Gene by Environment Interaction in Asthma*

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Abstract

Marked international differences in rates of asthma and allergies and the importance of family history highlight the primacy of interactions between genetic variation and the environment in asthma etiology. Environmental tobacco smoke (or secondhand smoke), ambient air pollutants, and endotoxin and/or other pathogen-associated molecular patterns are the ambient exposures studied most frequently for interactions with genetic polymorphisms in asthma. To date, results from the literature remain inconclusive. Most published studies are underpowered to study interactions between genetic polymorphisms and ambient exposures, each with weak effects. Strategies to increase power include cooperation across studies to increase sample sizes and improve measures of both exposure and asthma phenotypes. Genome-wide association studies hold promise for identifying unexpected gene environment interactions, but given the statistical power issues, candidate gene association studies will remain important. New tools are enabling the study of epigenetic mechanisms for environmental interactions.

RISK FACTORS FOR ASTHMA

LPS: lipopolysaccharide

Asthma is defined as a chronic inflammatory disorder of the airways (61). Despite decades of research, the causes of asthma remain obscure. Asthma has few strong and well-established risk factors. Family history of asthma and allergies is a strong and consistent risk factor, highlighting the importance of genetics in asthma etiology. Having one affected parent increases risk by about twofold, and having two affected parents increases risk by about fourfold (53). However, asthma is not just a genetic disorder. In addition to family history, one of the few other strong risk factors for asthma is living in a developed country. Over the past decade, the International Study of Asthma and Allergic Diseases in Children (ISAAC) has clearly demonstrated the higher prevalence of asthma and allergy in more developed countries, which does not reflect simply diagnostic preferences—asthma symptoms mirror trends in diagnosis (38). These studies also demonstrate that genetic differences among ethnic groups across the world do not explain the variation in rates of illness; children in Hong Kong have much higher rates of asthma and allergies than do genetically similar children in mainland China (38). Along with other data, international studies highlight the environment's role in asthma risk. In combination with the consistent association with family history, the international data point to the primacy of interactions between genetics and the environment in asthma etiology.

Reasons for the marked international variation in rates of allergy and asthma remain obscure. The hygiene hypothesis has emerged as a popular explanation. The hygiene hypothesis was first developed to explain the reduced rates of allergy among children with older siblings (33, 77). The underlying idea is that increased exposure to microbes and their products during the critical early period of immune maturation protects against development of allergic responses to common environmental antigens, such as dust mites, fungi, cockroach, and pollens, which are ubiquitous in places with both high and low prevalence of allergy and asthma. Although abundant epidemiology supports the hygiene hypothesis, not all of the epidemiology fits. A scenario that has provided supporting data for the hygiene hypothesis is the protection from allergies conferred by growing up on small farms in parts of Europe, where children live in close proximity with livestock (82). The specific exposure responsible for the protection against allergies afforded by this rural lifestyle is not known, but most of the epidemiologic studies have focused on endotoxin, which can be measured in house dust. Endotoxin, or biologically active lipopolysaccharide (LPS), a component of the cell walls of gram-negative bacteria, is only one of the pathogen-associated molecular patterns (PAMPs) that may play a role. More recent studies are examining other PAMPS, including peptidoglycan, from gram-positive bacteria, and beta-glucans, from fungi. Given that the specific agent responsible for the protective effect of rural upbringing is unknown, the exposure metric in some studies of gene-environment interaction in relation to allergies or asthma is simply growing up on a farm or self-reported contact with farm and other animals.

Atopy, or the tendency to mount an immunoglobulin E (IgE) response to common antigens in the environment, is one of the few other factors strongly and consistently associated with asthma, especially in children (61). However, much asthma, even in children, occurs without atopy. New asthma in adults, including occupational asthma, frequently occurs without atopy. In considering factors that may explain international variation, one should note that the patterns of variation in atopic and nonatopic asthma likely diverge and that factors related to the hygiene hypothesis probably better explain atopy than asthma per se. For example, increasing evidence suggests that early exposure to endotoxin might protect against atopy but may increase risk of nonatopic asthma (22). Viral infections are an important cause of asthma exacerbations, but whether they lead to the development of asthma, as opposed to early wheezing phenotypes, is less clear (61).

Family history, living in a developed country, and atopy are strong risk factors for asthma; effects of ambient environmental exposures may be more subtle. Environmental tobacco smoke (also called secondhand smoke) is a very consistent, albeit weaker (relative risk about 1.30) risk factor for the development of asthma in children (83). This association has been established using crude questionnaire metrics of exposure: generally whether mother smoked during pregnancy and whether mother, father, or other household residents smoked when the subject was a child.

