing the SNP selection process is outlined in Supplementary Figure 1. Genotyping methods are described in Supplementary Methods.

### Statistical Analysis

We estimated per-allele odds ratios (OR), 1df, using unconditional logistic regression with adjustment for potential confounding factors; current cigarette smoking status (ever/never), gender (male/female), age at diagnosis (continuous), exposure to secondhand smoke (SHS) during childhood (no/yes), exposure to SHS during adulthood (no/yes), and pack-years of cigarette smoking (continuous), unless otherwise stated. We assessed whether the effect of rs686 on lung cancer risk varied over strata of exposure to SHS during childhood (i.e., effect modification (25)) by adding a cross-product term to a logistic regression model adjusted for age, gender, cigarette smoking status, smoking exposure during childhood, smoking exposure during adulthood, and pack-years of smoking. To test whether these strata were significantly different, models with and without the cross-product term were compared using the likelihood ratio test.

To determine whether rs686 statistically interacted with childhood exposure to secondhand smoke, we tested for departure from additivity (26). Departure from additivity, or synergistic interaction, refers to a situation where the joint risk of rs686 and exposure to secondhand smoke during childhood are greater than would be expected from the joint risks of each factor (i.e., assuming independence). We tested for interaction with rs686 with reverse coding for the model given the inverse association with lung cancer risk (i.e., AA=1, AG/GG=no) and the need for the exposed group to be at higher risk in such models. (27) Four exposure groups were generated for the analysis; A = rs686 (AG/GG), exposure to secondhand smoke=no; B = rs686 (AG/GG), exposure to secondhand smoke=yes; C = rs686 (AA), exposure to secondhand smoke=no; D = rs686 (AA), exposure to secondhand smoke=yes. These groups were then compared in a single minimally adjusted (age, gender) logistic regression model and also a second fully-adjusted model (age, gender, smoking status, pack-years of smoking). The output of each of these models was used to estimate two interaction statistics: interaction contrast ratio (ICR) and attributable proportion (AP). When the ICR and AP $\neq$ 0, there is evidence for departure from additivity (synergistic interaction). ICR is the excess risk due to interaction relative to the risk without either exposure. AP is the proportion of disease attributable to interaction among individuals with both exposures (26).

Analyses were performed using STATA version 12 software (STATA Corp, College Station, TX). All statistical tests were two-sided.

## Results

Three SNPs in *DRD1CHRNA2* and *CHRNA9* were identified as potential miRNA-modulating SNPs and successfully genotyped in the NCI-MD European American population (n=316 controls, n=319 cases). The minor allele frequency for the three SNPs were as follows; rs686 (0.42), rs4809294 (0.05), rs2292975 (0.47). Of these, only rs686 was associated with lung cancer risk (OR: 0.72, 95% CI 0.56–0.93; *P* =0.011; n=316 controls, n=319 cases) (Supplementary Table 3). In an expanded analysis of the NCI-MD European American population (n=665 cases, 774 controls) (Table 1), we confirmed that the G allele of rs686 was associated with a lower risk of lung cancer after adjustment for age and gender (OR: 0.76, 95% CI 0.62–0.93; *P*=0.007). Since the effects of nicotine are mediated by dopamine release (14) and *DRD1* was previously associated with nicotine dependence (28), we reasoned that the relationship between DRD1 and lung cancer would be confounded by smoking. Although adjustment of the model for smoking status and pack-years of smoking altered the size of the risk estimate, it did not significantly modify the relationship between the SNP and lung cancer risk (OR: 0.70, 95% CI 0.55–0.88; *P*=0.002) (Table 2).

Our data indicated that the relationship between rs686 and lung cancer is independent of smoking behavior as an adult. To test this further, we analyzed a lung cancer case-control study of never smokers at Mayo Clinic (n=309 controls, n=319 cases). After adjustment for age and gender, we confirmed that the G allele rs686 was associated with lower risk of lung cancer (OR 0.77, 95% CI 0.62–0.97; *P* =0.027; n=628) (Table 2). As rs686 appeared to be independent of smoking behavior as an adult, we asked whether rs686 was associated with risk of lung cancer among those exposed to SHS during adulthood and childhood. Data on SHS exposure during both of these periods was collected in the NCI-MD study. When we stratified our results by SHS exposure during adulthood, we did not observe an interaction (Supplementary Table 4), however, when we stratified our data based on SHS during childhood, we found that the relationship between rs686 and lung cancer risk was only observed among those exposed during childhood (OR $_{(not\ exposed)}$ 0.84, 95% CI 0.51–1.39; *P*=0.510; n=284) (OR$_{(exposed)}$ 0.66, 95% CI 0.51–0.85; *P*=0.002; n=686) (model adjusted for age, gender, smoking status, pack-years of smoking and exposure to SHS during adulthood) (Table 2). We confirmed this result in the Mayo Clinic Study of never smokers (OR$_{(exposed)}$ 0.65, 95% CI 0.47–0.90; *P*=0.01; n=314) (OR$_{(not\ exposed)}$ 0.95, 95% CI 0.65–1.32; *P*=0.777; n=325) (model adjusted for age, gender and exposure to SHS during adulthood) (Table 2). These data suggest that the relationship between rs686 and lung cancer risk is restricted to those exposed to SHS during childhood. The main effects of SHS exposure during childhood or adulthood and active smoking for all studies are shown in Supplementary Table 5. The relationship between the other two SNPs analyzed in this study with lung cancer, stratified by exposure to SHS during childhood are presented in Supplementary Table 6.

