NOS2A Polymorphisms and Incident Asthma

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Nitric oxide (NO) is involved in oxidative stress, anti-microbial activity and immunoregulation. The inducible form of NO synthase (iNOS, encoded by NOS2A) produces NO in response to pro-inflammatory cytokines and microbial products. As oxidative stress can affect both lung growth and asthma, we hypothesized that multiple variants of NOS2A locus are associated with incident asthma and lung function growth during adolescence.

We tested the asthma hypothesis in a cohort of 1,577 children who participated in the Children's Health Study and were asthma- and wheeze-free at study entry. Trained field staff collected information on asthma diagnosis and lung function during annual interview. We genotyped 31 SNPs around *NOS2A* using Illumina platform and fitted age- and sex- stratified Cox proportional hazard models using haplotypes for the promoter region(One well conserved haplotype block of 7 SNPs) and the coding region. Based on the haplotype analysis, we analyzed individual SNPs. SNPs were then tested for association with lung function growth(change in FEV_1 levels over 8 year period) in a larger cohort of children (N=2,158) to determine the concordance of association across phenotypes.

A global test of haplotypes in the promoter region block was associated with incident asthma (p-value=0.02). The most common haplotype(frequency=35%) was associated with an 80% increased asthma risk. In SNP based analysis, 5 of the 7 promoter SNPs were associated with 50% increased asthma risk (p-value<0.0006) and 28-33ml/year decline in FEV_1 (p-value<0.05) and the other 2 SNPs were associated with 30% reduction in asthma risk (p-value<0.05) and 28-40 ml/year increase in FEV_1 level (p-value<0.06).

We conclude that the genetic variants of the promoter region of NOS2A are associated with respiratory health outcomes in children. SNPs that are protective/risk factor for asthma are also associated with higher/lower lung function growth.

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Haplotypes in Arginase I and II Genes and Childhood Asthma

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Arginase (encoded by ARG1 [11.1Kb] and ARG2 [31.8Kb] genes which are located on different chromosomes) plays an important role in nitrosative stress by reducing the substrate for generating nitric oxide in epithelial and immune cells. In murine asthma models, increased expressions of these genes are observed, which has been correlated with airway remodeling. We hypothesized common haplotypes in these genes are associated with asthma, and the associations vary by susceptibility and environmental factors.

We used data from non-Hispanic and Hispanic white children who participated in the Children's Health Study (N=3,103). Lifetime asthma was defined by parental report of physician-diagnosed asthma at study entry. Haplotype-based approach was used to determine significance of the entire locus (including >15Kb promoter regions) for asthma. We genotyped 6 SNPs for ARG1 and 9 SNPs for ARG2 using Illumina platform. Logistic regression models were fitted to compute odds ratios (ORs) and 95% confidence intervals (CIs).

SNPs in ARG1 were in strong linkage disequilibrium (LD); however, ARG2 SNPs showed limited LD. The ARG1 locus was significantly associated with asthma ($p = 0.02$) but not the ARG2 locus. One ARG1 haplotype (frequency ~5%) was associated with 40% (95%CI: 0.4-0.9) reduced asthma risk. This association was stronger in children who lived in high ozone communities or had atopy (based on history of allergy and/or hay fever). One haplotype in ARG2 (frequency ~16%) was associated with increased asthma risk (OR = 1.3; 95% CI: 1.0-1.6). This association was stronger in boys and in children without a history of atopy. These associations did not vary by ethnicity.

These results suggest that common haplotypes in ARG1 and ARG2 loci are associated with early childhood asthma and these associations may vary by susceptibility factors and ambient ozone levels.

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Effect of EPHX2 Variant on Childhood Lung Function

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Epoxide hydrolases(EPHX) play an important role in the detoxification of intermediate products of oxidative phase 1 enzyme activity. EPHX1 has been studied in respect to its effect on lung function but not EPHX2. We hypothesize that genetic variation in the soluble epoxide hydrolase(encoded by EPHX2 gene) is associated with lung function growth.

In the Children's Health Study, children (mean age 10 years, N=2,108) were followed for 8 years with annual lung function measurement. Nineteen SNPs from EPHX2 locus were genotyped using an Illumina platform.A hierarchical regression mixed model was used to examine the relationship between these SNPs and the lung function(forced expiratory volume in 1st s(FEV1), forced vital capacity(FVC) and maximum midexpiratory flow rate(MMEF)) levels at age 18 and growth over a 8-year period. Principal component(PC) analysis was used to determine whether this locus had a significant impact on lung function, followed by single-SNP analysis.