Although extensive data document the role of ambient air pollution in asthma exacerbation, fewer studies address whether air pollution induces asthma. The paucity of data is not surprising, given that long-term prospective studies are needed to address this question. Furthermore, even in prospective data, it can be difficult to say when asthma began; date of diagnosis may be a poor proxy for the onset of disease. However, in recent years, a growing literature suggests that ambient air pollution can lead to the development of asthma phenotypes (31, 56). In general, these associations tend to be modest, with relative risks of less than 1.4. Ambient ozone and measures of exposure to traffic have been associated with asthma incidence. In some studies of traffic-related air pollution, exposure is based on simple measures such as distance to busy roads; others include measurements of related pollutants such as particulate matter and/or nitrogen dioxide.

SUSCEPTIBILITY TO PULMONARY RESPONSES TO ENVIRONMENTAL POLLUTANTS RELEVANT TO ASTHMA

When studying weak effects of environmental pollutants, susceptibility is important. In addition to diet and early life factors, genetics appears to influence susceptibility to air pollution. If only a portion of the population experiences an adverse respiratory effect of an ambient pollutant and the magnitude is modest, associations will be difficult to detect in epidemiologic studies that do not distinguish between relatively susceptible and resistant populations. In 1991, McDonnell (57) pointed to the role of susceptibility to acute effects of ozone. He reported that the drop in pulmonary function (FEV1) in response to acute ozone exposure tends to track within an individual when measured on different days. This pattern of greater between-subject than within-subject variability in response to ozone suggests a measure of genetic control. Subsequent studies of inbred mouse strains confirmed a genetic component in respiratory responses to ozone. Quantitative trait linkage studies have identified loci involved in respiratory responses to ozone including airway inflammation, permeability, and airway hyperresponsiveness (42, 43, 66). Later in silico analyses of mouse strains suggest that different phenotypes of response are controlled by different loci (73). Specific genes identified in mice include tumor necrosis factor alpha (*TNF*) and toll-like receptor 4 (*TLR4*). Animal studies have also been performed on the genetics of response to particulate air pollution, but it has been more difficult to find specific genes involved in response variations (9, 62, 63). Unlike ozone, particles are a complex mixture, and we lack understanding of the specific components responsible for respiratory effects. Thus, choosing particle mixtures that are representative of the biologically active ambient exposure in humans is difficult. Of note, there appears to be some overlap in loci of response to particles and ozone; *TLR4* may be involved in both (9, 62). The animal studies generally examine acute or subchronic exposure. Long-term exposures may be more relevant for development of asthma, and it is conceivable that the genetic basis of some biologic responses may differ for acute and chronic exposure. Thus human cohort studies will be important in identifying susceptibility genes.

TLR: toll-like receptor

Endotoxin, or biologically active LPS, accounts for some of the inflammatory properties of ambient particulate matter (2). Comparable to the ozone literature, evidence exists for genetic control of endotoxin response. It has long been known that certain inbred mouse strains

Genetic polymorphism: a difference in DNA sequence among individuals in a population leading to one allele at a given locus

Single nucleotide polymorphism (SNP): DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered

(such as C3H/HeJ and C57BL/10ScCr) do not respond to endotoxin, rendering them susceptible to gram-negative sepsis. Missense mutations in the murine *TLR4* gene were found to underlie this endotoxin resistance (65). Subsequently, two common functional polymorphisms in the coding region of human *TLR4* (Asp299Gly and Thr399Ile) correlated with variability in the acute spirometric response to inhaled LPS (1). As described above, *TLR4* also plays a role in variability in ozone response among inbred mouse strains. However, *TLR4* does not explain all the variability in either murine or human reactions to endotoxin—many polymorphic genes, including *CD14* and many others, are involved in mechanistic pathways of reponse to this exposure (14, 54).

Environmental tobacco smoke is the most well-studied environmental exposure with respect to genetic interactions in asthma in humans. However, we are not aware of experimental data demonstrating the specific genetic bases of susceptibility in animal models. Parental history as a questionnaire-based proxy for genetic susceptibility interacts with maternal smoking during pregnancy in relation to the risk of early-onset persistent asthma in children (53), which suggests that specific genetic interactions may exist. Although the first generation of asthma genetics studies had little information on environmental exposures, most studies included at least one question about parental smoking. Reanalysis of asthma linkage data indicates different linkage peaks by strata of exposure to parental smoking (13, 17, 58); however, these studies do not indicate the specific genes responsible.

