Identification of imprinted 4q35 variant associated with the combined asthma-plus-rhinitis phenotype using both genetic and epigenetic data

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Several lines of evidence support the role for epigenetic mechanisms such as imprinting in asthma and allergic diseases. We conducted a genome-wide linkage scan for the combined asthma-plus-rhinitis phenotype (AST+AR) in 615 families from European ancestry (French (Epidemiological study on the Genetics & Environment of Asthma, EGEA), British (Medical Research Council Asthma, MRCA) and Italian (Verona)) and detected a linkage signal in the 4q35 region with increased evidence when accounting for maternal imprinting (p=7x10^-5).

We then investigated further this region using a panel of 1,300 SNPs (spanning 6 Mb) genotyped in 162 families from the EGEA study (207 offspring). We tested the association between these SNPs and AST+AR using the Parent-of-Origin-Likelihood Ratio Test (PO-LRT) which allows detecting parent-of-origin and/or maternal genotype effects. We identified 18 SNPs associated with AST+AR at p<0.005 that were investigated for replication in 152 asthmatic French Canadian families from the Saguenay-Lac-Saint-Jean study (SLSJ). Combination of EGEA and SLSJ results under a maternal imprinting best-fitting model showed evidence for association for one SNP (p_meta=4x10^-5), lying at 1.6 Mb from the linkage peak, that accounted for most of the 4q35 linkage signal.

Many cis-regulatory elements (enhancers, silencers, insulators) are described in a 50 kb surrounding region of the replicated SNP. Using the Quantitative Transmission Disequilibrium Test (QTDT), we tested for association between the replicated SNP 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 the replicated SNP was associated with increased methylation of the top-ranked probe (p<10^-5 after permutations). This probe was located at 529 bp from the SNP and lies 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-kB).

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

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