

Gene-environment interactions: The road less traveled by in asthma genetics

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Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.

—Robert Frost, “The Road Not Taken,” 1920

The genetics of asthma and allergy has come to a crossroads. After a period of incremental progress fueled by classical association and linkage studies,¹ the year 2007 witnessed a quantum leap in genotype-phenotype association analyses with the publication of the first genome-wide association study (GWAS) for an asthma trait (childhood asthma).² GWASs rely on dense sets of single nucleotide polymorphisms across the genome to survey the most common genetic variants for a role in disease or to identify the heritable quantitative traits that are risk factors for disease.³

Very few new approaches in biology and medicine have elicited as much enthusiasm and as much expectation as GWASs. 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.⁴ On the other hand, effect sizes for common variants are typically modest, and given the need to exceed stringent statistical thresholds, the power to discover novel associations has been relatively low.⁴ Another intriguing complication, rooted in biology as much as in statistics, also looms large and is clearly 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.² Because the region of association on chromosome 17q21.1 spanned 206 kb and included 19 annotated genes, the identification of the gene or genes responsible for the association was pursued by profiling transcription of the genes located within the relevant genomic interval. The rationale underlying this approach was that variation in gene transcription might mediate disease susceptibility and transcript abundance might 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 the asthma family panel showed that the single nucleotide polymorphisms associated with childhood asthma were consistently and strongly associated in cis with transcript levels of a novel candidate, *ORMDL3*, suggesting that genetic variants regulating *ORMDL3* expression are determinants of susceptibility to childhood asthma.

An interesting development took place more recently when the association between the variants at chromosome 17q21 and an increased risk of asthma was re-examined in a large, family-based data set from the Epidemiological Study on the Genetics and Environment of Asthma that included extensive phenotypic and environmental data.⁵ 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 marked developmental heterogeneity in the effects of chromosome 17q21 variants (association with early-onset but not late-onset asthma) and strong gene-environment interactions (effect on early-onset asthma is 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.

The *Journal of Allergy and Clinical Immunology* has a stellar record of publishing seminal studies of interactions between specific genes, such as *CD14*, Toll-like receptor 2, and chromosome 5 variants, and defined environments, such as compounds typically found in farming communities,⁶⁻⁹ microbial products from pets¹⁰ and households,¹¹ and tobacco smoke.¹² The conclusion prompted by all these studies is the same: a single polymorphism can be associated with either disease or protection depending on the environment to which a subject is exposed. Even gene expression data appear to reflect geographic and environmental differences. Recent studies in the Moroccan Amazighs, the Berber peoples of northwest Africa, show a strong genome-wide gene expression signature of regional population differences that presumably include lifestyle, geography, and biotic factors.¹³ The suggestion from this work is that the latter can play as great a role as genetic divergence in modulating gene expression variation in human subjects.¹³

That the environment critically modulates the effect of genetic variants is now clear. Often less clear is the identity of the relevant exposures. Environmental exposures are often complex: smoking is a factor involved in gene-environment interactions, but sex is also.¹⁴ Therefore it is not unreasonable to surmise that as-yet-undetected gene-environment interactions might contribute to the problems of replication that still plague association studies.

There is no question that gene-environment interactions introduce disturbing complications into genetic studies. The already steep demands of GWASs in terms of sample size (according to a

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recent estimate, achieving 90% power to detect an allele with 20% frequency and a factor of 1.2 effect at a statistical significance of 10^{-8} requires 8600 samples⁴) become even more daunting if the need arises to stratify populations by environmental exposure. Yet do we really have a choice? Hoping that hypothesis-independent genetic analyses of larger and larger populations will solve complex diseases without any consideration for environmental effects might be as unrealistic as or even more unrealistic than acknowledging the need to systematically include the environment in the analysis. Most importantly, this further quantum leap might well be necessary. Indeed, the role played by environmental exposures in complex disease pathogenesis is most likely not superimposed but integral to the nature of these disorders and as such cannot be neglected.

Unfortunately, the technological advances of genetics, which now make genotyping a million polymorphisms fairly feasible, have vastly outpaced progress in environmental assessments. As Erika Von Mutius writes in this issue, "As long as we are not able to relate individual exposures to quantities of specific compounds in the environment, our ability to understand the effects of environmental exposures will be very limited. Likewise, the understanding of mechanisms underlying gene-environment interactions will be very restricted. Therefore the enormous progress in the field of genetics and genomics calls for an investment in the development of better methods of environmental exposure assessment."¹⁵

Becoming more imaginative in our research might help. The scenario sketched out for us by Saffron Willis-Owen and William Valdar,¹⁶ which advocates the use of mouse models to interrogate and decipher gene-environment interactions, is simply tantalizing. Certainly a lot can be done in animal models that cannot be achieved in human subjects, and mechanistic analyses will greatly benefit from this complementary approach. Of course, the realization that gene-environment interactions (sometimes unplanned for) find their way even into mouse models is humbling because it shows how difficult it is to control for such effects, even under highly standardized conditions. The devil is most definitely in the detail, as our authors put it. This means perhaps it is time to rise to the occasion and consider the interactions between genes and environment no longer as a nuisance but as an opportunity to better characterize the plasticity of genetic programs, to understand how the environment (by definition an entity that allows effective interventions) modifies disease susceptibility, and to use this knowledge for prevention and treatment. At a time when the holy grail

of genetics is assembling larger and larger populations for hypothesis-generating studies, proposing gene-environment interaction analyses of adequate power might be daunting and even unpopular. However, adequate technologies lie within reach, and what we have learned, and our authors lucidly remind us of, is enough to motivate us to take the road less traveled by. Chances are, it will make all the difference.

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