The allele frequency of rs686 varies significantly across geographic regions. The ancestral allele, G, is highest among African populations. It decreases in European populations and is almost completely lost in Asian populations. We therefore asked whether the association between rs686, lung cancer risk and exposure to secondhand smoke during childhood is also found in populations of African descent. The NCI-MD case control study is an ongoing

study that also recruits African Americans. We initially genotyped rs686 in a relatively small sample set comprising 314 controls and 253 cases (size limited by sample availability). Although we did not observe a significant association (Table 2), the direction of the observation was the same as that observed in European Americans smokers ($OR_{(exposed)}$ 0.75, 95% CI 0.53–1.06; $P$=0.107, n=402) ($OR_{(not\ exposed)}$ 1.13, 95% CI 0.64–2.00; $P$=0.664; n=165) (model adjusted for age, gender and exposure to SHS during adulthood) (Table 2). We therefore leveraged a larger sample of AAs from the EXHALE study at Wayne State University that had greater power. In this analysis, we again validated the association between rs686-G with lung cancer risk only among individuals exposed to secondhand smoke during childhood ($OR_{(not\ exposed)}$ 1.28, 95% CI 0.87–1.87; $P$=0.214; n=286) ($OR_{(exposed)}$ 0.74, 95% CI 0.57–0.96; $P$=0.025; n=550) (model adjusted for age, gender, smoking status, pack-years of smoking and exposure to SHS during adulthood). Collectively, these results show that rs686-G is associated with a lower risk of lung cancer in both AAs and EAs, never smokers and ever smokers, and that the relationship is only evident among individuals exposed to SHS during childhood.

Since rs686 appeared to be associated with lung cancer risk only among those exposed to secondhand smoke during childhood, we tested whether there was a synergistic additive interaction (26) between rs686 and SHS exposure during childhood or whether the effect of rs686 was significantly modified by SHS exposure. As shown in Supplementary Table 7, we did not find evidence for synergistic interaction, however using a chi-squared test to assess heterogeneity in the odds ratios among those exposed and not exposed to SHS during childhood, we found statistical evidence that childhood exposure was an effect-modifier of the relationship between rs686 and lung cancer risk ($P$=0.002, n=2,919).

In a pooled analysis of the three studies (n=2,919), rs686-G was associated with a 29% decrease in lung cancer risk among those exposed to SHS during childhood ($OR_{(not\ exposed)}$ 1.01, 95% CI 0.83–1.24; $P$=0.891; n=952) ($OR_{(exposed)}$ 0.71, 95% CI 0.62–0.82; $P$<0.0001; n=1,945) (Table 3). The association remained significant after additional adjustment for age at smoking initiation ($OR_{(exposed)}$ 0.74, 95% CI 0.62–0.88; $P$=0.001; n=1,266). Among the pooled groups, the association between the SNP and risk of lung cancer among those exposed to SHS remained consistent among European Americans, African Americans, ever smokers, never smokers, males and females (Table 3). In support of the observation of risk among never smokers and ever smokers, we found that rs686 was associated with risk of both adenocarcinoma and squamous cell carcinoma (Table 4). Notably, this significant association was again only observed following stratification by exposure to secondhand tobacco smoke during childhood (Table 4).

## Discussion

In this three stage-candidate pathway analysis of miRNA-related SNPs, we asked whether SNPs that modulate miRNA binding in smoking-associated genes were associated with lung cancer risk. We acknowledge that not all 3'UTR SNPs will be miRNA-disrupting alleles, however we identified, and replicated, one such SNP, rs686 in *DRD1*.

A novel finding in our study is that the G allele of rs686 is associated with a lower risk of lung cancer among individuals exposed to SHS during childhood. Studies with data on SHS exposure, particularly during childhood, are rare. However, we were able to test, and validate, this key observation in three studies. The relationship was evident in both ever smokers and never smokers. While many susceptibility loci, such as the Chr15q24 locus are only found in smokers, some loci, such as the TERT locus (9, 11, 12, 29–31), are associated with risk of lung cancer in both never and ever smokers, suggesting that both diseases are likely to share some common molecular mechanisms. We also demonstrated cross-population convergence of the association as we replicated our observation in both AAs and EAs. We attempted to demonstrate further convergence in an Asian population but the frequency of the G allele is <2%. This SNP, or any *DRD1* SNPs, have not been identified in GWAS of lung cancer to our knowledge, which could question the strength of our findings. However, the key result in our study is the relationship between rs686 with exposure to SHS during childhood. As data regarding childhood exposure to SHS are not collected in many case control studies, or reported in GWAS of lung cancer, it likely explains why this association has not been uncovered previously.

