Published in final edited form as:

Trends Genet. 2011 March ; 27(3): 107–115. doi:10.1016/j.tig.2010.12.004.

Gene-Environment Interactions in Human Disease: Nuisance or Opportunity?

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Abstract

Many environmental risk factors for common, complex human diseases have been revealed by epidemiologic studies, but how genotypes at specific loci modulate individual responses to environmental risk factors is largely unknown. Gene-environment interactions will be missed in genome-wide association studies and may account for some of the ‘missing heritability’ for these diseases. In this review, we focus on asthma as a model disease for studying gene-environment interactions because of relatively large numbers of candidate gene-environment interactions with asthma risk in the literature. Identifying these interactions using genome-wide approaches poses formidable methodological problems and elucidating molecular mechanisms for these interactions has been challenging. We suggest that studying gene-environment interactions in animal models, while more tractable, is not likely to shed light on the genetic architecture of human diseases. Lastly, we propose avenues for future studies to find gene-environment interactions.

The Problem: Accounting for the Heritability of Common Human Diseases

Dissecting the genetics of common human diseases with complex etiologies continues to be challenging and the genetic architectures of these diseases remain elusive. Despite the many successes of genome-wide association studies (GWAS) during the past four years (refs.1,2 as examples), there is a growing consensus that the common variants with modest effects on disease risk discovered through GWAS do not account for the majority of the estimated heritabilities of these diseases. This observation was initially termed ‘missing heritability’^{3–5}, to suggest that additional genetic variation (such as rare variants or copy number variants) or interactions that are not explicitly modeled (such as epistasis or gene-environment interactions [GEIs]) have been missed by GWAS and may account for a significant proportion of the heritability. More recently, the term ‘hidden heritability’⁶ was suggested in response to the argument that the joint or simultaneous analysis of individual common risk alleles may account for more of the heritability than the sum of each allele^{7,8}. Of course, it is likely that the genetic architecture of most, if not all, common human diseases will include all of the above components, and it is timely in the post-GWAS era to begin to directly assess the contribution of each to the overall heritability of complex diseases. Here, we will

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focus on the role of GEIs on risk for human disease and propose asthma as a model disease for understanding the importance of genetic modifiers of environmental risk factors. We will first review the role of environmental exposures on asthma risk, using the term ‘environment’ to reflect any endogenous or exogenous non-genetic factor that influences risk; and then provide examples of specific GEIs that represent different patterns of associations. Finally, we will discuss potential mechanisms for GEIs and speculate on future directions for this field.

Asthma as a Model for Studying GEIs

Asthma is a heterogeneous disease that is characterized by reversible airway obstruction and airway inflammation. It is among the most common chronic diseases, affecting more than 300 million people worldwide⁹. Similar to other immune-mediated diseases, the prevalence of asthma is highest among developed countries and has risen significantly over the past few decades¹⁰, especially in countries transitioning to a western lifestyle⁹, attesting to the importance of environmental modifiers of disease risk.

Epidemiologic studies of asthma have revealed numerous associations between exposures and subsequent risk for asthma. The sheer number of validated risk factors for asthma, many of which are often known and measurable, have placed asthma at the forefront of studies on GEIs and some of the best and most replicated examples of such interactions have come from this field (see, for examples, recent reviews on this topic^{11–14}). Moreover, these studies have established that timing of exposure in the lifecycle is a critical variable in determining risk (Figure 1), and that risks differ for childhood-onset and adult-onset asthma.

The prenatal environment is the first exposure that establishes lifelong risks for asthma in the fetus. During this period, maternal smoking is a significant risk for subsequent asthma^{15–17}. Maternal asthma is among the most significant and consistent risk factors, and a greater risk factor than paternal asthma, for childhood asthma^{18–20}, thereby suggesting that the *in utero* environment differs between asthmatic and non-asthmatic mothers and contributes to subsequent risk of asthma in the fetus. Sex, which is established at conception, has opposite effects on asthma risk in the pre- and post-puberty periods, whereby many more boys receive a diagnosis of asthma by the age of 6 but diagnoses in girls predominate after puberty (reviewed in reference²¹). Moreover, asthma resolves in many boys with early-onset asthma so that by adulthood there are significantly more women than men with asthma. Sex may exert its effects on risk prenatally or throughout life by modifying responses to other environmental risk factors, or it may directly affect risk by differentially modifying gene expression (discussed in detail in reference ²¹).

