

Is it all in our genes? The “mite-y” truth

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Atopic states result from the interplay of environment and genetic factors. The identification of the importance of environmental causations in the development of atopic disorders occurred centuries ago. In 1819, John Bostock first described “catarrhus aestivus,” or hay fever, and in 1873 Charles Blackley recognized that pollen grains were the causative agents of hay fever.¹ The description of a genetic predisposition came later. In 1923, Coca and Cooke² coined the term *atopy* to refer to the “familial occurrence of asthma, allergic rhinitis, and atopic dermatitis associated with positive immediate skin tests to environmental antigens.” Since that time, atopy has continued to be defined as the genetic predisposition to produce IgE antibody in response to environmental antigens.

Many decades after the identification of the importance of both environmental and genetic factors in the development and expression of atopic disorders, we continue to struggle to identify the relevant exposures and genes. It has become clear that the pathogenesis of complex polygenic disorders is dependent on multilayered gene*environment interactions over time. This 3-dimensional model of gene*environment*time is the subject of this important issue of *The Journal of Allergy and Clinical Immunology*.

It is critical to consider all 3 dimensions when one is preparing to conduct or interpret a study. The interactions between the dimensions are bidirectional. The genes relevant to the development of allergic disorders might vary depending on the environmental exposures present in a given population; likewise, the relevant environmental exposures will be dependent on the genetic context. The immunologic milieu at any given time will be determined by the individual’s cumulative environmental exposures and his or her genetically influenced responses to these exposures. This immunologic milieu will shape the genetically influenced responses to the next relevant environmental exposures. Indeed, the immune system adapts over time, and the responses will change as a result. The immune state and local environment could be considered another dimension; however, these are intrinsically dependent on the genetic and environmental factors over

Abbreviation used

SNP: Single nucleotide polymorphism

time. For example, depending on the immunologic milieu and lung environment, a given exposure might or might not trigger allergic inflammation, and this will change with time as the immune system adapts. The interdependence of all of these variables makes it very difficult to conduct studies to elucidate any given effect. The final dimension of time further complicates the situation, inasmuch as certain genetic and environmental influences might be relevant only during specific “windows of opportunity.” Furthermore, multiple genetic and environmental influences occur simultaneously, and the collective contributions might be quite different from what is anticipated from any isolated individual effect as a result of the coexisting genetic and environmental subtext.

Despite the similarities of atopic disorders, they are quite heterogeneous in terms of their phenotypes and their natural history.^{3,4} Studies of gene and/or environmental influences first require accurate assignment and classification of phenotypes and recognition that atopic diseases likely express etiologic heterogeneity as well. This is further discussed in a review article in this issue by Dr von Mutius.⁵ As she points out, increased specific and total IgE levels, albeit a marker of atopic disease, are not found in the majority of atopic disorders.⁶ As such, use of this marker as the defining phenotype of atopy might lead to false results. Dr von Mutius also discusses the relevance of combinations of multiple genetic and sociocultural environmental factors in the occurrence and natural history of allergic disorders. She stresses that epidemiology should be used as a scientific tool to begin to dissect these heterogeneous interactions and that large population-based studies will be necessary to further our understanding. Identification of the temporal “windows” and the gene*environment interactions will require exactly these types of large, prospective, population-based studies.

To build the scaffold of understanding, the immunologic, genetic, and epigenetic mechanisms that underlie the influence of the environment must also be characterized. This will require not only epidemiologic studies but also concerted basic, clinical, and translational research. The immunologic and functional consequences of individual single nucleotide polymorphisms (SNPs) and SNP combinations (in the same and different genes) need to be studied through use of in vitro and in vivo models. Furthermore, an SNP might have different functional effects in different cell types. This is not surprising, given that the expression of potential interacting proteins might

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significantly differ among cell types. In another review article in this issue, Dr Vercelli⁷ discusses an SNP in the CD14 promotor (C-159T) and describes how differences in the relative expression levels of Sp transcription factors in hepatocytes versus monocytes led to distinct effects of the promotor SNP in these 2 cells types when they were studied in vitro. Dr Vercelli raises several excellent points. It is important to consider gene*environment interactions within the cell as well the classical meaning. A given SNP might yield different and even opposing effects when expressed in different cells types or under different developmental and/or environmental influences. This might be an important cause for the disparate results obtained in studies examining the same SNP in varied populations of different age, sex, and race distributions and subject to different environmental influences. Epigenetic mechanisms regulated by environmental influences add yet another layer of complexity to this paradigm. Environmental stimuli might induce acquired epigenetic states that affect gene expression and phenotypic outcome. Thus, gene*environment interactions are occurring at multiple levels—DNA, cell, tissue, organ, and human—and the interactions are subject to change over time depending on the developmental state and the immunologic milieu.