If the statistical interaction between rs686 and childhood exposure to SHS reflects a biological interaction, then one might expect to see a stronger association among smokers, while if anything, the effect seems to be stronger in never smokers. However, since we did not observe an association between rs686 and SHS exposure as an adult, we speculate that exposure during childhood, a window of time during which there is a heightened sensitivity to both the acute and chronic toxic effects of environmental exposures (32, 33). Epidemiological and experimental studies show that this increased sensitivity translates to a differential effect on cancer risk and outcomes (33–36). Indeed, a recent Surgeon's General report concluded that children exposed to parental smoke have higher risk of lower respiratory tract illnesses (2) and studies of long-term exposures starting at different time points in the life-course have shown that the earlier the exposure is encountered, the greater the tumor incidence that ensues (37). Interestingly, several recent studies also point to a role for pre-natal and early-life exposures in the modulation of DRD1 expression and function later in life (38, 39). As to how the pathobiological memory of an early-life exposure is maintained into adult life is largely unknown, but epigenetic modifications are one possibility (40–42). Recent evidence shows that nicotine exposure acetylates the *DRD1* promoter and increases DRD1 expression (43), suggesting that the effect modification between *DRD1* and childhood exposure to SHS we observed could reflect a direct biological relationship

It was surprising to us to find that an allele previously associated with nicotine dependence (28, 44) was significantly associated with a lower risk of lung cancer. However, we did not find an association between the SNP and cigarettes per day in either the NCI-MD or Wayne State studies (Supplementary Figure 2). In addition, the observation that rs686 was associated with cancer risk in never smokers and in ever smokers after adjustments for smoking in terms of status, pack-years and age at smoking initiation, supports the contention that the association with lung cancer could be independent of, or in addition to, any relationship with cigarette smoking behavior as an adult. Our finding that the SNP is

associated with risk of both adenocarcinoma and squamous cell carcinoma, albeit only after stratification by exposure to secondhand tobacco as a child, further supports this argument.

It is possible that dopamine, or *DRD1*, has tumor suppressive functions (45, 46). However, as dopamine cannot cross the blood brain barrier logic suggests that the relationship is somehow mediated outside of the central nervous system. DRD1 is expressed peripherally and is associated with immune function (47–49). Indeed, some of the most interesting literature suggesting that the dopamine axis plays a role in cancer comes from epidemiological studies that highlight an inverse link between cancer incidence and neurological disorders, such as Parkinson's disease, schizophrenia and Alzheimer's disease. Among these patient groups, which are characterized at least in part by aberrant dopamine signaling (50), there are reduced rates of cancer, including lung cancer (51–54). Interestingly, increased rates of smoking and other risk factors have been described in these patient populations, despite their reduced rates of cancer (55). Two other recent studies also point to a potential tumor suppressive role of dopamine in cancer: A dopamine receptor antagonist was identified as a selective agent that eradicate cancer stem cells (56), and a drug repositioning approach identified tri-cyclic anti-depressants as selective agents for the treatment of small cell lung cancer (57). Both approaches employed unbiased screens for effective agents. If the relationship between dopamine and cancer is independent of smoking, as suggested by the results of this study, it is possible that one mechanism could involve T and B cell function, given the strong relationship between inflammation and lung cancer (58) and inflammation and dopamine (47, 48, 59). However, extended functional studies will be needed to address these possibilities and a potential role for *DRD1* as a tumor suppressor in lung cancer.

The rs686 polymorphism represents a base change in the non-coding 3'UTR region of *DRD1*. Work by Huang and colleagues suggests that rs686 disrupts miR-504 binding (24, 28) and results in allelic-specific expression of DRD1; however it is unclear how or where this interaction might take place in relation to lung cancer. It is possible that rs686 is a marker allele, as opposed to a causative allele. In this regard, the entire *DRD1* gene is contained in a haplotype block that places rs686 in close linkage disequilibrium with rs4532 in the 5'UTR of *DRD1*. The possibility that transcriptional regulation through this site is driving the interaction cannot be dismissed.

Our study has several strengths and limitations. We only focused on SNPs that modulated 3'UTR sites, and miRNAs are known to also bind to coding regions. In addition, the initial gene selection was based on a candidate approach including cytochrome p450, dopamine receptor and nicotinic acetylcholine receptor genes. As such, this is not an exhaustive study of the association between miRNA-modulating SNPs, smoking behavior-associated genes and lung cancer. However, we replicated our key findings in three studies, which strengthens the validity and interpretation of our results. Another limitation is the potential for recall bias regarding childhood exposures. However, as the exposure window in question in our study was during childhood, this was not possible. Of note however, previous studies of adult non-smokers and children comparing exposure biomarkers with self-reported data indicated that these exposure data are likely to be legitimate (60). In addition, the mean age at diagnosis was 65. Given that smoking prevalence rates among men and women in the

1950's to 1970's (i.e., the period when most of our population would have been children) ranged between 40% and 60%, this makes our data on childhood exposure consistent with these trends (54% of controls reported exposure to SHS during childhood). Moreover, the validation of our work in three studies further limits the likelihood that recall bias may have confounded our analysis. Finally, it is possible that the selection of controls from the Dept. of Motor Vehicles in the NCI-MD study could introduce a bias based on socioeconomic factors. The prevalence of SHS exposure can be higher among children living in poverty and among those whose parents had less than 12 years of education (61). Therefore, we also adjusted our model for education level, income at the time of diagnosis and income in 1980. These data were only available for the NCI-MD study; however, the adjustments did not alter the relationship between rs686 and risk of lung cancer ($OR_{(exposed)}$ 0.66, 95% CI 0.48–0.90; $P$=0.008) ($OR_{(not\ exposed)}$ 0.92, 95% CI 0.46–1.86; $P$=0.825).

