Taking into account gene-by-early environmental tobacco smoke exposure interactions to detect genetic variants influencing time-to-asthma onset


ABSTRACT

The number of genetic factors identified for asthma remains limited. The study of gene-by-environment interactions may facilitate the discovery of new genes. Environmental tobacco smoke (ETS) exposure in utero and/or during infancy is a known risk factor for childhood-onset and late-onset asthma. Our goal was to identify genetic variants interacting with early ETS exposure that influence time-to-asthma onset (TAO). 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-) subjects of European ancestry) using survival analysis methodologies. Since the power of GEWIS depends on the statistical test used according to the underlying genetic model which is unknown, two tests were performed: 1) a joint test of SNP and GxETS interaction effects and 2) a test of GxETS interaction alone. While the joint test identified two asthma regions (9p24 & 17q12-q21) interacting with ETS on TAO at $P \leq 10^{-13}$, the interaction test revealed three potential new loci ($P < 10^{-5}$): 13q21, 16p13 and 19q13. Further analysis of 9p24 and 17q12-q21 loci stratified on asthma age-of-onset ($\leq 6$yrs versus $> 6$yrs) confirmed the 17q12-q21xETS interaction in childhood-onset asthma and evidenced a complex effect of 9p24 SNP on asthma risk with: 1) a strong effect in ETS+ early-onset group (HR [95%CI]=1.4 [1.3-1.6]), 2) intermediate effects in both ETS- early-
onset and ETS+ later-onset groups (HR [CI]=1.2 [1.1-1.4]), and 3) no effect in ETS− later-onset group. This study evidences a role of both early ETS exposure and 9p24 genetic variants in asthma risk and age-of-onset.

Funding: FRSR, GABRIEL, ANR-GWIS-AM