SELECTING GENES TO STUDY FOR INTERACTION WITH ENVIRONMENTAL FACTORS IN RELATION TO ASTHMA

Given the experimental and other data, the rationale is compelling for studying the interaction between genetic variation and exposure to environmental pollutants in epidemiologic studies. The issue that arises is how best to select specific genetic polymorphisms to examine for effect modification with environmental exposures in asthma. An obvious class would be genes clearly implicated in asthma etiology. Some of these could work by modifying the impact of inhaled pollutants. Although several asthma genes have been identified in family-based studies using positional cloning (*ADAM33*, *PHF11*, *DPP10*, *GPRA*) (81), they have not been consistently replicated. Association studies have shown some relation between asthma and a much larger group of candidate genes, chosen generally on mechanistic grounds and/or location in linkage regions. Given the importance of inflammation in the asthma phenotype, genes involved in inflammation and innate immunity have been most frequently studied. However, in a review of association studies published through December 2007, Vercelli has appropriately concluded that the literature remains indeterminate regarding which genes underlie asthma risk (81).

A new way to identify genes for asthma, or other diseases, is through genome-wide association studies based on dense single nucleotide polymorphism (SNP) genotyping. The only genome-wide SNP association study of asthma, published in April 2008, identified a single gene: *ORMDL3* (59). SNPs in *ORMDL3* have been associated with asthma in subsequent studies (26, 34, 79, 89). Additional genome-wide association studies of asthma are underway and combining data across these studies may lead to firmer conclusions about the responsible genes. Of note, genes identified in genome-wide association studies of asthma and other common conditions have weak effects—relative risks generally below 1.3. Genome-wide associations require large sample sizes because of the multiple comparisons, and detecting weak associations for a difficult-to-define phenotype creates additional challenges to power in asthma studies.

In addition to asthma genes, genes clearly involved in pathways of biologic response to specific agents are logical candidates to study for interactions with exposures. One way to identify these is to expose inbred mouse strains to

the pollutant of interest and use genetic analyses techniques to identify the specific genes involved in response (10). As mentioned above, inbred mouse quantitative trait linkage studies have identified a few genes involved in response to ozone and LPS. However, only few specific genes have emerged to date because finding the responsible gene within a broad region of linkage is laborious (10).

Variants in genes underexpressed or overexpressed in relevant tissues after exposure to environmental pollutants in humans or animals may also be interesting candidates for studies of gene-environment interaction. For studies of asthma, humans or animals can be exposed to the agent of interest and cells collected from peripheral blood or the respiratory tract. To date, there are few examples of novel candidate genes identified in this way, but the number should increase. A study in mice identified genes in the arginase pathway as overexpressed in response to antigen and fungal challenges, and these genes were then found to be overexpressed in asthmatic human airway epithelial cells (93). A human association study supports a role for SNPs in arginase genes in genetic susceptibility to asthma (49). Arginase 1 was recently reported to be overexpressed in response to cigarette smoke in human asthmatic airways (4), but no interaction with environmental tobacco smoke exposure was found in the single human association study (49).

Bioinformatic techniques hold promise to discover novel polymorphic genes in pathways of response to environmental agents. Wang et al. (84) recently used a bioinformatic approach to identify genetic variants that may be involved in oxidative stress response. In response to oxidative stress, the transcription factor NRF2 (nuclear factor erythroid-derived 2-like 2) binds to antioxidant response elements (AREs), leading to transcriptional activation of various genes involved in defense. Using novel computational tools, Wang et al. identified polymorphic AREs with possible functional relevance. Given the presumed importance of oxidative stress in air pollution responses (41), identification of novel candidate genes is of considerable interest.

Genome-wide association studies hold great promise for discovering novel gene-environment interactions in asthma. However, the statistical power issues for identifying interaction in these studies are daunting (44), and thus candidate gene studies will likely continue to be important.

REVIEW OF PUBLISHED STUDIES OF INTERACTIONS BETWEEN GENETIC POLYMORPHISMS AND ENVIRONMENTAL POLLUTANTS IN ASTHMA

We tabulated the human literature on interactions between specific genetic polymorphisms and exposure to the following environmental pollutants—environmental tobacco smoke (**Table 1**); ambient air pollution (**Table 2**); and ambient or home exposures to either endotoxin, other pathogen-associated molecular patterns, allergens, or correlates of bioaerosol exposure such as rural life or regular animal contact (**Table 3**)—in relation to phenotypes relevant to asthma. Literature accessible in PubMed as of March 6, 2008, was searched. We did not include articles on genetic interactions with occupational exposures, which would be a suitable topic for a separate review paper. Studies that did not specifically address joint or interacting effects of the genetic polymorphisms and the environmental factors of interest were not included, even if the paper addressed both of these factors separately. Although we may have missed some studies, we believe that we give a reasonable overview of the available literature.