As these concepts become increasingly recognized, studies are now examining the effects of combinations of factors. Recently, a significant gene*gene interaction between an IL-4RA SNP and an SNP in the IL-13 promotor was reported, whereby individuals with the risk genotype for both genes were at almost 5 times greater risk for the development of asthma than individuals with both non-risk genotypes ($P = .0004$).⁸ The molecular mechanisms that are responsible for this genetic predisposition are not yet understood. To begin to understand how these and other genetic SNPs contribute to the final phenotype, the immunologic phenotypes associated with given genotypes over time need to be understood. Toward this end, in an original contribution in this issue, Hoffjan et al⁹ examined the effect of genetic variation in 35 genes (61 SNPs) on the cytokine response profiles in 207 European children at birth and at age 1 year. Furthermore, they related this to several atopic phenotypes, including atopic dermatitis, IgE, and allergic sensitization as determined by skin test at age 1. Although the sample size is too small to allow for determination of gene*gene interactions, the investigators identified 5 SNPs associated with atopic phenotypes in the first year of life. In addition, they found 2 of these to be associated with altered cord blood IL-13 responses at birth. The study is interesting and supports the concept that different patterns of cytokine responses in early life might be due in part to genetic influences. The relevance of these findings remains to be determined, as do the molecular mechanisms responsible for the different patterns of cytokine responses. Although the authors examined cytokine responses in cord blood at birth, unknown environmental influences during pregnancy have no doubt impacted the findings. Despite these limitations and the small sample size, the findings of Hoffjan et al can shape

hypotheses to test in larger studies examining the cumulative effects of multiple genes and environmental exposures in a prospective longitudinal design.

In another original contribution in this issue, Khoo et al¹⁰ investigated the genetic contribution of an SNP in the promotor region of the *IL12B* gene in a population derived from the Melbourne Asthma Study cohort. The use of this well-studied cohort with long-term longitudinal phenotypic data is a considerable advantage of the study by Khoo et al. They found that the *IL12B* promotor SNP was not associated with the presence of atopy or asthma or with asthma severity at several different ages. Unfortunately, the study does not provide any information about the functional relevance of this SNP or the levels of IL-12 in the subjects at baseline and during infections. Again, these questions are best assessed in a prospective design in which information about infections can be obtained, IL-12 levels can be determined, and environmental exposures can also be assessed. In addition, the functional relevance of the SNP can be directly determined through basic promotor studies. Again, a blend of epidemiologic, clinical, translational, and basic research is needed to dissect these questions.

Interestingly, in the 1800s Bostock and Blackley described allergy as “a rare disorder restricted to the privileged class.”¹ This is clearly no longer the case. Atopic disorders are very prevalent, affecting up to 40% of populations in western civilizations,¹¹⁻¹³ and the incidence is on the rise.¹⁴ The widespread incidence of atopic conditions and their effects on quality of life impose a heavy burden on society. The direct costs of just one disorder, allergic rhinitis, are estimated to be approximately \$4 billion; indirect costs, including missed workdays, push the costs to over \$7 billion. Despite this marked increase in asthma and allergy in some parts of the world, the prevalence of these disorders has not appreciably changed in developing countries. The increasing prevalence of allergic disease over the last 3 decades and the differences in prevalence rates between developed and less developed countries and between rural and urban areas strongly support environmental causations.¹⁵ The hypothesis that has come to the forefront was first proposed by David Strachan¹⁶ in 1989. This “hygiene hypothesis” proposes that infections in early childhood might prevent the development of allergic disease. Several epidemiologic studies have supported the idea that reduced microbial exposure in childhood can contribute to the development of allergic disorders.¹⁷⁻²⁰ Mechanistic explanations for the hygiene hypothesis initially invoked the T_H1/T_H2 model, arguing that in the absence of infections there is a lack of shift from the T_H2 -biased immune system of an infant.^{21,22} Recently, an alternate hypothesis has been raised that proposes that an absence of counterregulation would explain the simultaneously observed recent increases in allergic diseases, as well autoimmune diseases.²³⁻²⁵ A comparison of these 2 theories is provided in a Rostrum article in this issue by Dr Romagnani.²⁶

Although a “dirty” environment might be protective in early life, dust mite exposure later in life contributes to

allergic symptoms in sensitized individuals. The identification of the dust mite and the first demonstration of its relevance in allergic respiratory diseases was first published in this Journal in 1967 (see the Allergy Archives feature in this issue). The landmark findings of those Dutch investigators are still very relevant today, as we continue to debate the “mite-y” truth.

Is dust mite exposure relevant to allergic disease? It seems intuitive that if one is sensitized to dust mite, avoidance would be beneficial. Nevertheless, studies examining this have been contradictory. This is the topic of a separate editorial in this issue by Dr Platts-Mills,²⁷ who raises several key points. Avoidance studies aimed at investigating the relevance of an intervention that decreases exposure with clinical outcome must demonstrate that the exposure was significantly changed and that the outcome changed. Exposure needs to be defined as total exposure, not only in terms of total load but also in terms of time and space. A child might be in the home for the greater part of a given day, but one cannot ignore the contributions of school, grandmother's house, or even a summer spent with another parent.