While studying susceptibility variants can extend our understanding of the etiology of disease, it can also help to elucidate the underlying process of carcinogenesis and provide clues for cancer prevention and treatment. Previous epidemiological evidence linking various neurological disorders with lower rates of cancer, combined with our data linking *DRD1* with cancer, suggest that unraveling the connection between lung cancer and the dopamine pathway will lead to a new and significant impact on our understanding of lung carcinogenesis.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

## References

1. Ferlay, JSH.; Bray, F.; Forman, D.; Mathers, C.; Parkin, DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. 2010.

2. U.S. Department of Health and Human Services. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006.

3. Olivo-Marston SE, Yang P, Mechanic LE, Bowman ED, Pine SR, Loffredo CA, et al. Childhood exposure to secondhand smoke and functional mannose binding lectin polymorphisms are associated with increased lung cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009; 18:3375–3383.

4. Vineis P, Airoldi L, Veglia F, Olgiati L, Pastorelli R, Autrup H, et al. Environmental tobacco smoke and risk of respiratory cancer and chronic obstructive pulmonary disease in former smokers and never smokers in the EPIC prospective study. Bmj. 2005; 330:277. [PubMed: 15681570]

5. Janerich DT, Thompson WD, Varela LR, Greenwald P, Chorost S, Tucci C, et al. Lung cancer and exposure to tobacco smoke in the household. The New England journal of medicine. 1990; 323:632–636. [PubMed: 2385268]

6. Sellers TA, Chen PL, Potter JD, Bailey-Wilson JE, Rothschild H, Elston RC. Segregation analysis of smoking-associated malignancies: evidence for Mendelian inheritance. American journal of medical genetics. 1994; 52:308–314. [PubMed: 7810562]

7. Jonsson S, Thorsteinsdottir U, Gudbjartsson DF, Jonsson HH, Kristjansson K, Arnason S, et al. Familial risk of lung carcinoma in the Icelandic population. JAMA : the journal of the American Medical Association. 2004; 292:2977–2983.

8. Wassenaar CA, Dong Q, Wei Q, Amos CI, Spitz MR, Tyndale RF. Relationship between CYP2A6 and CHRNA5-CHRNA3-CHRNB4 variation and smoking behaviors and lung cancer risk. Journal of the National Cancer Institute. 2011; 103:1342–1346. [PubMed: 21747048]

9. Thorgeirsson TE, Geller F, Sulem P, Rafnar T, Wiste A, Magnusson KP, et al. A variant associated with nicotine dependence, lung cancer and peripheral arterial disease. Nature. 2008; 452:638–642. [PubMed: 18385739]

10. Tobacco, Genetics C. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. Nature genetics. 2010; 42:441–447. [PubMed: 20418890]

11. Hung RJ, McKay JD, Gaborieau V, Boffetta P, Hashibe M, Zaridze D, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature. 2008; 452:633–637. [PubMed: 18385738]

12. Amos CI, Wu X, Broderick P, Gorlov IP, Gu J, Eisen T, et al. Genome-wide association scan of tag SNPs identifies a susceptibility locus for lung cancer at 15q25.1. Nature genetics. 2008; 40:616–622. [PubMed: 18385676]

13. Caporaso N, Gu F, Chatterjee N, Sheng-Chih J, Yu K, Yeager M, et al. Genome-wide and candidate gene association study of cigarette smoking behaviors. PloS one. 2009; 4:e4653. [PubMed: 19247474]

14. Corrigall WA, Franklin KB, Coen KM, Clarke PB. The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology. 1992; 107:285–289. [PubMed: 1615127]

15. Spitz MR, Gorlov IP, Amos CI, Dong Q, Chen W, Etzel CJ, et al. Variants in inflammation genes are implicated in risk of lung cancer in never smokers exposed to second-hand smoke. Cancer discovery. 2011; 1:420–429. [PubMed: 22586632]

16. Li Y, Chang SC, Niu R, Liu L, Crabtree-Ide CR, Zhao B, et al. TP53 genetic polymorphisms, interactions with lifestyle factors and lung cancer risk: a case control study in a Chinese population. BMC cancer. 2013; 13:607. [PubMed: 24369748]

17. Ryan BM, Robles AI, Harris CC. Genetic variation in microRNA networks: the implications for cancer research. Nature reviews Cancer. 2010; 10:389–402.

