TNFα -308 Genotype and Ozone Effects on Asthma and Wheezing: Results from the Children's Health Study (CHS)

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RATIONALE: We investigated effects of tumor necrosis factor-α 308 (TNFα) on asthma and wheezing and determined whether ambient air pollutants modify effects of TNFα. METHODS: Risk factors, asthma and wheeze outcomes, TNFα genotype, and community air pollution levels were collected at entry from 2896 CHS participants. Logistic regression was used to estimate the effects of TNFα on the wheezing and physician-diagnosed asthma. We assessed modification of the TNFα associations with current asthma and wheezing with O_3, PM_{10}, $PM_{2.5}$, NO_2, and acids in a subset of 1123 fourth graders. RESULTS: The variant TNFα was associated with increased risk of asthma and wheezing. The effects of TNFα on wheezing outcomes were significantly larger in low than high O_3 communities (Table 1). There was no modification by the other air pollutants. CONCLUSIONS: TNFα-308 variant genotypes were associated with increased asthma and wheezing risk, and the effect on current wheezing decreased with increasing O_3 level.

Table 1. The effects of TNFα on wheezing outcomes in the lowest and highest ozone communities in the subgroup of CHS participants

Wheezing outcomes in the past 12 months	Lowest O_3 OR	Lowest O_3 (95% CI)	Highest O_3 OR	Highest O_3 (95% CI)
Wheeze with cold	2.2	(1.0,4.8)	0.8	(0.4,1.5)
Wheeze without cold *	3.6	(1.4,8.9)	0.6	(0.2,1.4)
Shortness of breath *	3.9	(1.5,10.5)	0.8	(0.3,2.0)
Awakened at night *	3.8	(1.2,11.8)	0.4	(0.1,1.3)
Wheeze with exercise *	3.6	(1.3,9.7)	0.6	(0.2,1.5)
Medication for wheeze *	3.7	(1.5,9.3)	0.7	(0.3,1.7)

* Significant interaction of TNFα and O_3 ($p < 0.05$)

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Antioxidant Supplementation and Generic Susceptibility to Ozone: A Randomized Controlled Trial of Children with Asthma

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Ozone is a powerful oxidant that has been shown to impair respiratory lung function in susceptible individuals. Genetic factors may influence variations between individuals in their response to O_3. We hypothesized that a deletion polymorphism which abolishes the activity of glutathione S-transferase M1 (GSTM1), a gene involved in response to oxidative stress, may be associated with susceptibility to ozone exposure. **Methods:** Using a PCR method, we genotyped 158 asthmatic children, residents of Mexico City who participated in a randomized double blind controlled trial of antioxidant vitamin supplementation. Children were followed through October 1998 to April 2000. **Results:** Among children assigned to the placebo group and with an homozygous deletion of the GSTM1 gene (GSTM1 null genotype), significant ozone-induced decrements in lung function were seen (-4.6% 95% CI -1.7% to -7.6% for FEF_{25-75} and -1.8% 95% CI - 0.11% to -3.4% for FEV_1 per 50 ppb of ozone 1-h maximum) but no decrement was observed among subjects with one or two copies of GSTM1 (GSTM1 [+] genotype). Among children who received the supplement, no significant changes in lung functions were observed in either GSTM1 null nor GSTM1 [+]. **Conclusion:** We conclude that asthmatic children with GSTM1 null genotype are more susceptible to ozone exposure and that supplementation with antioxidants might compensate for this genetic susceptibility by increasing the antioxidant defense mechanisms of these children.

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ICOS (inducible co-stimulator) is the newest member of the CD28 co-stimulatory super-family. The gene is located at 2q32-33 near the genes for CD28 and CTLA4 and near the region linked to increased IgE production, a key asthma phenotype. Unlike CD28 and CTLA-4, ICOS does not bind CD28/CTLA4 B7 ligands and is not involved in T-cell activation, but is induced after T-cell activation and stimulates T-cell proliferation. In addition, ICOS has been shown to promote the Th2 phenotype and induce the synthesis of IL4. In this study, the ICOS gene was sequenced in a subset of 96 individuals from four different asthma case/control populations, US Caucasians, African American, Hispanic, and Dutch Caucasians (16 affected and 8 unaffected per population), to identify polymorphisms. A total of 41 polymorphisms were identified in this study, 29 of which are novel. No coding polymorphisms were identified. Eleven frequent polymorphisms were tested for association with asthma phenotypes. Polymorphisms in intron1, intron 3, and in the 3' UTR were associated with BHR ($p<0.05$) in the US Caucasian, Dutch Caucasian, and Hispanic populations. In addition, polymorphisms in the promoter region, intron 3, and intron 4 were found to be associated with asthma susceptibility (case vs control, $p<0.05$) in US Caucasian, Dutch Caucasian, and African American populations. This data suggests that ICOS may have a functional role in asthma etiology.