During the first year of life, and in some cases prenatally, a number of exposures have been associated with protection from asthma in childhood. For example, exposure to large animals among European farmers^{22–25}, having a dog in the home^{26–28}, attending daycare^{29–31}, or drinking unprocessed cow’s milk^{32,33} has been associated with protection against asthma in childhood, and gives support to the ‘Hygiene Hypothesis’ (Box 1) as an explanation for the rising prevalence of asthma risk in westernized countries³⁴. In contrast, some ‘exposures’ during the first three years of life are associated with higher risk for asthma. These include allergic sensitization and the presence of wheezing illnesses with respiratory viral infections, particularly those due to rhinovirus or respiratory syncytial virus^{35–38}. Whether these conditions themselves alter the risk profile of the child or are merely early manifestations of asthma in genetically susceptible children is not known, but their associations with the subsequent development of asthma by age 6 is undisputed.

Beyond infancy, additional exposures are important in establishing risk for asthma, including obesity or high body mass index (BMI)^{39–41}, occupational exposures^{42,43}, and

air pollution^{44–46}. These risks are likely increasing the penetrance of asthma in genetically susceptible individuals, but it is noteworthy that the risk alleles associated with occupational asthma^{47,48}, for example, are often at loci that have not been implicated in asthma in non-exposed individuals. Moreover, it is likely that childhood- and adult-onset asthma (i.e., age of onset of asthma) have only partially overlapping genetic etiologies^{2,49,50}.

Demonstrating that a particular exposure is associated with risk for or protection from a disease does not necessarily imply that GEIs are at play, but the fact that not all exposed individuals develop the disease suggests that genetic variation between individuals may be important. To establish a GEI one must show that specific genotypes have different responses to the same ‘exposure’ by demonstrating that the effects of ‘exposure’ (for example, the development of or protection from a disease) vary between individuals with different genotypes. GEIs can show different patterns of associations, which are described below for asthma and in Table 1 for other phenotypes and diseases. The different patterns of GEIs are illustrated in Figure 2.

Examples of GEIs in Asthma

Microbial Exposure, Genotype, and Protection from Asthma

One of the most established and best replicated GEI on risk for asthma or allergic disease is that resulting from interactions between genotype for a promoter polymorphism (–159C/T, a.k.a. –260C/T, rs2569190) at the locus encoding a subunit of the endotoxin receptor on mononuclear cells, *CD14*, and exposure to microbes, as assessed by house dust endotoxin levels^{51,52}, having a pet in the house at birth^{53,54}, working with laboratory animals⁵⁵, contact with farm animals⁵⁶, and country living during childhood⁵⁷. In these studies, the –159T allele is associated with asthma or allergic disease among the highly “exposed” subjects, whereas the –159C allele is associated with asthma or allergic disease among “non-exposed” subjects. No associations with this polymorphism is seen among subjects with intermediate levels of exposure. This “flip-flop” pattern of association results in overall poor replicability of associations with the *CD14* –159C/T polymorphism when environmental exposures are not considered, as has been reviewed elsewhere^{58–60}.