18. Croce CM. Causes and consequences of microRNA dysregulation in cancer. Nature reviews Genetics. 2009; 10:704–714.

19. Vannini I, Fanini F, Fabbri M. MicroRNAs as lung cancer biomarkers and key players in lung carcinogenesis. Clinical biochemistry. 2013; 46:918–925. [PubMed: 23396164]

20. Zheng YL, Loffredo CA, Yu Z, Jones RT, Krasna MJ, Alberg AJ, et al. Bleomycin-induced chromosome breaks as a risk marker for lung cancer: a case-control study with population and hospital controls. Carcinogenesis. 2003; 24:269–274. [PubMed: 12584177]

21. Yang P, Allen MS, Aubry MC, Wampfler JA, Marks RS, Edell ES, et al. Clinical features of 5,628 primary lung cancer patients: experience at Mayo Clinic from 1997 to 2003. Chest. 2005; 128:452–462. [PubMed: 16002972]

22. Schwartz AG, Cote ML, Wenzlaff AS, Land S, Amos CI. Racial differences in the association between SNPs on 15q25.1, smoking behavior, and risk of non-small cell lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2009; 4:1195–1201.

23. Cichon S, Nothen MM, Erdmann J, Propping P. Detection of four polymorphic sites in the human dopamine D1 receptor gene (DRD1) . Human molecular genetics. 1994; 3:209. [PubMed: 8162032]

24. Huang W, Li MD. Differential allelic expression of dopamine D1 receptor gene (DRD1) is modulated by microRNA miR-504. Biological psychiatry. 2009; 65:702–705. [PubMed: 19135651]

25. VanderWeele TJ. On the distinction between interaction and effect modification. Epidemiology. 2009; 20:863–871. [PubMed: 19806059]

26. Skrondal A. Interaction as departure from additivity in case-control studies: a cautionary note. Am J Epidemiol. 2003; 158:251–258. [PubMed: 12882947]

27. Knol MJ, VanderWeele TJ, Groenwold RH, Klungel OH, Rovers MM, Grobbee DE. Estimating measures of interaction on an additive scale for preventive exposures. European journal of epidemiology. 2011; 26:433–438. [PubMed: 21344323]

28. Huang W, Ma JZ, Payne TJ, Beuten J, Dupont RT, Li MD. Significant association of DRD1 with nicotine dependence. Human genetics. 2008; 123:133–140. [PubMed: 18092181]

29. Hsiung CA, Lan Q, Hong YC, Chen CJ, Hosgood HD, Chang IS, et al. The 5p15.33 locus is associated with risk of lung adenocarcinoma in never-smoking females in Asia. PLoS genetics. 2010; 6

30. McKay JD, Hung RJ, Gaborieau V, Boffetta P, Chabrier A, Byrnes G, et al. Lung cancer susceptibility locus at 5p15.33. Nature genetics. 2008; 40:1404–1406. [PubMed: 18978790]

31. Lan Q, Hsiung CA, Matsuo K, Hong YC, Seow A, Wang Z, et al. Genome-wide association analysis identifies new lung cancer susceptibility loci in never-smoking women in Asia. Nature genetics. 2012; 44:1330–1335. [PubMed: 23143601]

32. Wild CP, Kleinjans J. Children and increased susceptibility to environmental carcinogens: evidence or empathy? Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2003; 12:1389–1394.

33. Balansky R, Ganchev G, Iltcheva M, Nikolov M, Steele VE, De Flora S. Differential carcinogenicity of cigarette smoke in mice exposed either transplacentally, early in life or in adulthood. International journal of cancer Journal international du cancer. 2012; 130:1001–1010. [PubMed: 21484788]

34. Smith AH, Marshall G, Yuan Y, Ferreccio C, Liaw J, von Ehrenstein O, et al. Increased mortality from lung cancer and bronchiectasis in young adults after exposure to arsenic in utero and in early childhood. Environmental health perspectives. 2006; 114:1293–1296. [PubMed: 16882542]

35. Korde LA, Wu AH, Fears T, Nomura AM, West DW, Kolonel LN, et al. Childhood soy intake and breast cancer risk in Asian American women. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2009; 18:1050–1059.

36. Miller DG. Cancer in Hiroshima: 35 years after the bomb. Medical and pediatric oncology. 1984; 12:224–227. [PubMed: 6727779]

37. Peto R, Gray R, Brantom P, Grasso P. Nitrosamine carcinogenesis in 5120 rodents: chronic administration of sixteen different concentrations of NDEA, NDMA, NPYR and NPIP in the water of 4440 inbred rats, with parallel studies on NDEA alone of the effect of age of starting (3, 6 or 20 weeks) and of species (rats, mice or hamsters). IARC scientific publications. 1984:627–665. [PubMed: 6533057]

38. Tobon KE, Kuzhikandathil EV. Preadolescent drd1-EGFP mice exhibit cocaine-induced behavioral sensitization. Neuroscience letters. 2014; 558:20–25. [PubMed: 24095672]

39. Sasaki A, Constantinof A, Pan P, Kupferschmidt DA, McGowan PO, Erb S. Cocaine exposure prior to pregnancy alters the psychomotor response to cocaine and transcriptional regulation of the dopamine D1 receptor in adult male offspring. Behavioural brain research. 2014; 265:163–170. [PubMed: 24583058]