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Investigations of Genetic Susceptibility to Asbestos-Related Diseases

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RATIONALE: The contributions that inherited differences in DNA sequence make to phenotypic variation, disease risk, and response to the environment have been hypothesized for many years. A promising approach to dissect these contributions is to systematically explore the common gene variants that may be associated with disease. Although asbestos-related diseases (ARD) are among the most well studied occupational diseases, relatively little is known about the host factors that may affect individual susceptibility. We are interested in the role of single nucleotide polymorphisms (SNPs) in these genes in the association between asbestos exposure and the development of ARD. Since 93% of genes contain a SNP, and 98% of genes are within 5 kilobases of a SNP, this approach provides a powerful tool for genetic analysis. METHODS: DNA was isolated from blood samples donated by Libby MT and Missoula MT residents (as exposed and control populations, respectively). The distribution of the constitutional deletion of glutathione S-transferase M1 gene (GSTM1) and SNP analysis of the GSTP1 and IL1B genes were completed. RESULTS: Constitutional deletion of GSTM1 was not significant. A statistically significant effect was found for the presence of the GSTP1*C allele ($F(1,88)=6.492$, $p=.013$). A statistically significant interaction was found between the presence of GSTP1*A and IL1B (+3952T) ($F(1,88)=7.301$, $p=.008$). In this interaction, the presence of a GSTP1*A allele removed any effect of IL1B (+3953T). CONCLUSIONS: We have successfully shown the effect of SNP interactions on the development of ARD. Further studies will be needed as asbestos-response genes are identified in other ongoing investigations.

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Association between a Promoter Polymorphism of the CD14 Gene and Airway Disease in Non-Atopic Farmers

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INTRODUCTION: CD14 is a pattern recognition receptor for LPS. Homozygotes with a C-to-T transition at base pair -159 from the major transcription start site for the CD14 gene are known to have significantly higher soluble CD14 levels than individuals with the CC and CT genotypes. Farmers are routinely exposed to large amounts of LPS. Non-atopic farmers can develop airway obstruction, for which LPS exposure is a risk factor. The mechanisms by which LPS has this effect are incompletely understood. **RATIONALE**: To determine if there is an association between the CD14 -159 polymorphism and airway disease in non-atopic farmers. **METHODS**: 98 non-atopic, never-smoker male farmers were chosen from the Keokuk Country Rural Health Study cohort in Iowa. Subjects completed a respiratory health questionnaire based on the ATS Epidemiology Standardization Project and performed spirometry. Genomic DNA was extracted from blood and screened for the CD14-159 C→T polymorphism. **RESULTS**: Obstruction was seen on spirometry in 20% and wheezing reported by 21% of subjects. There was an association between a C→T transition of the CD14 gene at the -159 position and wheezing ($p = .006$). Also, airway obstruction was more prevalent in these subjects ($p = .051$). **CONCLUSIONS**: The C→T transition in the promoter region of the CD14 gene at the -159 position was associated with non-atopic wheeze and airway obstruction. This polymorphism could be a risk factor for airway disease in farmers.

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Haplotypes of IL-4 Receptor and CD14 Genetic Polymorphisms Are Markers of Susceptibility for Diisocyanate Asthma

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Rationale. Diisocyanate asthma (DA) is associated with specific HLA-DQ alleles, glutathione-s-transferase and N-acetyltransferase genotypes. We evaluated polymorphisms for IL-4 receptor alpha (IL-4Rα), a common component of IL-4 and IL-13 receptors, IL-13, and CD14, a key constituent of the toll receptor complex. **Methods.** Studies were conducted in 18 workers with DA confirmed by inhalation challenge (DA+) and in 30 challenge negative (DA-) workers. Single nucleotide polymorphisms (snp) for IL-4Rα (Ile75Val, Glu400Ala, Glu 576 Arg or Q576R, Cys431Arg), IL-13 (R130Q) and CD14 (C159T) were analyzed to elucidate disease-associated genotypes. **Results.** No associations were detected between DA and individual alleles. However, combinations of snps in the IL-4Rα and CD14 genes were found to be significantly associated with DA. The frequency of the IC haplotype (shared between I75V and C159T) was 0.44 in DA + workers vs. 0.23 among DA- subjects ($p=0.04$). The QC haplotype frequency (Q576R, C159T) of 0.667 in the DA + group was more frequent (0.425) than in the DA- groups ($p=0.03$). Furthermore, the frequency of IQC haplotype (I75V, Q576R, C159T) was 0.44 in DA + workers vs. 0.217 in the DA - group ($p=0.04$). **Conclusions.** The IC, QC and IQC haplotypes are significantly associated with the DA phenotype. Although the functional significance of these findings is uncertain, these haplotypes could be susceptibility markers for DA and may be useful aids in the diagnosis of DA.

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