Genetic modifiers of environmental tobacco smoke (ETS) exposure on asthma risk

ETS exposure in early life is a well established risk factor for reduced lung function, increased numbers of lower respiratory tract infections, and asthma^{15–17}. However, not all exposed children show these effects. Interactions between *in utero* or neonatal exposures to ETS and a number of genetic loci were first suggested by family-based linkage studies^{61–63}, with some chromosomal regions showing linkage to asthma or bronchial hyperresponsiveness (BHR) only in exposed children (chromosomes 1p⁶¹, 1q63, 3p62, 4q63, 5q61, 62, 17p61) or only in non-exposed children (chromosomes 1q⁶¹, 5p63, 6p61, 9q61, 17p63, 19p62). The 5q region, which harbors many asthma candidate genes, was linked to asthma in the exposed children in two studies; one other region on 1q43 showed interaction effects in two studies but in opposite groups (in exposed children in one study and in non-exposed children in the other). In the past three years alone, interactions between *in utero* or neonatal ETS exposure and genotypes at candidate loci on risk for asthma or wheezing have been reported, including but not limited to single nucleotide polymorphisms (SNPs) in ADAM metalloproteinase domain 33 (*ADAM33*)⁶⁴, glutathione S-transferase M1 (*GSTM1*)⁶⁵, interleukin 13 (*IL13*)⁶⁶, interleukin 1 receptor antagonist (*IL1RN*)⁶⁷, tumor necrosis factor (*TNF*)^{68,69}, and the 17q21 asthma locus^{49,70}. In all but one of these studies⁶⁹, associations with asthma were significant in exposed children only⁶⁹. It is notable that the *IL13* gene resides at chromosome 5q31 within the locus showing interactions in two linkage studies. In all three studies, the linkage^{61,62} or association⁶⁶ with asthma was only among

children exposed to ETS *in utero* or in the first year of life, providing consistent evidence for an '*IL13*-ETS exposure' association with asthma risk. Accounting for this easily measurable exposure in genetic studies may enhance our ability to identify important risk loci.

Maternal asthma as a prenatal 'environmental' exposure

Maternal asthma remains among the most significant risk factors for the development of childhood asthma in her offspring^{18–20}. Because asthma risk alleles are inherited from both parents, this suggests that the *in utero* environment differs between mothers with and without asthma. Such differences could result in differential 'prenatal programming'⁷¹ of immune cells in the fetus depending on the asthma status of the mother, or from exposure to asthma medications (e.g. corticosteroids) taken by asthmatic mothers during pregnancy. Evidence that fetal genotype interacts with 'maternal asthma' to determine risk for asthma in the child was first provided by a positional cloning study that identified human leukocyte antigen (*HLA*)-*G* as an asthma susceptibility gene⁷². In that study, the –964G allele was associated with asthma only in families with an affected mother, and the –964A allele was associated with asthma in families with an unaffected mother. Paternal asthma status had no effect. Moreover, the parental origin of the fetal alleles had no effect on risk, indicating that paternal imprinting is not involved. Subsequent studies⁷³ implicated a SNP (+3142C/G; rs1063320) that resides in the 3' untranslated region (UTR) within a target site for three microRNAs (miRNAs)⁷³. In the presence of any of these miRNAs, expression of the G allele is suppressed whereas expression levels are unchanged for the C allele⁷³. The GG genotype, which is suppressed in the presence of the miRNAs, was associated with significant protection from asthma among children of mothers with asthma but with modest risk for asthma among children of mothers without asthma. The mechanism through which the 'maternal asthma-fetal HLA-G genotype' interaction influences subsequent risk for asthma in the child is still unknown, but modulation of expression via miRNA targeting could be involved. Because asthma in the mother is such a strong predictor of asthma in her children, it is likely that other, as yet undiscovered, genes also play a role in modulating this effect.

Genotype-by-sex interactions and asthma risk

Although sex itself is genetically determined, the *in utero* environment with respect to sex hormones and all downstream targets differs between male and female fetuses beginning in the first trimester of pregnancy. Sex-specific differences in hormonal milieu and gene expression persist throughout life, and likely account for observed sex differences in disease prevalences²¹. Thus, it is possible that risk alleles for common diseases may have different effects in males and females, or affect males and females differently at specific stages of the lifecycle. In fact, sex-specific genetic effects are ubiquitous in the genomes of model organisms^{74–76}, and there are likely to be significant sex-specific genetic architectures for human quantitative traits in general^{21,77}, and for asthma-related quantitative traits in particular (reviewed in references 21,78).

