The 5p15 locus is associated with bronchial hyperresponsiveness in siblings unexposed to tobacco smoke in early life in French families ascertained through asthma.

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A genome-wide linkage analysis conducted in the French Epidemiological study on the Genetics and Environment of Asthma (EGEA) detected four chromosomal regions linked to bronchial hyperresponsiveness (BHR) and interacting with exposure to tobacco smoke (ETS) in early life (Dizier et al, 2005, 2007). Among these four regions, 1q43-q44 and 4q34 showed linkage to BHR in presence of ETS while 5p15 and 17p11 showed linkage in absence of ETS. Our goal was to conduct fine-scale mapping of these 4 regions to identify the genetic variants interacting with ETS that have an effect on BHR.

Association analyses using the family-based association test (FBAT) were conducted in the whole sample of 388 EGEA families (322 sibs with BHR), and in sub-sets stratified according to ETS exposure (138 unexposed sibs with BHR and 184 exposed sibs with BHR). We used a two-step strategy including: 1) selection of SNPs showing association signals with BHR (p<5x10^-3) in the subset where linkage was detected; 2) test of homogeneity of association of selected SNPs with BHR between exposed and unexposed siblings using FBAT to detect SNPxETS interaction. We then applied logistic regression analysis to those variants showing significant interaction with ETS by FBAT, as internal validation to confirm the interaction.

In the 5p15 and 17p11 regions, 18 and 15 SNPs showed association signals with BHR (p<5x10^-3) in unexposed siblings, while in the 1q43-q44 and 4q34 regions, 27 and 8 SNPs showed association in exposed siblings. Among these SNPs, only one in 5p15 showed significant evidence for interaction with ETS in the stratified analysis (p=8x10^-4 before correction and p=0.05 after correction for multiple testing). Logistic regression provided some support for this interaction (p=0.11, in 490 siblings with 63% of them having BHR).

Although replication of our results is needed, it is interesting to note that the 5p15 locus that is found associated with BHR in ETS-unexposed siblings has been previously reported to be associated with lung cancer in non-smoking women.