Association of *IL18* and *IL18R1* Polymorphisms with Coal Workers' Pneumoconiosis

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We tested the hypothesis that functional polymorphisms in the pro-inflammatory interleukin-18 gene (*IL18*) and its receptor (*IL18R1*) contribute to the pathogenesis of [illegible] inflammatory lung disease.

[illegible] ore and CWP prevalence with *IL18* C-[illegible] polymorphisms were studied in 200 [illegible] and 1999) from the Lorraine Bassin [illegible] rent) was assessed by job history and [illegible] 990 and 1994 and standardized chest [illegible] conducted considering each polymorphism separately, and by haplotype.

All genotype distributions fit predictions for Hardy-Weinberg equilibrium. *IL18* –137, +113 and +127 genotypes were in complete linkage disequilibrium. *IL18* –137 C allele associated with lower 1994 CT score (1.57 *vs.* 2.46, C carriers *vs.* others, P = 0.03), lower increase in CT score between 1990 and 1994 (0.32 *vs.* 0.77, P = 0.03) and lower 1999 CWP prevalence (OR = 0.36 [0.15 – 0.88], P = 0.02). Adjustment for coal dust exposure and stratification on *IL18R1* genotype did not change the results. Haplotype -607A/-137C/+113G/+127T (13.5%) associated with lower 1994 CT score (difference (d) = -0.51 95% CI [-1.06 – +0.02], P = 0.06), lower increase in CT score between 1990 and 1994 (d = -0.29 [-0.57 – +0.0005], P = 0.05), and lower 1999 CWP prevalence (OR = 0.50 [0.25 – 0.99] P < 0.05) as compared to haplotype CGTC (58.0%). No association was found with haplotype AGTC (28.5%).

Results support the hypothesis that *IL18* and *IL18R1* contribute significantly to the development of CWP.

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Glutathione S-Transferase Mu 1 Polymorphism and Asbestos-Related Lung Disease

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Rationale: Cases of asbestos related disease (ARD) continue to increase around the world. Disease rates are variable with similar exposures suggesting genetic susceptibility contributes to disease risk. The pulmonary response to asbestos appears to involve pathways of oxidative damage leading to fibrosis and cancer. Glutathione S-transferases (GST) are important modifiers of oxidative stress and demonstrate significant genetic variation in expression in humans.

Methods: The 220 study subjects were selected from a subset of the Beta-Carotene and Retinol Efficacy Trail (CARET) cohort based upon the availability of polymorphism data, spirometry, lung cancer endpoint and chest x-ray data. The 220 subjects were divided into 2 groups based on GSTM1 gene presence or deletion and compared by baseline CARET ILO scores and spirometry. Pulmonary fibrosis was defined by ILO opacity profusion category on chest radiographs ≥1/0, or spirometric evidence of restrictive disease. A secondary analysis evaluated GSTM-1 deletion and lung cancer.

Results: No statistically significant association between the GSTM1 deletion and the presence of pulmonary fibrosis, ILO score ≥1/0, or restrictive or mixed pattern on spirometry was found after adjusting for age, smoking, years of asbestos exposure, and years in high risk trade. The sample lacked sufficient power to determine a difference less than a relative risk of 2 for this endpoint. For lung cancer, the odds-ratio was 1.92 (95% CI 1.11-3.32, p= 0.02) for GSTM1 deletion.

Conclusions: This study demonstrated an association between GSTM1 gene deletion and lung cancer in asbestos exposed workers. No relationship was seen between this deletion and pulmonary fibrosis endpoints though a small risk may have been missed.

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The CD14/-159 T Allele Is Associated with Sensitization to Laboratory Animals in Research Scientists and Technicians Who Work with Animals

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RATIONALE: The CD14/-159 C allele is associated with an increased number of positive prick skin tests and asthma, while T alleles are associated with increased IgE and airflow limitation in endotoxin-exposed workers. We analyzed the distribution of the CD14/-159 alleles in a group of laboratory animal (LA) workers characterized by LA sensitization and symptoms. We hypothesized that the CD14/-159 T allele contributes to risk for sensitization and/or symptoms in research scientists and technicians exposed to workplace allergen and endotoxin. **METHODS**: We evaluated 90 LA workers by questionnaire and prick skin testing or RAST to common laboratory research animals, including mouse, rat, rabbit, hamster and guinea pig allergens. CD14/-159 T and C alleles were determined by SSP-PCR. Workers were grouped by presence/absence of LA sensitization and presence/absence of LA symptoms. The distribution of the CD14/-159 alleles was examined in Caucasians (n=76) and in the entire cohort by chi square analysis. **RESULTS**: 37% of LA workers were allergic to one or more LA. In Caucasians, the T allele was present in 57% of those not allergic to LA, and in 80% of those with LA allergy, p=0.04. Results were similar in the entire cohort, p=0.04. We found no association between CD14/-159 alleles and LA symptoms. **CONCLUSIONS**: The CD14/-159 T allele is associated with LA sensitization of workers in environments containing airborne endotoxin and animal allergen. This suggests a possible role for endotoxin in LA sensitization.