For example, sex-specific linkages⁷⁸—and associations^{79,81,82} with asthma traits have been reported. One recent example is quite intriguing. The thymic stromal lymphopoietin (*TSLP*) gene encodes thymic stromal lymphopoietin, an IL-7-like cytokine that regulates allergic asthma in mouse models and shows increased expression in human airway epithelial cells from patients with asthma compared to controls (reference⁸¹ and citations therein). Expression of *Tslp* in mice leads to a more severe phenotype in females compared to males⁸³. In a follow-up of a linkage study in Costa Rican families, a SNP upstream of *TSLP* showed a female-specific association with elevated IgE levels⁸⁴. A subsequent study of *TSLP* in more than 13,000 subjects, revealed a complex pattern of interaction at this locus emerged. The T allele at a SNP upstream of the gene (rs1837253) was inversely associated

with asthma in boys but not in girls; however, the T allele at a second SNP in exon 1 (rs2289276) showed a stronger inverse association with asthma in girls than in boys, although the effect of this SNP on asthma risk was more variable between study samples. The investigators proposed that variation in *TSLP* may account for some of the curious epidemiological observations of age-sex interactions on asthma risk, as discussed above²¹.

GEIs in the nucleus

The nuclear milieu is a powerful determinant of GEIs, particularly for SNPs in regulatory regions. For example, the relative transcriptional activities of the –159C and –159T alleles of *CD14* (rs2569190), discussed above, differ between monocytes and hepatocytes, depending on the relative expression of SP1 and SP3, the transcription factors that bind the polymorphic promoter region and control its activity⁸⁵. An *IL13* reporter construct carrying the minor –1112T allele (rs1800925) is significantly more active than the –1112C allele in primary human polarized T helper 2 cells (Th2 cells), but is less active than the –1112C allele in CD4+ Jurkat T cells. The two *IL13*–1112 alleles had comparable activity in non-polarized, freshly isolated CD4+ T cells. The allele-specific patterns of transcription factor binding in these different cellular models determine, at least in part, the differential activity of the *IL13* promoter⁸⁶, an observation that has recently been validated in humanized mice⁸⁷. Remarkably, this “flip-flop” pattern of gene expression was detected at distinct stages of differentiation of the same cell, rather than the more commonly reported differences between distinct cell types (as described above for the *CD14* promoter variants). The implication of these data is that specific genetic variants may remain functionally silent until the carriers of that variant are exposed to relevant environmental stimuli (allergens and/or parasites, in the case of *IL13*) that promote the differentiation of the cell. These findings illustrate the very essence of GEIs: both the functional variant and the environmental stimulus that modifies the cellular environment are required for the interaction to be manifested.

Epigenetics: The Link Between Genes and Environment?

Understanding the mechanisms that underlie GEIs is a formidable challenge. It is difficult enough to characterize the impact of polymorphisms on gene expression and function under static conditions (i.e., within a constant environment); it is considerably more challenging to elucidate the dynamic intertwining of polymorphic variation and environmental stimuli. This is why very little has been published to date about the mechanisms of GEIs, and no major finding has yet been reported for asthma. Nonetheless, there is consensus within the community that epigenetic mechanisms could explain the interplay between genes and the environment. The dynamic nature of this interplay is a quasi-perfect fit for the plasticity of epigenetic processes, which can be seen as the functional transducers of environmental cues⁸⁸. Stable epigenetic alterations can arise during cell development and proliferation, making it possible for cells of multicellular organisms to be genetically identical but structurally and functionally heterogeneous⁸⁹. Modifications in gene expression in response to environmental and/or developmental cues can result from modifications of DNA (e.g., by methylation) or from proteins that intimately associate with DNA (e.g., acetylation, methylation or phosphorylation of histones) (reviewed in references 90,91).