In the end, the “mite-y” truth is that considerable progress has been made in terms of our understanding of the pathogenesis of allergic diseases and the molecular mechanisms that underlie the recent rise in their prevalence. This issue of the Journal provides a “window of opportunity” for the allergist to evaluate the current state of gene*environment*time interactions before the next landmark discovery.

REFERENCES

1. Cohen SG, Samter M. Classics in allergy. Carlsbad (CA): NIH Symposia Foundation; 1992.
2. Coca AF, Cooke RA. On the classification of the phenomena of hypersensitization. *J Immunol* 1923;8:163-82.
3. Sly RM. Changing prevalence of allergic rhinitis and asthma. *Ann Allergy Asthma Immunol* 1999;82:233-48; quiz 48-52.
4. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;332:133-8.
5. von Mutius E. Influences in allergy: epidemiology and the environment. *J Allergy Clin Immunol* 2004;113:373-9.
6. Weiland SK, von Mutius E, Hirsch T, Duhme H, Fritzsche C, Werner B, et al. Prevalence of respiratory and atopic disorders among children in the East and West of Germany five years after unification. *Eur Respir J* 1999;14:862-70.
7. Vercelli D. Genetics, epigenetics, and the environment: switching, buffering, releasing. *J Allergy Clin Immunol* 2004;113:381-6.
8. Howard TD, Koppelman GH, Xu J, Zheng SL, Postma DS, Meyers DA, et al. Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *Am J Hum Genet* 2002;70:230-6.
9. Hoffjan S, Ostrovskaja I, Nicolae D, Newman DL, Nicolae R, Gangnon R, et al. Genetic variation in immunoregulatory pathways and atopic phenotypes in infancy. *J Allergy Clin Immunol* 2004;113:511-8.
10. Khoo S-K, Hayden CM, Roberts M, Horak E, de Klerk N, Zhang G, et al. Associations of the *IL12B* promoter polymorphism in longitudinal data from asthmatic patients 7 to 42 years of age. *J Allergy Clin Immunol* 2004;113:475-81.
11. Holford-Strevens V, Warren P, Wong C, Manfreda J. Serum total immunoglobulin E levels in Canadian adults. *J Allergy Clin Immunol* 1984;73:516-22.
12. Peat JK, Britton WJ, Salome CM, Woolcock AJ. Bronchial hyperresponsiveness in two populations of Australian schoolchildren. III. Effect of exposure to environmental allergens. *Clin Allergy* 1987;17:291-300.
13. Cline MG, Burrows B. Distribution of allergy in a population sample residing in Tucson, Arizona. *Thorax* 1989;44:425-31.
14. Mannino DM, Homa DM, Pertowski CA, Ashizawa A, Nixon LL, Johnson CA, et al. Surveillance for Asthma—United States, 1960-1995. *Morb Mortal Wkly Rep* 1998;47:1-27.
15. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995;8:483-91.
16. Strachan DP. Hay fever, hygiene, and household size. *Bmj* 1989;299:1259-60.
17. Kilpelainen M, Terho EO, Helenius H, Koskenvuo M. Farm environment in childhood prevents the development of allergies. *Clin Exp Allergy* 2000;30:201-8.
18. Bodner C, Godden D, Seaton A. Family size, childhood infections and atopic diseases. The Aberdeen WHEASE Group. *Thorax* 1998;53:28-32.
19. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;343:538-43.
20. Matricardi PM, Franzinelli F, Franco A, Caprio G, Murru F, Cioffi D, et al. Sibship size, birth order, and atopy in 11,371 Italian young men. *J Allergy Clin Immunol* 1998;101:439-44.
21. Prescott SL, Macaubas C, Holt BJ, Smallacombe TB, Loh R, Sly PD, et al. Transplacental priming of the human immune system to environmental allergens: universal skewing of initial T cell responses toward the Th2 cytokine profile. *J Immunol* 1998;160:4730-7.
22. Barrios C, Brawand P, Berney M, Brandt C, Lambert PH, Siegrist CA. Neonatal and early life immune responses to various forms of vaccine antigens qualitatively differ from adult responses: predominance of a Th2-biased pattern which persists after adult boosting. *Eur J Immunol* 1996;26:1489-96.
23. Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. *Nat Rev Immunol* 2001;1:69-75.
24. Yazdanbakhsh M, Kremsner PG, van Ree R. Allergy, parasites, and the hygiene hypothesis. *Science* 2002;296:490-4.
25. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347:911-20.
26. Romagnani S. Immunologic influences on allergy and the T_H1/T_H2 balance. *J Allergy Clin Immunol* 2004;113:395-400.
27. Platts-Mills TAE. Allergen avoidance. *J Allergy Clin Immunol* 2004;113:388-91.