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Gene-Environment Interactions in Asthma and Allergy: The End of the Beginning?

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Abstract

Purpose of review—The pathogenesis of asthma and allergy typically involves not only distinct genetic and environmental factors, but also interactions between the two. Innate immunity genes (particularly CD14, Toll-like receptor (TLR)4 and TLR2, the critical mediators of responses to bacteria in the extracellular space) play a prominent role in gene-environment interactions relevant to asthma-related phenotypes, because the interaction between microbial load and the innate immune system is a critical determinant of both immune function and allergy/asthma susceptibility. This review presents recent findings illustrating the role of gene-environment interactions in asthma/allergy susceptibility.

Recent findings—Population studies have extended our understanding of the role of CD14 and innate immune genes in the interplay between genetic variants and the environment, highlighting the complexity of these interactions and their significant influence on susceptibility to asthma and allergy.

Summary—Gene-environment interactions have become a leitmotiv in asthma and allergy genetics, especially over the last three years. The next challenge awaiting asthma and allergy geneticists will be to define the extent to which the search for gene-environment interactions can be successfully integrated with hypothesis-generating, genome-wide approaches aimed at the identification of genetic variants involved in the pathogenesis of complex lung diseases.

Keywords

Gene-environment interactions; innate immunity; asthma; allergy; genome-wide association studies

Introduction

The pathogenesis of common complex diseases, asthma and allergy first and foremost, typically involves not only distinct genetic and environmental factors, but also interactions between the two [1]. Indeed, gene-environment interactions have become a leitmotiv in asthma and allergy genetics. According to the HuGE Navigator (www.hugenavigator.net), an online curated and searchable data base in human genome epidemiology [2], over one hundred papers discussing asthma-related gene-environment interactions were published between 2000 and 2009. Interestingly, more than half of these papers appeared during the last three years, testifying to the mounting attention the scientific community is paying to gene-environment interactions as critical determinants of asthma and allergy susceptibility.

Gene-environment interactions in allergy and asthma

Innate immunity genes (particularly CD14, Toll-like receptor (TLR)4 and TLR2, the critical mediators of responses to bacteria in the extracellular space) play a prominent role among gene-environment interaction studies of asthma-related phenotypes. A large body of epidemiological literature supports the interaction between microbial burden and prevalence of allergy (reviewed in [3]). Because gene-environment interactions are typically detected through targeted searches driven by biological hypotheses about the candidate genes most likely to interact with a given environmental exposure, innate immunity genes have been tested in depth [4*] because they are placed at the sensing interface with the microbial environment and at the same time fine-tune regulatory responses [5]. CD14, in particular, has proven a rewarding candidate. On the one hand its ability to interact with, and facilitate the response of, multiple primary receptors (TLR4, TLR2 [6] and even TLR3, the sensor for double-stranded RNA [7]) places this molecule at the intersection of a large spectrum of anti-microbial responses. Moreover, these responses are elicited by ligands often amenable to direct or indirect measurements, making it possible to analyze gene-environment interactions quantitatively (based on level of exposure) as well as dichotomously (exposure present or absent). Finally, CD14 polymorphisms are quite common and therefore accessible to analysis even in relatively small population samples – the ones for which accurate environmental assessments are more often available.

CD14 has provided the most complete and complex paradigm for gene-environment interactions so far, including the classical finding of opposite effects of a given genotype depending on the quantity and/or quality of the relevant microbial load [8,9]. We have discussed elsewhere the concept of the endotoxin switch, which likely provides the mechanistic underpinning of CD14-mediated gene-environment interactions [10–12]. It is noteworthy that the ability of CD14 to influence allergen-induced immune responses in opposite directions depending on the microbial load is best understood in the broader context of the Hygiene Hypothesis [13*] and the regulatory interplay between immune system and microbial environment [12]. Here we will succinctly review the most relevant findings published in late 2008 and 2009 that have extended our understanding of gene-environment interactions mediated by CD14 and its microbial receptor partners, TLR2 and TLR4. One significant caveat is that this literature typically carries a publication bias, that is, a tendency to present positive more than negative or neutral findings.