40. Fry RC, Navasumrit P, Valiathan C, Svensson JP, Hogan BJ, Luo M, et al. Activation of inflammation/NF-kappaB signaling in infants born to arsenic-exposed mothers. PLoS genetics. 2007; 3:e207. [PubMed: 18039032]

41. Hughes LA, van den Brandt PA, de Bruine AP, Wouters KA, Hulsmans S, Spiertz A, et al. Early life exposure to famine and colorectal cancer risk: a role for epigenetic mechanisms. PloS one. 2009; 4:e7951. [PubMed: 19956740]

42. Breton CV, Byun HM, Wenten M, Pan F, Yang A, Gilliland FD. Prenatal tobacco smoke exposure affects global and gene-specific DNA methylation. American journal of respiratory and critical care medicine. 2009; 180:462–467. [PubMed: 19498054]

43. Gozen O, Balkan B, Yildirim E, Koylu EO, Pogun S. The epigenetic effect of nicotine on dopamine D1 receptor expression in rat prefrontal cortex. Synapse. 2013

44. Novak G, LeBlanc M, Zai C, Shaikh S, Renou J, DeLuca V, et al. Association of polymorphisms in the BDNF, DRD1 and DRD3 genes with tobacco smoking in schizophrenia. Annals of human genetics. 2010; 74:291–298. [PubMed: 20456319]

45. Asada M, Ebihara S, Numachi Y, Okazaki T, Yamanda S, Ikeda K, et al. Reduced tumor growth in a mouse model of schizophrenia, lacking the dopamine transporter. International journal of cancer Journal international du cancer. 2008; 123:511–518. [PubMed: 18470912]

46. Basu S, Dasgupta PS, Chowdhury JR. Enhanced tumor growth in brain dopamine-depleted mice following 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treatment. Journal of neuroimmunology. 1995; 60:1–8. [PubMed: 7642739]

47. Bergquist J, Tarkowski A, Ekman R, Ewing A. Discovery of endogenous catecholamines in lymphocytes and evidence for catecholamine regulation of lymphocyte function via an autocrine loop. Proceedings of the National Academy of Sciences of the United States of America. 1994; 91:12912–12916. [PubMed: 7809145]

48. Saha B, Mondal AC, Majumder J, Basu S, Dasgupta PS. Physiological concentrations of dopamine inhibit the proliferation and cytotoxicity of human CD4+ and CD8+ T cells in vitro: a receptor-mediated mechanism. Neuroimmunomodulation. 2001; 9:23–33. [PubMed: 11435749]

49. Basu S, Dasgupta PS, Lahiri T, Chowdhury JR. Uptake and biodistribution of dopamine in bone marrow, spleen and lymph nodes of normal and tumor bearing mice. Life sciences. 1993; 53:415–424. [PubMed: 8336520]

50. Karlsson P, Farde L, Halldin C, Sedvall G. PET study of D(1) dopamine receptor binding in neuroleptic-naive patients with schizophrenia. The American journal of psychiatry. 2002; 159:761–767. [PubMed: 11986129]

51. Hammond EC. Smoking in relation to the death rates of one million men and women. National Cancer Institute monograph. 1966; 19:127–204. [PubMed: 5905667]

52. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J. 1976; 2:1525–1536. [PubMed: 1009386]

53. Driver JA, Logroscino G, Buring JE, Gaziano JM, Kurth T. A prospective cohort study of cancer incidence following the diagnosis of Parkinson's disease. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007; 16:1260–1265.

54. Driver JA, Kurth T, Buring JE, Gaziano JM, Logroscino G. Prospective case-control study of nonfatal cancer preceding the diagnosis of Parkinson's disease. Cancer causes & control : CCC. 2007; 18:705–711. [PubMed: 17562193]

55. Baron JA. Cigarette smoking and Parkinson's disease. Neurology. 1986; 36:1490–1496. [PubMed: 3531917]

56. Sachlos E, Risueno RM, Laronde S, Shapovalova Z, Lee JH, Russell J, et al. Identification of drugs including a dopamine receptor antagonist that selectively target cancer stem cells. Cell. 2012; 149:1284–1297. [PubMed: 22632761]

57. Jahchan NS, Dudley JT, Mazur PK, Flores N, Yang D, Palmerton A, et al. A drug repositioning approach identifies tricyclic antidepressants as inhibitors of small cell lung cancer and other neuroendocrine tumors. Cancer discovery. 2013; 3:1364–1377. [PubMed: 24078773]

58. Hussain SP, Harris CC. Inflammation and cancer: an ancient link with novel potentials. International journal of cancer Journal international du cancer. 2007; 121:2373–2380. [PubMed: 17893866]

59. Saha B, Mondal AC, Basu S, Dasgupta PS. Circulating dopamine level, in lung carcinoma patients, inhibits proliferation and cytotoxicity of CD4+ and CD8+ T cells by D1 dopamine receptors: an in vitro analysis. International immunopharmacology. 2001; 1:1363–1374. [PubMed: 11460316]

60. Moritsugu KP. The 2006 Report of the Surgeon General: the health consequences of involuntary exposure to tobacco smoke. American journal of preventive medicine. 2007; 32:542–543. [PubMed: 17533072]

61. Overpeck MD, Moss AJ. Children's exposure to environmental cigarette smoke before and after birth. Health of our nation's children, United States, 1988. Advance data. 1991:1–11.

