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Allergic diseases and gene-environment interactions

The family history of asthma and atopic diseases is a significant risk factor for the development of allergies in the offspring. These findings have resulted in the search for the genes of asthma and allergic conditions. Recently, a number of genome-wide association (GWA) studies have been performed investigating the determinants of asthma and allergies in very large populations of cases and controls. These GWA studies revealed some significant hits for asthma in the European GABRIEL and North American EVE Consortium. Interestingly, these hits differed from those for total IgE. In other words, the genes found for asthma did not give a signal for the production of IgE antibodies. From a clinical perspective, the results were somewhat disappointing. The 7 single nucleotide polymorphisms (SNPs) in the 6 genes identified in GABRIEL (IL18R1, HLA-DQ, IL33, SMAD3, GSDMB, IL2RB) resulted in only 35% sensitivity, 75% specificity and 38% PARF (population attributable risk fraction) for the prediction of childhood asthma. In other words, asking for a positive family history of asthma and atopic diseases is still a better predictor than those newly identified SNPs. This 'missing heritability' has given rise to many discussions. What are the factors that we missed? These may encompass rare variants, copy number variants, epigenetic signatures and gene-gene or gene-environment interactions.

There are a number of possible gene-environment interactions. There is evidence for effect modification in such a way that the environment has an effect in subjects with a certain genotype, but not in others. A number of studies have shown that only subjects with SNPs coding for the glutathione S-transferases are susceptible to adverse environmental effects conferred by toxicants, such as outdoor pollutants or environmental tobacco smoke exposure. There is however no specificity in such interactions: other genes have also been shown to interact with environmental tobacco smoke exposure. There are also other forms of gene-environment interactions, the socalled cross-over interactions where genotype and exposure have effects, but the interaction is in opposite directions. The best examples to date relate to cross-over interactions with relation to endotoxin exposure in the environment.