Precisely how epigenetic processes impact gene regulation, and to a lesser extent how environmental exposures impact epigenetic marks (such as methylation), has been extensively studied in recent years, and many striking examples of the latter have emerged (see reference ⁹² for a review of asthma genes). For example, diet can modulate gene expression by impacting DNA methylation in mice⁹³. The fidelity of methylation in the newly synthesized DNA strand depends on the availability of dietary methyl donors and cofactors required for S-adenosylmethionine synthesis, and the concentration of S-

adenosylmethionine affects DNA methyl transferase activity⁹⁴. In a mouse model, a maternal diet supplemented with methyl donors enhanced the severity of allergic airway disease that was inherited transgenerationally by litters exposed prenatally, but not among litters exposed during lactation or adulthood⁹⁵. Genome-wide methylation revealed 82 genes that were differentially methylated after prenatal supplementation with a methyl-rich diet; and methylation was associated with decreased transcriptional activity and increased disease severity. In particular, the runt-related transcription factor 3 gene (*Runx3*), which negatively regulates allergic airway disease, was excessively methylated and *Runx3* mRNA and protein levels were suppressed in progeny exposed *in utero* to a high-methylation diet. These findings indicated that dietary factors can modify the heritable risk of allergic airway disease through epigenetic mechanisms during a vulnerable period of fetal development. Consistent with this observation, maternal folic acid supplementation in the Norwegian Mother and Child Cohort Study (>32,000 children) resulted in a modest increase in wheezing and lower respiratory tract infections in children up to 18 months of age⁹⁶, although neither gene expression nor methylation studies were performed in these children. Therefore, the mechanism for the observed association can not necessarily be attributed to epigenetic modifications.

In summary, the evidence in favor of a strong relationship between environmental exposure, epigenetic changes, and asthma-related phenotypes is plentiful. What is still missing is an explicit link to specific genetic variants; that is, demonstration that an observed GEI results from an allele-specific epigenetic change at the implicated SNP.

GWAS, GWIS, and GEIs

The question as to how much of the ‘missing’ heritability in GWAS will be accounted for by GEIs remains unanswered at this time, although genome-wide interaction studies (GWIS) are beginning to emerge. One of the greatest challenges for this unbiased approach to gene (or interaction) discovery is that of power (see references 97,98 for further discussion). The first GWIS for childhood asthma and farming exposures has recently been completed in approximately 1700 children from four rural regions in central Europe who participated in the larger GABRIEL study⁹⁹. This carefully designed investigation of interactions between genome-wide SNP genotypes and farming exposures on asthma risk highlights some of the challenges inherent to taking studies of GEIs to the genome-wide level. This study was well-powered to detect interactions with common alleles in the frequency range of 40–70%. Nevertheless, no interactions in the GWIS were significant, not even those involving SNPs in genes previously identified in an asthma GWAS² or SNPs in genes that showed interactions with farming exposures in previous candidate gene studies (including the *CD14* polymorphism discussed above). That no interactions were found with the SNPs identified in a previous GWAS is not surprising because those variants were selected based on their very significant main effects on asthma risk and because the earlier GWAS examined largely non-farming populations. However, the lack of interactions with the SNPs in genes previously showing interactions was surprising, particularly because many of the original studies were conducted in central European farming populations. Only two of the latter genes showed interactions, and both were quite modest in effect: SNPs at the toll-like receptor 4 (*TLR4*) and nucleotide oligomerization domain containing 1 (*NOD1*) genes interacted with ‘contact with cows’ to modify asthma risk. The investigators attributed the lack of interactions with SNPs in these genes in part to the fact that they did not directly measure endotoxin levels, an important environmental variable in many of the earlier studies. In contrast, using a two-step strategy that allows for less stringent thresholds of significance in the second step⁹⁷, 97 SNPs showed interactions with at least one environmental exposure on asthma risk, providing at least eight intriguing candidate genes for further studies. Of the 97 SNPs, 38% showed protection only in the exposed group, none

showed protection only in the non-exposed group, and 62% showed a ‘flip-flop’ pattern of association (Figure 2).