PC analysis showed that the EPHX2 locus was associated with FEV1, FVC and MMEF at p-value 0.02 ,0.07and 0.18, respectively. Single-SNP analysis showed that 8 of the 19 SNPs had significant association with FEV1 growth(p-value:0.004-0.05) and level at age 18(p-value:0.0006-0.05). The variants of the SNPs were associated with a decline in growth over the 8 year period by 30 to 54 ml/s per year for FEV1 and lower level of FEV1 (-15 to -62ml/s) at age 18. The same 8 SNPs were also associated with decline in growth over the 8 year period by 46 to 56 ml per year for FVC and 59 to 99 ml/s for MMEF and lower level of FVC(-54 to -70 ml) and MMEF(-69 to -104ml/s) at age 18.

We conclude that EPHX2 may be an important locus associated with lung function development. Several variant alleles of EPHX2 showed detrimental effect on both lung function level at age 18 and lung function growth from age 10 to 18.

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Genetic Risk Factors for Accelerated Lung Function Decline over Time

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Objective: The measurement of forced expiratory volume in 1 second (FEV_1) and its decline over time are prognostic indicators of early chronic airflow obstruction resulting in various pulmonary and cardiovascular diseases. The aim of this study was to investigate whether genetic variants within genes encoding for cytokines may be associated with the age-related rate of FEV_1 decline. **Methods:** Single nucleotide polymorphisms (SNPs) in the TNFα, TGFβ1, IL-1β, IL-1RN, IL-13 and IL-8 genes were investigated in 374 active firefighters with at least five pulmonary function tests. Genotyping was done using polymerase chain reaction-restriction fragment length polymorphism and 5' nuclease real-time PCR assays. Rate of decline in FEV_1 was calculated for each subject by running a simple linear regression of FEV_1 over age. Multiple linear regression analyses adjusted for potential confounders were run to evaluate the association of specific genotypes with the rate of FEV_1 decline. **Results:** After adjusting for covariates, a protective effect was found between the presence of the TGFβ1 -509 TT genotype and rate of decline in FEV_1 (p=0.043). Carrying an A allele at TNFα -308 (p=0.010) and GG genotype at TNFα -238 (p=0.028) were associated with a more rapid rate of FEV_1 decline. The TNFα -308A/-238G haplotype was associated with more rapid decline as compared with the referent -308G/-238G haplotype (p=0.031). The IL-1RN +2018 TT genotype was associated with a steeper rate of decline (p=0.052). **Conclusions:** Inter-individual variability in progressive decline in FEV_1 may be explained in part by genetic variations within genes involved in inflammatory responses.

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Association between Genetic Variants in Leptin Receptor and Lung Function Decline in COPD

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Introduction: Leptin receptor, which is present in human lung tissue, has been shown to have increased expression in the airway sub-mucosa in COPD patients when compared with normal subjects and smokers. We examined the association of genetic variants in the leptin receptor (*LEPR*) gene with lung function decline in COPD.

Methods: DNA was isolated from 429 European Americans participating in the NHLBI Lung Health Study. Lung function was measured annually over five years, with mean annual decline in post-bronchodilator FEV_1 % predicted as outcome of interest. Single nucleotide polymorphisms (SNPs) in *LEPR* were genotyped using the Illumina™ platform. Analysis was performed in STATA and PLINK using a genetic additive model, adjusting for potential confounders (smoking, age, baseline FEV_1, airway responsiveness and change in body mass index).

Results: Participants were 65% male, with mean age of 49 years, and mean baseline FEV_1 of 2.81 L (79.2 % predicted). Genotype frequencies were in Hardy-Weinberg equilibrium. Twenty of 28 tested SNPs in *LEPR* were associated with mean annual decline of FEV_1 %predicted. For example, on average, addition of the variant G allele on marker rs1137100 improved mean changes in FEV_1 %predicted by 0.33 %/yr compared to the wildtype C allele (p=0.005). Haplotype analysis revealed multiple association signals that overlapped with single-SNP results.

Conclusions: Polymorphisms in *LEPR* are associated with lung function decline, supporting a role of the leptin receptor in COPD pathogenesis.

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CT Findings in Relation to Lung Function and Smoking Profile in MZ and DZ Twins

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Background

The main environmental risk factor for COPD is tobacco smoking but since only a subset of smokers develops the disease genetic factors are of great importance. In order to understand the interplay between gene-environment in COPD, twin cohorts provide an interesting opportunity due to their genetic homogeneity.

Material and methods

A sample of 392 monozygotic (MZ) and dizygotic (DZ) twins (193 complete pairs and 6 singletons) were selected from the Swedish Twin registry, and those with FEV1/FVC below 90% of predicted (n = 108, 23 complete pairs, 19 pairs with at least one sibling as smoker) underwent low dose thin slice computed tomography (CT) scans. CT images were analyzed using YACTA software and emphysema index % at -950 HU or RA were obtained. Within-pair differences in RA were compared for smoking concordant (n=14 pairs, both ever-smokers) and smoking discordant (n=5 pairs, one never-smoker and one ever-smoker) pairs.

