

Genetic studies on childhood asthma and allergy – role of interactions

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The occurrence of asthma and allergic diseases is influenced by inherited and environmental factors, and symptoms of asthma and allergy usually begin in early childhood. The overall aim with this thesis was to study the role of genetic factors for the development of childhood asthma and allergy, and to evaluate potential interaction between genetic and environmental factors.

Using the BAMSE birth cohort study, children with wheezing episodes up to the age of four were classified into the following groups: transient wheezing (n=266, 8%), persistent wheezing (n=319, 9%) and late-onset wheezing (n=195, 6%). Children with persistent and late onset wheezing had the highest occurrence of sensitisation to inhalant allergens (23% and 30%, respectively), whereas lower mean peak expiratory flow values were seen in children with transient and persistent wheezing (mean difference -8.9 and -8.5 l/min, respectively). Both maternal and paternal allergic disease were of importance for all wheezing outcomes in the children, but the influence of parental allergic disease on the risk of persistent wheezing seemed to be more pronounced in boys than in girls.

For the genetic analyses, around 500 children with asthma symptoms up to four years and 500 controls were selected from the BAMSE study. Single nucleotide polymorphisms (SNP) and their corresponding haplotypes in six candidate genes for asthma and allergy were analysed and their associations with various phenotypes were evaluated. Variations in the *IL9R* gene seemed to influence the susceptibility to both wheezing and sensitisation, predominantly in boys. No overall effect of the *IL4RA* SNPs was observed and only weak associations to wheezing and sensitisation were indicated when haplotypes were considered. Variants in the *ADRB2* gene showed no overall association to any of the outcomes, whereas the *TNF- α* -308 SNP seemed to affect the risk of sensitisation at the age of four. Ala114Val was the only SNP in the *GSTP1* gene that showed any association (particularly to asthma). For the *GPRA* association analyses, asthma and allergic sensitisation were used as major outcomes and the study was designed to evaluate the role of certain haplotypes on these study subjects both from BAMSE and a multinational European project (PARSIFAL). Both risk haplotypes (H5/H6) and non-risk haplotypes (H1/H3) could be identified, and these haplotypes seemed to predominantly influence the risk of sensitisation, but also asthma and allergic rhinoconjunctivitis.

Interaction analyses between the *IL9R* and *IL4RA* genes showed that the effect of *IL4RA* SNPs on wheezing up to the age of four was modified by SNPs in the *IL9R* gene. Combinations of the *IL4RA* Gln576Arg variant and an intron *IL9R* variant seemed to influence the risk of wheezing particularly, and both risk and non-risk combinations were observed.

Air pollution from road traffic in the study area was evaluated as nitrogen oxides (traffic-NO_x) and inhalable particulate matter (traffic- PM₁₀) using emission databases and dispersion modelling. Individual exposure levels during the first year of life were estimated through geocoding of the children's home addresses. Significant gene-environment interaction effects were suggested between SNPs in the *GSTP1* gene and exposure to traffic-NO_x during the first year of life with regard to allergic sensitisation at 4 years. Heterozygous *GSTP1* carriers seemed to have the most pronounced risk of disease and this pattern was seen for all *GSTP1* SNPs tested. Similar interaction was seen for exposure to traffic- PM₁₀.

In summary, we have shown that parental allergic disease is important for development of wheezing up to the age of four, but the hereditary influence seemed to be more pronounced in boys than in girls. Variants in several of the analyzed genes were associated with symptoms of asthma and allergic sensitisation. The association between these genetic variants and allergic diseases are likely to be influenced by other genetic variants, here exemplified by gene-gene interaction between *IL4RA* and *IL9R* variants, and environmental factors, here exemplified by gene-environment interaction between *GSTP1* variants and exposure to traffic-NO_x.

Keywords: air pollution, asthma, allergy, BAMSE, child, environment, epistasis, GPRA, genetics, haplotype, heredity, interaction, polymorphism, wheezing

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