Overall, the authors argue that the absence of significant GEIs in the GWIS suggests that interacting alleles may be in the frequency range <40%, for which their study was not well powered. Alternatively, differences in the microenvironments between the four population samples included in the study may have influenced the ability to detect GEIs. It is even possible that subtle genetic substructure, particularly at key loci, is not accounted for by the global genomic control parameter typically used in such studies (for example, as in reference 2). Because very large samples of human subjects are required for studies of interactions, these studies will nearly always be composed of individuals who differ with respect to relevant environmental exposures and to some degree by ethnicity or genetic backgrounds, which may mask true interactions. That is, the genetic and environmental heterogeneity that is inevitably present in large samples may make this approach less amenable to revealing GEIs than more focused studies. While some exposures, such as prenatal exposure to ETS or sex, may be more straightforward to assess and sufficiently robust in their effects to withstand subtle sample heterogeneity, others may not be amenable to very large studies of human subjects. The fact that the GWIS did not detect interactions between a SNP in nearly perfect linkage disequilibrium (LD) with the *CD14* –159C/T variant and exposure to animals, despite the high replicability of this association in previous smaller studies, as discussed above, suggests to us cryptic heterogeneity between study samples.

In fact, both background genes and gene-gene interactions (epistasis) can mask or enhance GEIs, as elegantly demonstrated in yeast¹⁰⁰, and at least one example of a gene-by-gene-by-environment interaction in humans has been put forth¹⁰¹. Using yeast as a model system, pairwise epistatic interactions between four variants accounted for a majority of the heritability of sporulation efficiency in strains grown in different media (environments), but the nature of the pairwise interactions differed between strains grown in different environments so that when environment and strain are ignored, none of the pairwise gene-gene interactions are significant. In other words, the relative importance of alleles and their interactions varied with respect to both genetic background and environment, and were not constant between individuals¹⁰⁰. We can expect that the genetic architecture of common diseases and quantitative phenotypes in humans will be at least this complex and it may therefore be unrealistic to assume that the same constellation of SNPs will explain the same proportion of the heritability in all populations and in all environments. Thus, the ‘missing’ heritability may not just be ‘hidden’ due to failure to consider the combined effects of associated SNPs but rather because we are averaging over environments and genetic backgrounds, i.e., ignoring ‘context’.

Conclusions and Future Perspectives

It is for this and related reasons that animal models are often proposed as powerful tools for studies of complex interactions¹⁰². While we agree that studies in model systems can provide valuable insights into the architecture of gene-gene, gene-environment, and gene-gene-environment interactions¹⁰⁰, it is unclear that animal models will offer insights into specific interactions contributing to disease risk in humans because of the context-dependency of these effects. In contrast, cellular human models may provide one approach and a reasonable compromise for studies of GEIs. Although these studies will sacrifice organismal context, cellular systems can reveal a finite number of genotype-dependent interactions occurring in response to specific ‘exposures’ under relatively controlled conditions and, in addition, allow direct studies of mechanism. For example, using a systems genetics approach to identify GEIs, transcript abundance was measured in primary

endothelial cells from 96 individuals in the basal state and after exposure to proinflammatory oxidized phospholipids¹⁰³. In parallel, the same cultures were genotyped for genome-wide SNPs. Roughly one-third of the 59 transcripts that were most regulated (i.e., more than two-fold change in transcript levels) and heritable across cell passages showed evidence of interactions. More than one-quarter of individual SNPs showing GEIs explained 24–32% of the fold-change in transcript levels and six gene-environment ‘hotspots’ were identified as co-localized SNPs that regulated the response of 10 or more transcripts to proinflammatory oxidized phospholipids. Causal candidates were identified and subjected to further functional and validation studies. The investigators suggested that GEIs affecting gene expression might be an important attribute of common, complex human diseases. We further suggest that this approach, applied to additional cell types and exposures, is a powerful tool both for identifying candidates that can be subjected to more targeted GEI studies in human populations and for elucidating the mechanism(s) that underlie GEIs.