Results

MZ twin pairs in both groups had differences compared to DZ twins in relation to mean within pair differences in RA, FEV1% predicted (table 1).

	Smoking Concordant		Smoking Discordant	
	MZ (n=8)	DZ (n=6)	MZ (n=4)	DZ (n=1)
Pack-years	-11.21	-12.14	-5.6	-15
FEV1%predicted	-2.3	6.1	-4.8	28.2
RA	-0.5	-1.1	-0.9	-5.5

Mean with-in pair differenes

Conclusions

The preliminary findings indicate the role of genetics in the development of the emphysematic component of COPD. We are currently carrying out an heritability analysis to further characterize smoking behavior and disease presentation in association with genetics.

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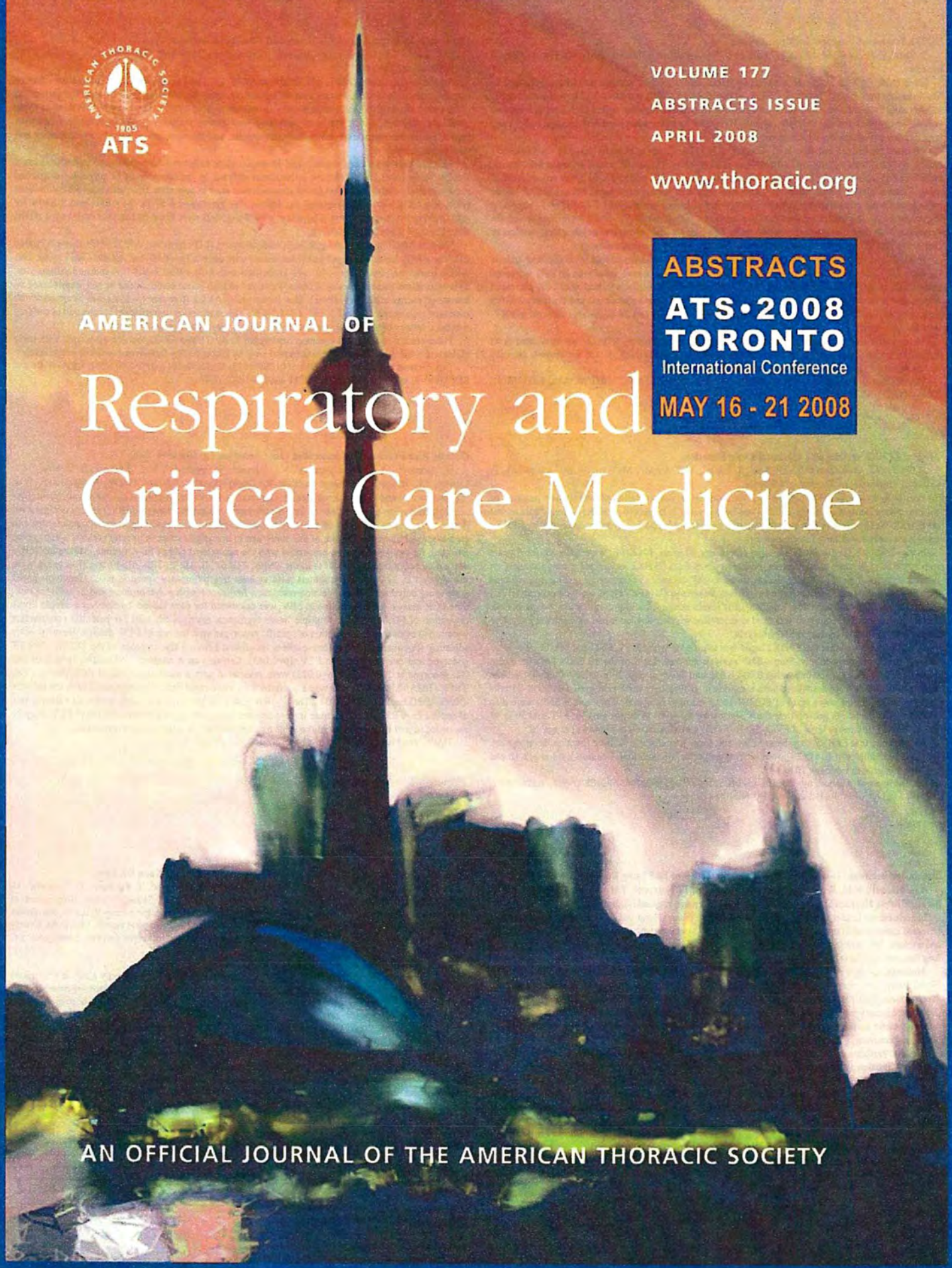

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