**Table 1**

Characteristics of cases and controls from three studies

| | NCI | | | | | Mayo Clinic | | | | | Wayne State | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Controls | % | Cases | % | P | Controls | % | Cases | % | P | Controls | % | Cases | % | P |
| Age (Mean ± SD) | 67.2 ± 8.2 | | 65.7 ± 10.4 | | **0.002** | 61.8 ± 13.2 | | 61.9 ± 13.2 | | **0.923** | 62.8 ± 10.4 | | 62.8 ± 10.3 | | **0.42** |
| Gender | | | | | 0.364 | | | | | 0.962 | | | | | 0.725 |
| Male | 398 | 51.4 | 326 | 49.0 | | 87 | 27.1 | 87 | 26.9 | | 210 | 47.5 | 192 | 48.7 | |
| Female | 376 | 48.6 | 339 | 51.0 | | 234 | 72.9 | 236 | 73.1 | | 232 | 52.5 | 202 | 51.3 | |
| Smoking Status | | | | | **<0.0001** | | | | | NA | | | | | **<0.0001** |
| Never | 322 | 41.7 | 77 | 11.8 | | 321 | 100 | 323 | 100 | | 146 | 33.0 | 19 | 4.80 | |
| Ever | 451 | 58.3 | 578 | 88.2 | | 0 | 0 | 0 | 0 | | 296 | 67.0 | 375 | 95.20 | |
| Race | | | | | 0.340 | | | | | 0.998 | | | | | NA |
| African American | 314 | 40.6 | 253 | 38.1 | | 1 | 0.3 | 1 | 0.3 | | 422 | 100 | 394 | 100 | |
| European American | 460 | 59.4 | 411 | 61.9 | | 311 | 99.7 | 312 | 99.7 | | 0 | 0 | 0 | 0 | |
| Packyrs (Mean ± SD) | 14.5 ± 21.0 | | 39.2 ± 29.5 | | **<0.0001** | | | | | | 18.2 ± 21.2 | | 37.1 ± 28.4 | | **<0.0001** |
| Childhood Exposure | | | | | **<0.0001** | | | | | 0.500 | | | | | **0.044** |
| No | 217 | 28.0 | 132 | 19.9 | | 166 | 52.2 | 159 | 49.5 | | 165 | 37.3 | 121 | 30.7 | |
| Yes | 557 | 72.0 | 532 | 80.1 | | 152 | 47.8 | 162 | 50.5 | | 277 | 62.7 | 273 | 69.3 | |
| Adulthood Exposure | | | | | **<0.0001** | | | | | **0.004** | | | | | 0.454 |
| No | 403 | 52.1 | 211 | 31.7 | | 139 | 43.7 | 105 | 32.7 | | 151 | 34.2 | 125 | 31.7 | |
| Yes | 371 | 47.9 | 545 | 68.3 | | 179 | 56.3 | 216 | 67.3 | | 291 | 65.8 | 269 | 68.3 | |
| Tumor Histology | | | | | | | | | | | | | | | |
| Adenocarcinoma | | | 309 | 51.8 | | | | 211 | 65.3 | | | | 134 | 34.0 | |
| Squamous | | | 157 | 26.3 | | | | 14 | 4.3 | | | | 110 | 27.9 | |
| Large Cell | | | 119 | 19.9 | | | | 19 | 5.9 | | | | 51 | 12.9 | |
| Other | | | 12 | 2.0 | | | | 79 | 24.5 | | | | 99 | 25.1 | |

SD denotes standard deviation

Numbers in subcategories might not add total due to missing data

**Table 2**

Association between rs686 and lung cancer risk stratified by exposure to secondhand smoke during childhood

| Gene | Un-stratified | | | | | | | Unexposed to SHS During Childhood | | | | | | | Exposed to SHS During Childhood | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Case | OR | LCI | - | UCI | P-value# | Control | Case | OR | LCI | - | UCI | P-value# | Control | Case | OR | LCI | - | UCI | P-value# |
| All | 1525 | 1378 | 0.76 | 0.64 | - | 0.9 | **0.002** | 548 | 412 | 0.92 | 0.76 | - | 1.12 | 0.405* | 986 | 967 | 0.69 | 0.60 | - | 0.79 | **<0.0001*** |
| NCI -EA* | 774 | 665 | 0.70 | 0.55 | - | 0.88 | **0.002** | 113 | 71 | 0.84 | 0.51 | - | 1.39 | 0.510* | 347 | 339 | 0.66 | 0.51 | - | 0.85 | **0.002*** |
| NCI -AA* | 314 | 253 | 0.83 | 0.62 | - | 1.11 | 0.209 | 104 | 61 | 1.13 | 0.64 | - | 2.00 | 0.664* | 210 | 192 | 0.75 | 0.53 | - | 1.06 | 0.107* |
| Mayo Clinic^ | 309 | 319 | 0.77 | 0.62 | - | 0.97 | **0.027** | 166 | 159 | 0.95 | 0.69 | - | 1.32 | 0.777^ | 152 | 162 | 0.65 | 0.47 | - | 0.90 | **0.01^** |
| Wayne State* | 442 | 394 | 0.89 | 0.72 | - | 1.1 | 0.268 | 165 | 121 | 1.28 | 0.87 | - | 1.87 | 0.214* | 277 | 273 | 0.74 | 0.57 | - | 0.96 | **0.025*** |

