Combining genetic and epigenetic information identified imprinted 4q35 variant associated with the combined asthma-plus-rhinitis phenotype

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We previously detected a linkage signal in the 4q35 region with the combined asthma-plus-rhinitis phenotype (AST+AR) in 615 European families when accounting for maternal imprinting (p=7x10^{-5}). To further investigate this region, we tested the association between 1,300 SNPs (spanning 6 Mb) and AST+AR in 162 French EGEA families ascertained through asthma using the Parent-of-Origin-Likelihood Ratio Test. Replication analysis was performed in 152 asthmatic French Canadian SLSJ families for 18 SNPs detected at p<0.005. The top-replicated SNP (rs10009104) lying at 1.6 Mb from the linkage peak was detected under a best-fitting maternal imprinting model (p_{meta}=4x10^{-5}) and accounted for most of the linkage signal.

Many cis-regulatory elements were described in a 50 kb surrounding region of this SNP. Using the Quantitative Transmission Disequilibrium Test (QTDT), we tested for association between rs10009104 and 26 DNA methylation probes of that region, measured in white blood cells of 159 individuals (40 SLSJ families), while accounting for parent-of-origin effect and adjusting for AST+AR. Maternally inherited risk allele of rs10009104 was associated with increased methylation of the top-ranked probe (p<10^{-5} after permutations). This probe lies at 529 bp from the SNP and within regulatory elements that include a predicted active promoter in lung fibroblasts, DNase I hypersensitive clusters, and binding sites of two transcription factors involved in inflammatory response initiation (RelA and NF-κB).

This study identified a maternally imprinted SNP that affects AST+AR through an epigenetic mechanism.

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