Influence of gene-by-early environmental tobacco smoke exposure interactions on time-to-asthma onset


ABSTRACT

Background: The number of genetic factors identified for asthma remains limited. The study of gene-by-environment interactions may facilitate the discovery of new genes. Early environmental tobacco smoke (ETS) exposure (in utero or during infancy) is a known risk factor for childhood-onset and late-onset asthma.

Objective: Our goal was to identify genetic variants interacting with early ETS exposure that influence time-to-asthma onset (TAO).

Methods: We conducted a large-scale meta-analysis of five genome-wide interaction studies (GEWIS) of TAO (totaling 3,643 exposed (ETS+) and 5,275 non-exposed (ETS−) individuals of European ancestry) using survival analysis methodologies. Two tests were performed: 1) a joint test of SNP effect and GxETS interaction and 2) a test of GxETS interaction alone.

Results: While the joint test confirmed two asthma regions (9p24 & 17q12-q21) interacting with ETS on TAO at the genome-wide significant level (P<5x10^-8), the interaction test revealed three new loci: 13q21, 16p13 and 19q13 (6.7x10^{-7}<P<10^{-6}). Further analysis of the 9p24 and 17q12-q21 loci stratified on asthma age-of-onset (before and after six years) confirmed the known ETSx17q12-q21 interaction in childhood-onset asthma and evidenced a complex effect of 9p24 top SNP on asthma risk with: 1) the strongest effect in ETS+ early-onset subjects (HR [CI]=1.41 [1.25-1.58]), 2) an intermediate effect in both ETS− early-onset
(HR=1.23 [1.12-1.34]) and ETS’ late-onset subjects (HR=1.26 [1.14-1.39]) and 3) no effect in ETS’ late-onset subjects (P=0.38).

Conclusion: This study suggests an important role of early ETS exposure and 9p24 genetic variants in asthma age-of-onset.