It has been repeatedly shown that country living protects against asthma, which may be explained by microbial exposures [13*]. A recent study genotyped single nucleotide polymorphisms (SNPs) in CD14 as well as TLR2 and TLR4 in adult subjects from the French Epidemiological study on the Genetics and Environment of Asthma, bronchial hyperresponsiveness, and atopy (EGEA) in order to study whether SNPs in these genes are associated with asthma in adults, and whether these SNPs modify associations between country living and asthma. The TLR2/+596 C allele was strongly associated with an increased risk for asthma in both case-control and family-based analyses. In skin prick test-positive subjects, the CD14/-260 (rs2569190) C allele was negatively associated with asthma. Significant gene-environment interactions between variation in CD14 and TLR genes and country living during childhood were found for ten SNPs. In skin test-positive subjects carrying CD14/-260 CC, country living protected against asthma, whereas country living was not associated with asthma in subjects who were atopic and carried CD14/-260 T. Therefore, TLR2 and CD14 SNPs were associated with asthma and atopic asthma respectively. In addition, SNPs in CD14 as well as TLR2 and TLR4 modified associations between country living and asthma [14].

The Karelian population provides an excellent opportunity to analyze how genetic background and ‘Western’ or ‘Eastern’ environments interact to affect allergic disease susceptibility.

Indeed, Finnish Karelians have a higher prevalence of allergic disease than Russian Karelians, yet both populations belong to the same ethnic group. A recent study compared associations between allergic diseases and CD14-159C/T (rs2569190) in Finnish and Russian Karelian women. The CD14-159 risk allele for atopic phenotypes in Finnish Karelia turned out to be the protective allele in Russian Karelia. A strong interactive effect on several phenotypes (ever itchy rash, itchy rash <12 months and dry cough at night in the past 12 months) was found, but the risk allele was C in Russians and T in Finns. Thus, an Eastern or Western environment appeared to affect risk of allergic disease in adult women through opposite alleles [15].

Studying gene-environment interactions typically requires large populations because analyses need to be stratified by both genotype and environmental exposure. Obviously, collecting large populations renders such studies more difficult and expensive. Pooling data from several cohort studies may help but may also create problems of interpretation if heterogeneity exists in genetic background and/or environmental exposures. A recent study from The Netherlands focused on gene-environment interactions in the development of atopy, and also assessed the potential benefits of pooling data. Haplotype-tagging polymorphisms in CD14 were genotyped in 3,062 children from three birth cohorts: the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) study, the Prevention of Asthma in Children (PREVASC) study, and the Child, Parent, Health, Focus on Lifestyle and Predisposition (KOALA) study, and tested for association with total and specific IgE and interaction with tobacco smoke and pet exposure at ages 1, 2, 4 and 8 yrs. In CD14, the rs2569190 TT (CD14-260C/T) and rs2569191 CC genotypes were associated with lower IgE and decreased risk of sensitization at 4 and 8 yrs in children exposed to pets, with an opposite effect in non-exposed children. Findings were comparable in separate cohorts. These results indicated that atopy is significantly influenced by CD14 in interaction with pet exposure at ages 4 and 8 yrs. Access to pooled data improved effect estimates, and genetic effects could be detected in interaction with important environmental factors [16].

Children enrolled in the KOALA birth cohort were also studied to evaluate the relationship between perturbations in the gut microbiota and atopic diseases, a gene-environment interaction that may play an important role in early life. Specifically, the study examined the interaction between detection of fecal *E. coli* and genetic variants in the CD14 and TLR4 genes, in relation to atopic manifestations. Fecal samples of 957 one-month-old infants were collected and quantitatively screened for *E. coli*. Fourteen haplotype-tagging polymorphisms in TLR4 and CD14 were genotyped in 681 children. Atopic outcomes were parentally reported eczema in the first two years of life and clinically diagnosed eczema and allergic sensitization at age 2 years. Most SNPs showed no significant interaction with *E. coli* exposure for eczema and allergic sensitization. A borderline significant multiplicative interaction was found between *E. coli* and rs2569190 (CD14-159C/T) regarding allergic sensitization. Furthermore, a statistically significant multiplicative interaction was found for rs10759932 in TLR4. *E. coli* colonization was associated with a decreased risk of sensitization in children with the rs10759932 TT genotype but not in children with the minor C allele. This interaction remained statistically significant after controlling for multiple testing and pointed to the potential effect-modifying role of genetic variation in the relationship between the intestinal microbiota and allergy development [17*].

