Asthma has increased in prevalence worldwide and the causes are largely unknown. Although evidence from twin studies indicates a strong genetic component, genetic studies of asthma have produced heterogeneous results with little replication. Reasons for this lack of replication are at least in part consequent to the fact that most studies have focussed on adults, often with phenotypic heterogeneity or relatively poor phenotype definition. In addition, little or no account has been taken of environmental exposures. Within the context of asthma, antenatal and early life exposures to environmental factors are more likely to have a greater impact on the immature immune system and airways (and thus subsequent development of symptomatic disease) than those occurring in adulthood.

The fundamental role of the environment in asthma development is emphasised by the marked increase in prevalence which occurred since the 1960s – a time frame too short to be attributable to genetic factors alone. The environmental changes which have occurred in parallel include changes in diet and exercise, patterns of microbial exposure in early life with antibiotic usage and childhood immunisations, family size and childcare arrangements and changes to housing design. However, as with genetic studies, there is heterogeneity of results of studies which investigated the importance of environmental exposures in allergy and asthma; for example, breastfeeding has been shown to increase, decrease or have no effect on allergic disease, and similar discrepancies have been reported on the effect of exposure to domestic pets. The
increase in asthma prevalence is likely a consequence of environmental factors increasing the risk in genetically susceptible individuals mediated through gene-environment interactions.

Onset and causality

In contrast to most other complex diseases (e.g. diabetes), asthma and allergic diseases start early in life and are unstable phenotypes that may progress or remit over time. The preferred study design to investigate the onset and causality of 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. 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 allergic sensitisation by showing that high endotoxin exposure is protective, but only in children with a particular genotype group (C allele homozygotes of CD14/-159 rs2569190; Figure 1). These results explain the disparities in previously published association studies, where the gene was studied in isolation and emphasise the point that if the genotype was studied without the knowledge of the relevant environmental exposure, this effect would be missed (irrespective of the size of the population).
Figure 1. Fitted predicted probability curves for allergic sensitization at age 5 years in relation to environmental endotoxin load in children with CC, CT and TT genotypes in the promoter region of the CD14 gene (CD14/-159 C to T), derived from the logistic regression analysis. There was no association between endotoxin load and sensitization for the TT and CT genotypes (p=0.7 and p=0.16 respectively. However for the CC genotype group increasing endotoxin load was associated with a marked and significant decrease in the risk of sensitization (0.70, 0.55-0.89, p=0.004). From: Simpson A et al Am J Respir Crit Care Med 2006;174(4):386-92

It has been suggested that in order to detect gene-environment interactions it is necessary to study tens of thousands of subjects. However, we detected the above interaction with a modest sample size of 442. In contrast, the largest study of genetic determinants of IgE (with no measure of environmental exposures) was able to explain <1% of the variance, despite a suggested heritability of ~60%. The accompanying
editorial emphasized 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’. Thus, the power to detect associations clearly depends not only on size of population studied, but on accurate phenotyping and measurement of environmental exposures.

Our results suggest that in complex diseases such as asthma and allergies, genetic predisposition may need to be taken into account when assessing the effect of environmental exposures, and vice-versa, relevant environmental exposures may need to be factored into the genetic association studies. Furthermore, we often use epidemiological data to identify potentially modifiable risk factors to help devise primary prevention strategies. If we extrapolate our data to the context of primary prevention, the results suggest that only individuals with particular genotypes may benefit from a specific intervention, whilst the same intervention amongst individuals with different susceptibility may cause harm.
SUGGESTED READING:


Vercelli D, Martinez FD. The Faustian bargain of genetic association studies: bigger might not be better, or at least it might not be good enough. J Allergy Clin Immunol 2006;117(6):1303-5.