# Adjusted for age, gender (male vs female), smoking status (never/ever), pack-years of smoking

* Adjusted for age, gender (male vs female), smoking status (never/ever), secondhand adult smoking exposure (no/yes) & pack-years

^ Adjusted for age, gender (male vs female), smoking exposure as an adult

OR denotes odds ratio, 1df test, UCI, upper confidence limit, LCI, lower confidence limit

**Table 3**

Pooled analysis of the association between rs686 and lung cancer risk stratified by exposure to environmental tobacco smoke during childhood

| Gene | Unexposed to SHS During Childhood | | | | | | | Exposed to SHS During Childhood | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Control | Case | OR | LCI | - | UCI | P-value | Control | Case | OR | LCI | - | UCI | P-value |
| All[1] | 542 | 410 | 1.01 | 0.83 | - | 1.24 | 0.891 | 980 | 965 | 0.71 | 0.62 | - | 0.82 | <0.0001 |
| European American[2] | 269 | 223 | 0.90 | 0.68 | - | 1.18 | 0.449 | 488 | 493 | 0.65 | 0.53 | - | 0.80 | <0.0001 |
| African American[3] | 269 | 182 | 1.17 | 0.87 | - | 1.57 | 0.311 | 488 | 466 | 0.73 | 0.62 | - | 0.88 | 0.001 |
| Ever Smokers[4] | 202 | 219 | 1.17 | 0.86 | - | 1.57 | 0.311 | 545 | 733 | 0.74 | 0.62 | - | 0.88 | 0.001 |
| Never Smokers[5] | 340 | 190 | 0.91 | 0.69 | - | 1.21 | 0.513 | 434 | 223 | 0.61 | 0.47 | - | 0.79 | <0.0001 |
| Male[6] | 322 | 238 | 1.13 | 0.86 | - | 1.47 | 0.391 | 507 | 532 | 0.70 | 0.58 | - | 0.86 | <0.0001 |
| Female[6] | 220 | 172 | 0.87 | 0.63 | - | 1.19 | 0.381 | 473 | 433 | 0.71 | 0.58 | - | 0.87 | 0.001 |

[1] Adjusted for age, gender (male/female), race (AA/EA), study (NCI-MD/Mayo Clinic/Wayne State), smoking status (never/ever), smoking exposure as an adult and pack-years of smoking

[2] Adjusted for age, gender (male/female), smoking status (never/ever), study (NCI-MD/Mayo Clinic), smoking exposure as an adult and pack-years of smoking

[3] Adjusted for age, gender (male/female), smoking status (never/ever), study (NCI-MD/Wayne State), smoking exposure as an adult and pack-years of smoking

[4] Adjusted for age, gender (male/female), race (AA/EA), pack-years of smoking, study (NCI-MD/Mayo Clinic/Wayne State), secondhand smoking exposure as an adult and pack-years of smoking

[5] Adjusted for age, gender (male/female), race (AA/EA), study (NCI-MD/Mayo Clinic/Wayne State), secondhand smoking exposure as an adult

[6] Adjusted for age, race (AA/EA), smoking status (never/ever), study (NCI-MD/Mayo Clinic/Wayne State), smoking exposure as an adult and pack-years of smoking

OR denotes odds ratio, 1df test, UCI, upper confidence limit, LCI, lower confidence limit

**Table 4**

Association between rs686 and lung cancer risk stratified by histology

| | Adenocarcinoma | | | | | Squamous Cell Carcinoma | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Genotype | Odds Ratio | LCI | - | UCI | P-value | Odds Ratio | LCI | - | UCI | P-value |
| rs686 | 0.72 | 0.63 | - | 0.73 | **<0.0001** | 0.85 | 0.71 | - | 1.03 | 0.093 |

| | **Exposed to SHS During Childhood** | | | | | **Exposed to SHS During Childhood** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Odds Ratio | LCI | - | UCI | P-value | Odds Ratio | LCI | - | UCI | P-value |
| rs686 | 0.68 | 0.60 | - | 0.80 | **<0.0001** | 0.76 | 0.61 | - | 0.94 | **0.013** |

[a] Adjusted for age, gender (male vs female), smoking status (never/ever), smoking exposure as an adult and pack-years of smoking

SHS denotes secondhand smoke

OR denotes odds ratio, 1df test, UCI, upper confidence limit, LCI, lower confidence limit