A complementary, and equally important, avenue of investigation is to characterize GEIs in human populations. The important question of how to maximize our ability to detect GEIs given their subtle effects and therefore elusive nature remains. A critical consideration in this context is that most of the well-validated GEIs have not been found by chance. Rather, they were discovered using models based on our knowledge of biological processes and/or pathways. How, then, do these prior successes inform our ability to discover additional GEIs and where should we look for them? We propose that GEIs are most likely to occur in, and impact on, signaling pathways regulated by threshold effects – that is, whenever *quantitative* differences in the intensity of the signal delivered by exogenous or endogenous stimuli result in *qualitative* differences in the outcome of that signal. In the immune system, for instance, weak versus strong signals can result in distinct and often opposite effects, particularly on cell fate determination. The choice between a Th2 and a Th1 cell fate in response to weak or strong T cell receptor cross-linking is a paradigmatic case¹⁰⁴. Such environmental stimuli and gain- or loss-of function variants in the receptors and/or adaptors that transduce these signals are excellent candidates for GEIs. Indeed, the reason why candidate gene studies have been so successful in discovering and characterizing GEIs may be that these studies have explicitly, or more often implicitly, focused on processes, such as innate immunity, in which the strength of the environmental signal plays a pivotal role.

In conclusion, the evidence for GEIs in the literature is compelling, as is the argument that the failure to model GEIs in genetic studies will result in missing potentially important loci that show interactions, particularly those with ‘flip-flop’ patterns of association. Thus, although the ‘environment’ may be considered a ‘nuisance’ to genetic studies, we prefer to think of it as an outstanding ‘opportunity’ to understand disease heterogeneity, to provide clues to the causative pathways in asthma pathogenesis, and to inform us on the complex genetic architecture of common diseases and quantitative phenotypes.

The Hygiene Hypothesis

The Hygiene Hypothesis is an evolving concept. The hypothesis was initially formulated to explain the protective effect of having older siblings on risk of hay fever and eczema³⁴ and later extended to explain the marked increase in the prevalence of allergies observed in western societies over the last few decades. Reduced exposure to infections in early childhood not only due to smaller family sizes, but also to improved living standards and higher personal hygiene, has been proposed to result in increased risk of developing allergic diseases. This theory was then integrated with the then dominant Th1/Th2 paradigm and further suggested that the hygienic environments associated with western lifestyles deprive the immune system of stimuli required to boost Th1 responses in early

childhood, leading to a surge in the prevalence of Th2-mediated allergic disease¹⁰⁵. When it became clear that both Th2-mediated allergic disorders and Th1-mediated autoimmune diseases are on the rise in the western world¹⁰, the hygiene hypothesis was further updated with a regulatory twist. According to its most recent version, immunoregulatory mechanisms are activated by interactions between the innate immune system and the microbial environment, particularly when these interactions occur *in utero* and/or in early life^{106,107}. These mechanisms balance and fine tune both Th1 and Th2 responses, but are currently compromised by a decrease in, and possibly by qualitative alterations of, the microbial burden the immune system encounters in western societies¹⁰⁸. This hypothesis awaits further integration with our still incomplete understanding of the role that genetic variation plays in shaping immune responses to environmental stimuli¹⁰⁹.

Acknowledgments

This work was supported by National Institutes of Health grants HL085197, HL7831, HL101651 to C.O. and HL100800, HL66391, AI076715 to D.V. The authors acknowledge S.A. Willis-Owen and W. Valdar for first using the expression “nuisance or opportunity” in the context of GEIs in their 2009 review and F. D. Martinez, J. E. Gern, R. J. Lemanske, E. von Mutius, and M. Ege for helpful discussions. The authors apologize to those investigators whose work was not cited due to space constraints.

