Abstract Preview

Accounting for parent-of-origin effects detects association between 4q35 genetic variants and combined asthma-plus-rhinitis phenotype.

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A strong linkage signal was previously detected in the 4q35 region with the combined phenotype asthma-plus-rhinitis in 640 families from European ancestry (French (EGEA), British (MRCA) and Italian) when accounting for imprinting (LOD=3.14, P=2.5x10\textsuperscript{-5}). We further investigated this region in 161 families (206 offspring) from the French EGEA study (Epidemiological study on the Genetics and Environment of Asthma) using a panel of 1300 SNPs (spanning 6Mb). Two different methods aiming to detect parent-of-origin and/or maternal genotype effects were used to test for association between these SNPs and asthma-plus-rhinitis phenotype: 1) the Monte-Carlo Pedigree Parent-Asymmetry-Test (MCPPAT) and 2) the Parent-of-origin-Likelihood ratio Test (PO-LRT). We identified 26 markers associated with asthma-plus-rhinitis (P\textleq;0.005) among which one reached the multiple testing-corrected threshold of P\textleq;6.5x10\textsuperscript{-5}. Analyses conducted with imputed data (Hapmap2) strengthened the evidence for association with three genes. In order to replicate our findings, we conducted association analysis in 152 French Canadian families (Saguenay-Lac-Saint-Jean) under the same epigenetic model detected in the discovery set. The combination of EGEA and SLSJ results using a fixed-effect model evidenced association with two SNPs (P_{comb}=9x10\textsuperscript{-5} and P_{comb}=9x10\textsuperscript{-4}) under parent-of-origin effect model. Further linkage analyses performed in EGEA sibships stratified according to the genotypes at each of the two significant SNPs showed that one SNP accounted for most of the linkage signal detected in the 4q35 region. Moreover, association analyses performed separately with each allergy-related phenotypes (asthma, rhinitis, atopy) suggested that one SNP is more likely associated to atopy (P=5x10\textsuperscript{-5}) than the combined asthma-plus-rhinitis phenotype. Further investigation is needed to confirm our findings and to better understand the role of these loci in asthma-plus-rhinitis and their relationships with respect to allergy. For that purpose, replication of our results in MRCA families which were part of the original scan is ongoing. Moreover, the combination of these results with expression and methylation data will help pinpointing towards the functional SNPs influencing asthma-plus-rhinitis and allergy phenotypes.

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