

Genetic Predictors Of Bronchial Reactivity In Adult Chinese Females

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Objective: To identify candidate single nucleotide polymorphisms (SNPs) as predictors of bronchial reactivity using a customized high-density SNP array in predominantly young adult Han Chinese females in Shanghai, China.

Methods: Methacholine challenge was performed in 412 female participants (median age 19.1 years) who were healthy non-smokers. Whole blood was collected, and DNA was extracted and genotyped using the Illumina HumanCVD Beadchip 50K SNP array. A total of 32,003 SNPs with minor allele frequency ≥ 0.01 and call rate $\geq 95\%$ were included for analysis. Bronchial reactivity was characterized as a continuous slope between percentage decrements in forced expiratory volume in 1 second (FEV_1) per μmol methacholine on a logarithmic scale. Using linear regression in PLINK software, methacholine slope was modeled as a function of each SNP on an additive scale, after adjustment for baseline FEV_1 , second hand smoke, age, height, weight, total IgE concentration, atopy, and past occupational exposure to respiratory toxicants. To address multiple comparisons, we applied the Benjamini-Hochberg false discovery rate (FDR-BH).

Results: Four SNPs were identified with uncorrected p-values $\leq 10^{-5}$, and all were in Hardy Weinberg Equilibrium ($p \geq 0.10$). One SNP in 3'UTR of PON1 (rs845552, β : 0.43, $p = 1.9 \times 10^{-6}$) was positively associated with log methacholine slope, as was two SNPs in intronic regions of LEPR (rs7555955, β : 0.50, $p = 4.2 \times 10^{-6}$; rs1046011, β : 0.50, $p = 1.1 \times 10^{-5}$; respectively). A 3'UTR SNP of NLRP3 (rs10802501, β : -1.1, $p = 3.8 \times 10^{-6}$) was inversely associated with methacholine slope. Putative functions for the genes of the identified SNPs are associated with oxidative stress (PON1), immune (NLRP3) and inflammatory pathways (NLRP3, LEPR). After adjustment for FDR-BH, SNPs rs845552 of PON1, rs10802501 of NLRP3, and rs7555955 of LEPR remained statistically significant ($p < 0.05$).

Conclusions: SNPs associated with oxidative stress, immune and inflammatory pathways were identified as predictors of bronchial reactivity in this sample of predominantly young healthy adult Han Chinese females. The precise mechanisms by which these genetic variants confer airway reactivity need to be elucidated.

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