Glossary

Atopic dermatitis	also called eczema, is an inflammatory skin disease; it is particularly common in young children
Bronchial hyperresponsiveness (BHR)	a clinical measure of airway reactivity, usually in response to inhaled methacholine, which many studies use as a criterion for asthma diagnosis
CD4+ T cells	the population of T cells (typically, with helper function) that express the CD4 surface marker and, depending on the cytokine milieu, will differentiate along the Th1 or Th2 pathway
Endotoxin	a structural component of the gram-negative bacterial cell that is recognized by the innate immune system and has been associated with complex effects on human diseases
Epigenetic	heritable changes in gene expression that are not encoded in the DNA sequence, but attributed to mechanisms such as methylation of CpG dinucleotides or post-translational histone modifications
Epistasis	interaction between genes that are not additive; or when the expression of one gene is dependent on the expression of a second gene
Flip-flop	when opposite alleles are associated with risk for a disease or a phenotype in different groups (e.g., ethnic groups, groups stratified by an environmental exposures)
Heritability	the proportion of the total phenotypic variance that is attributed to genetic variance
Penetrance	the proportion of individuals with the risk genotype that express the phenotype (or disease)

Th2 cells

polarized CD4⁺ T cells that differentiate in response to allergen exposure or parasitic infections and provide signals (cytokines) responsible for production of IgE antibodies, eosinophilia, mucus metaplasia, alternative macrophage activation and fibrosis. In the lung, these immune responses are associated with bronchial hyperresponsiveness and ultimately allergic inflammation and asthma.

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Figure 1.

Risk and Protection Factors Influence Asthma Risk Throughout the Lifecycle.

Epidemiologic studies of asthma have established numerous risk and protection factors that exert their effects at specific stages of the lifecycle. The relationship of some investigated exposures that have equivocal associations with risk or protection are not shown. These include breastfeeding effects and cat in the home at birth on subsequent risk for asthma in the child, as examples. A. Environmental exposures that have been associated with increased risk for asthma. B. Stages of the lifecycle that are “sensitive” to the epidemiologic risk and protective factors. C. Environmental exposures associated with protection from asthma.

Figure 2. Types of GEIs. The yellow line in each panel corresponds to risk in exposed individuals; the red line corresponds to risk in non-exposed individuals. Examples from this review that illustrate each type of interaction are shown below the panels. It is notable that no clear examples of specific SNPs or genes involved in GEIs limited to non-exposed individuals were reported in the studies reviewed here, including the recent GWIS of farming exposures and asthma⁹⁹. Not all interactions shown have been replicated or substantiated by other reports in the literature.

Table 1

Examples of recent (2009–2010) reports of GEIs for behavioral, gene expression, and disease phenotypes.

Disease or Phenotype(Sample)	Environmental Exposure(s)	Genetic Variant(s)	Results	Reference
Cleft lip with/without cleft palate (N=326 cases-parent trios)	Multivitamin supplementation, ETS, parent-of-origin	22 SNPs in <i>IRF1</i>	GEI with multiple SNPs and vitamin supplement; risk reduced for specific genotypes in 'exposed' group	110
Delinquency (1825 high school students)	Maltreatment (self-reported) and gender	Functional VNTR in <i>MAOA</i>	GEI with 'flip-flop' association by gender; opposite alleles interact with maltreatment in males and females	111
Mortality (184 adults age 70–80 yrs at initial assessment)	Depression	Functional <i>IL6</i> promoter SNP	GEI with –174C/G genotype; increased mortality among depressed individuals with GG genotype	112
Preterm birth (743 women)	Bacterial vaginosis	1536 SNPs in candidate genes in inflammatory pathways	GEI with SNPs in <i>PRKCA</i> , <i>FLT1</i> , <i>IL6</i> ; risk increased in or confined to exposed women	113
Global gene expression in human aortic endothelial cells (96 heart transplant donors)	Oxidized phospholipid treatment	~500k genome-wide SNPs	GEI at multiple SNPs (<i>cis</i> and <i>trans</i>); fold-changes in expression in treated cells confined to specific genotypes	103
Coronary artery disease (735 cases and 519 controls undergoing coronary angiography)	Sex, presence of hypertension (HTN)	6 SNPs in <i>AGT</i>	GEI with 'flip-flop' association of a haplotype in men and women with HTN (risk increased in women and decreased in men); haplotype effect not significant in men or women without HTN	114