

GENETIC AND ENVIRONMENTAL INFLUENCES ON CHILDHOOD ASTHMA

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Asthma is the most common chronic disease in childhood and usually starts before school age.¹ It has increased in prevalence worldwide and the causes are largely unknown.¹ Evidence from twin studies indicates a strong genetic component;² however genetic studies of asthma have produced heterogeneous results with little replication.³ Although reasons for this are common to many complex diseases,⁴ more specific to asthma is the fact that studies have focused mainly on adults, often with phenotypic heterogeneity or poor phenotype definition. In addition, little or no account has been taken of environmental exposures.⁵ Furthermore, antenatal and early life exposures to environmental factors are more likely have a greater impact on the immature immune system and airways, and the subsequent development of disease than those occurring in adulthood. The fundamental role of the environment in asthma development is emphasised by the increase in asthma prevalence seen since about 1960 – a time frame too short to be attributable to genetic factors alone.¹ The environmental changes which have occurred in parallel include changes in diet and exercise, patterns of microbial exposure in early life with antibiotic use and childhood immunisations, family size and childcare arrangements, and changes to housing design.⁶ The increase in asthma prevalence is likely to be a consequence of environmental factors increasing the risk in genetically susceptible individuals mediated through gene-environment interactions.

In contrast to most other complex diseases (e.g. diabetes), asthma and allergic diseases start early in life and are unstable phenotypes which may progress or remit over time. Therefore, the optimum study design to investigate these disorders is the population-based prospective birth cohort, overcoming problems of recall bias (due to retrospective data collection) and permitting careful longitudinal phenotyping of subjects. Allergic status, lung function and bronchial hyperresponsiveness, physician diagnosis and medication use can be accurately defined. In addition contemporaneous measurement of environmental exposures (e.g. domestic endotoxin, allergen exposures, diet) is essential to facilitate the study of gene-environment interactions.

We have recently demonstrated the existence of a gene-environment interaction in the development of allergy and eczema within the setting of a birth cohort study (the Manchester Asthma and Allergy Study, MAAS⁷). By taking objective measure of endotoxin exposure in the home and carefully phenotyping the children, we have shown that high endotoxin exposure is protective against the development of allergies and eczema but only in children with a particular genotype

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group (C allele homozygotes of CD14/-159 rs2569190). Furthermore, these results explain the disparities in association studies of this SNP in different settings around the world. From our results it is clear that when the gene is studied in isolation, in communities with naturally high exposure to endotoxin, e.g. farming communities like the Hutterites,⁸ the T allele would appear to be the risk allele. In contrast, in communities with naturally low exposure to endotoxin, the C allele would appear to be the risk allele.⁹ In communities with a wide range of exposures there would be no apparent association between genotype and disease outcome,¹⁰ emphasising the point that if the genotype were studied in isolation, irrespective of the size of the population studied, this effect would have been missed.

It has been suggested that in order to detect gene-environment interactions it is necessary to study tens of thousands of subjects.¹¹ However, we detected this interaction (and provided a plausible explanation for apparently irreconcilable differences in previously published data) with a modest sample size of 442. These results have been replicated by other groups with comparable numbers of subjects.^{12,13} In contrast, the largest study of genetic determinants of IgE (which has not taken environmental exposures into account) was able to explain <1% of the variance,¹⁴ despite the fact that twin studies suggest heritability of ~60%¹⁵ and the selected genes were appropriate. The accompanying editorial⁵ emphasised that the study of subjects from a broad geographic area with diverse unmeasured environmental exposures overlooked the fact that many associations between genes and phenotype may not be linear or unidirectional and that true associations may be lost in studies of this scale, concluding that 'hypothesis driven genetic epidemiology might be a more effective and interesting partner for disease-oriented biologic research.'⁵

Power to detect associations clearly depends not only on size of population studied, but critically on accurate phenotyping and measurement of environmental exposures. Furthermore, for a disease that starts early in life, the use of birth cohorts allows phenotyping at or around the onset of disease and contemporaneous measurement of relevant environmental exposures. This approach is not applicable to disease areas such as maturity-onset diabetes.

Declaration of conflict of interest

The authors declare no conflict of interest.

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