Interactive effect between ATPase-related genes and early-life tobacco smoke exposure on bronchial hyper-responsiveness detected in asthmatic families

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In a previous positional cloning study of the 17p11 region, we identified genetic variants interacting with tobacco smoke (ETS) exposure in early life for bronchial hyper-responsiveness (BHR) in the French Epidemiological study on the Genetics and Environment of Asthma (EGEA). These variants were located in DNAH9 (Dizier et al., 2016), a gene having a key role in motile cilia function.

Our objective was to identify other genetic variants interacting with ETS for BHR by investigating genes involved in 'ATPase binding' and 'ATPase activity' pathways. They both include DNAH9, are target of cigarette smoke and implicated in the movement of respiratory cilia.

Family-based association test (FBAT) analyses were first conducted in 388 EGEA families. We applied FBAT-homogeneity test between exposed vs. unexposed siblings to detect SNPxETS interaction for BHR. Replication was performed in 253 families from the Saguenay-Lac-Saint-Jean (SLSJ) asthma collection.

In EGEA families, 25 SNPs showed interaction signals ($P \leq 5 \times 10^{-3}$) with ETS among BHR siblings. One SNP on 4p13 reached the threshold ($P = 2 \times 10^{-5}$) for a significant interaction with ETS when correcting for multiple testing. This result did not quite reach the nominal level for replication in SLSJ families ($P = 0.13$) but there was improvement of evidence for interaction in the meta-analysis of the two samples ($P = 10^{-5}$). Another SNP on 9q31 showed a stronger interaction signal for replication in SLSJ families ($P = 0.003$), and a suggestive interaction by meta-analysis ($P = 6 \times 10^{-5}$).
Further analyses based on log linear modeling and further replication in additional samples will be conducted to confirm these findings.