Imprinting and maternal genotype effects of 4q35 genetic variants on combined asthma-plus-rhinitis phenotype

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A previous genome-wide linkage scan conducted in 640 families from European ancestry (French, British and Italian) detected linkage of 4q35 to a combined phenotype asthma-plus-rhinitis, with increased evidence when taking into account imprinting (LOD=3.14, P=2.5x10\textsuperscript{-5}). We investigated further this region by genotyping a panel of 3,000 SNPs (spanning 20Mb) in 161 families (206 offspring) from the French EGEA study (Epidemiological study on the Genetics and Environment of Asthma). To test for association between these SNPs and asthma-plus-rhinitis phenotype, we used two different methods aiming to detect parent-of-origin and/or maternal genotype effects: 1) the Monte-Carlo Pedigree Parent-Asymmetry-Test (MCPAT) and 2) the Parent-of-origin-Likelihood ratio Test (PO-LRT). Irrespective of the method used, we identified 50 markers associated with asthma-plus-rhinitis with P-value < 0.005. These associations were replicated in 245 French Canadian families (Saguenay-Lac-Saint-Jean) for four SNPs with P-values ranging from 0.06 to 0.005 under the same model as in the discovery set. The combination of P-values (P\textsubscript{comb}) from the EGEA and SLSJ samples using Fisher’s method enhanced the evidence for association of asthma-plus-rhinitis with SNPs in two genes. The most significant SNP in one gene had P\textsubscript{comb}=2x10\textsuperscript{-4} under a parent-of-origin effect model while the best SNP in the other gene had P\textsubscript{comb}=5x10\textsuperscript{-4} under a maternal genotype effect model. This study highlights that taking into account complex mechanisms, such as imprinting and maternal genotype effect, facilitates the identification of new susceptibility genes.

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