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Cytokine Gene Polymorphisms and Rate of Decline in Lung Function in Firefighters

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Rationale: Specific genotypes of cytokine genes (such as IL-1, TGFβ and TNFα) have been associated with chronic obstructive lung disease and a rapid decline of lung function. Based on this, the influence of genetic variations in cytokine genes, which may modify the coded protein levels and/or activity, on the risk of rapid decline in lung function in firefighters was investigated. **Methods:** IL-1β +3953, TGFβ -509, TNFα -308 and TNFα -238 single nucleotide polymorphisms were examined in 445 firefighters recruited during their annual medical surveillance examinations and assessed for associations between genotypes and longitudinal rate of decline in lung function measured by prior annual medical surveillance including FVC and FEV_1. **Results:** The presence of IL-1β +3953 and TNFα -238 variants were found to be associated with the rate of decline in lung function ($p<0.05$) as measured by FEV_1. **Conclusion:** These data suggest that IL-1β +3953 and TNFα -238 variants may influence individual susceptibility for accelerated decline in lung function in firefighters.

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Macrophage Migration Inhibitory Factor Gene Polymorphisms and the Development of Coal Workers' Pneumoconiosis (CWP)

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Background: Coal worker's pneumoconiosis (CWP) is an occupational lu disease characterized by fibrotic nodular lesion resulting from inhalation of occup tional dusts including coal and crystalline silica. Inter-individual variation in lu responses to the same amount of dust exposure suggests the genetic influence on t development of CWP. Macrophage migration inhibitory factor (MIF) is one of the pr inflammatory cytokine and regulates the function of macrophages. It is also report to facilitate granulomatous inflammation and to activate fibroblasts. MIF ge promoter -173G/C polymorphisms are associated with increased production of M and have been found to confer increased risk of susceptibility to chronic inflammatc diseases. In this study, we investigated whether -173G/C polymorphism of the M gene is associated with susceptibility to CWP.

Subjects and Methods: 215 patients with CWP who had heavy and similar d exposure history, and 157 non-exposed regional controls were studied. According the ILO classification, patients with CWP were divided into two groups, nodular C (n=134) and PMF (4C, n=81). MIF gene promoter -173 G/C genotypes were exa ined by an allelic-specific amplification method using real-time PCR.

Results: The frequencies of mutant C-allele were significantly higher in patie with CWP compared to controls (23.5% vs.17.2%, respectively, $p<0.05$). C-all frequency for nodular CWP and PMF were 24.6% and 21.6%, respectively. C-all frequency in nodular CWP was significantly higher than controls ($p<0.05$).

Conclusion: The MIF gene promoter -173G/C polymorphism is associated v the susceptibility to CWP.

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Differential Gene Expression Induced by Chapel Hill Fine Particles in Hun Alveolar Macrophages

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Pollutant particles (PM) induce systemic and lung inflammation. Alveolar ma phages (AM) are one of the lung cells directly exposed to PM that may initiate t responses. In this study, we determined the gene expression profile induced by Ch Hill fine particles (PM2.5) in human AM. AM were obtained from normal subject bronchoscopic lavage and incubated for 18 hours with or without 1 μg/ml of PM collected in October of 2001. The RNAs were extracted and amplified with the Ag low RNA input fluorescent linear amplification kit, and hybridized to the Ag Human 1A(v1) microarrays (n = 6 for each group, dye flip replicates inclu Differentially expressed genes were identified using the Significance Analysis Microarray (SAM) algorithm with FDR at 10%. 34 and 43 genes were up- and d regulated with treatment/control ratio > 1.5 or < 0.5 respectively. The top thi differentially expressed genes were confirmed by RT-PCR. Fourteen genes involved in oxidative stress, including upregulation of metallothioneins, N (p47phox), CYP1B1, NQO1, MMP9, AMID, ATOX1 and downregulation of DH and HADHSC. Using the Database for Annotation, Visualization and Integ Discovery (http://apps1.niaid.nih.gov/david/) (GOCharts), we found that the de response and the response to pest/pathogen/parasite were the two biological proc with the most number of genes (10 and 8 respectively). The hierarchical clust using the 77 genes completely separated PM2.5 from the control. These results cate that exposure to Chapel Hill PM2.5 induced novel genes associated with o tive stress and host defense in human AM. The gene expression profile may be u identify genes and pathways involved in the biological response to ambie pollutant. (Abstract does not reflect USEPA policy).

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