Several epidemiologic studies have shown an association between day care attendance and lower serum IgE levels (reviewed in [13*]). A recent analysis of Japanese elementary school children examined potential gene-environment interactions between day care attendance in early life and CD14 550C/T (rs5744455). Day care significantly decreased total IgE levels, mite-specific IgE levels, and rate of atopy in individuals with the CT or TT genotype, but not in those with the CC genotype, and the interaction between the CD14 550C/T polymorphism and day care remained significant after adjusting for age, sex, family history, and number of

siblings [18]. The interaction between a CD14 polymorphism and day care attendance supports the possibility that the mechanisms underlying the protective effects of day care involve innate immune responses to environmental microbial products.

Gene-environment interactions in the era of GWAS

Very few new approaches in biology and medicine have elicited as much enthusiasm and as many expectations as genome-wide association studies (GWAS). The main strength of these studies lies in their ability to discover truly novel disease candidate genes, especially those associated with moderate risks and common variants [19–21**]. However, an intriguing complication, rooted in biology as much as in statistics and possibly due to the intrusion of gene-environment interactions, has emerged and is illustrated by the outcome of the first asthma GWAS and its aftermath.

This study identified a strong association between variants at chromosome 17q21 and an increased risk of asthma in white subjects of Northern European ancestry [22]. Since the region of association on chromosome 17q21.1 spanned 206 kb and included 19 annotated genes, the identification of the variants responsible for the association was pursued by profiling transcription of the genes located within the relevant genomic interval, reasoning that variation in gene transcription may mediate disease susceptibility, and transcript abundance may be directly modified by polymorphisms in regulatory elements. The analysis of the relationships between markers in the 17q21 locus and transcript levels in lymphoblastoid cell lines from children in an asthma family panel showed that the SNPs associated with childhood asthma were consistently and strongly associated in cis with transcript levels of a novel candidate gene, *ORMDL3*, suggesting that genetic variants regulating *ORMDL3* expression are determinants of susceptibility to childhood asthma.

An interesting development relevant to gene-environment interactions took place more recently when the association between the variants in chromosome 17q21 and an increased risk of asthma was re-examined in a large, family-based data set from the EGEA population that included extensive environmental as well as phenotypic data [23**]. This study showed that the increased risk of asthma conferred by 17q21 variants was essentially restricted to subjects with early onset asthma who had been exposed to environmental tobacco smoke in early life. Thus, this study unveiled both a developmental heterogeneity in the effects of chromosome 17q21 variants (association with early, but not late onset asthma), and strong gene-environment interactions (impact on early onset asthma dependent on early exposure to tobacco smoke). In hindsight, one wonders how and to what extent these environmental and developmental factors influenced the results of the initial GWAS. Notably, the association between asthma and *ORMDL3* has been replicated in several studies [24–26], and the interaction with smoking was also replicated [25].

Conclusion - Looking at the Future: From GWAS to GEWIS

Virtually all the gene-environment interactions known to date have been identified through hypothesis-driven research and candidate gene approaches. On the other hand, the trend in human complex disease genetics is shifting more and more towards hypothesis-generating GWAS, so much so that the increasing rate of published studies focusing on gene-environment interactions pales against the exploding acceleration in published reports of genetic associations [27*]. GWAS for common diseases have been successful at identifying novel variants in unexpected genes, but they have come up mostly with common variants of modest effects, which cannot explain more than a minimal fraction of heritability [28]. Several burning questions now face complex disease geneticists pursuing GWAS-based approaches, and several of these questions revolve around the role of the environment in disease susceptibility:

To what extent do environmental factors and gene-environment interactions contribute to the “missing heritability”? How well can GWAS identify gene-environment interactions? How feasible is the integration between GWAS and gene-environment interactions in terms of population size and analytical power? Because both gene-environment interactions and GWAS appear to be with us to stay, several groups are already busy developing novel analytical methods aimed at allowing efficient testing for gene-environment interactions in GWAS [29–31*]. While these efforts are still in their infancy, their success would usher in a new era of gene-environment-wide interaction studies (GEWIS) [27] that may truly change our understanding of gene-environment interactions and their impact on complex disease susceptibility. In words from more eloquent times, “This is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning” [32].

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