We can draw no firm conclusions about interactions between specific genetic polymorphisms and environmental tobacco smoke using the available body of literature (**Table 1**) (11, 28, 29, 45, 49, 50, 52, 64, 67, 70, 71, 74, 87–89, 92). Neither do we feel confident that, using the published literature, we can propose specific genetic polymorphisms that definitely interact with ambient air pollution to produce

Table 1 Studies of interactions between specific genetic polymorphisms and exposure to ETS[a]

First author, year	Study type, population	Exposure metric	Main outcome(s)	Case *N* or total *N* for if no cases[b]	% ETS+	Gene	Variant (s)	*P* for interaction[c]	Interaction findings
Zhang 2007 (92)	Cohort Australia, children	Lived with smoker >1 year	PFTs: FEV1, FVC Exhaled NO ($N = 86$)	150 Total	45	*ADRB2*	ArgGly16 Gln27Glu	NG	Arg16 lowers FEV_1 + FVC only in ETS+ Arg16 eNO only in ETS–
Sadeghnejad 2008 (70)	Birth cohort, age 10 years and under Isle of Wight, United Kingdom	In utero + later	Wheeze, early-onset persistent at age 10	70	20	*IL13*	5 SNPs	$P < 0.02$	3 SNP haplotype > association in ETS+
Ramadas 2007 (67)	Birth Cohort, age 10 years and under Isle of Wight, UK	In utero + later	Asthma at age 10	134	21	*IL1RN*	rs2234678	NG	SNP associated only in ETS+
Lee 2007 (45)	Case-control Taiwan, children	in utero + later	Ever wheezing Current wheezing	216 109	55	*GSTM1* *GSTP1*	deletion Ile-105	<0.03	GSTM1, no interaction GSTP1, higher OR in ETS–
Palmer 2007 (64)	Cross-sectional Asthmatics, ages 3–21 years	Smoking in first-degree relatives	PFTS: FEV1, FVC, PEF	504 Total	32	*GSTM1* *GSTP1*	Deletion Ile-105	NG	PEF lower in ETS+ only in GSTM1 null No differences for FEV1, FVC
Gilliland 2002 (28)	Cohort, California, United States Children, multiethnic	In utero	Current asthma Current wheeze	305 510	16	*GSTM1*	Deletion	$P < 0.05$	OR for ETS higher in GSTM1 null

Salam 2007 (71)	Cohort, California, United States Children, multiethnic	In utero	Asthma, early-onset persistent	170	17	*TGFB1*	–509 rs4803457	$P = 0.11$	Stronger association in ETS+
Li 2008 (52)	Cohort, California, United States Children Whites, including Hispanic	In utero	Ever asthma Early-onset asthma Late-onset asthma Current wheezing Medication for wheeze	457 217 240 584 340	17	*GSTP1*	rs6591255 rs4147581 Ile105Val rs749174	$P < 0.05$ for 1 haplotype for wheeze	Haplotype with 105Val > associated with the 2 wheeze outcomes in ETS+, no interactions with asthma outcomes
Choudry 2005 (11)	Case triad Mexico, Puerto Rico	Household, before case age 2 years	Asthma Asthma severity Brochodilator response IgE	659	41	*CD14*	C – 810A C – 159T G + 1437C	$P < 0.05$ only for IgE Others NG	Asthma, no differences Severity: 2 SNPs, $P < 0.05$ only in ETS+ IgE: 1 SNP- $P < 0.05$ only in ETS+ BDR: 2 SNPs, $P < 0.05$ only in ETS+

(*Continued*)

Table 1 (*Continued*)

First author, year	Study type, population	Exposure metric	Main outcome(s)	Case *N* or total *N* for if no cases[b]	% ETS+	Gene	Variant (s)	*P* for interaction[c]	Interaction findings
Schedel 2007 (74)	2 cohorts Germany, children	Parent smokes In utero	Asthma +/– BHR PFTs	720	NG	*ADAM33*	10 SNPs	Yes	No ETS interactions
Wu 2007 (87)	Case triad Mexico, children	Parent smoked	Asthma	596	50	*TNF* *LTA*	4 in TNF 2 in LTF	$P = 0.01$	–308, –238, > association with asthma in ETS–
Li 2007 (50)	Case triad Mexico, children	Parent smoked	Asthma Skin tests	546	50	*TGFB1*	–509 T869C +3 SNPs	NS	No ETS interaction
Li 2006 (49)	Case triad Mexico, children	Parent smoked	Asthma Skin tests	433	50	*ARG1* *ARG2*	4 SNPs 4 SNPs	NS	No ETS interaction
Wu 2007 (89)	Case triad Mexico, children	Parent smoked	Asthma Skin tests	532	50	*GSNOR*	7 SNPs	NS	No ETS interaction
Wu 2008 (88)	Case triad Mexico, children	Parent smoked	Asthma Skin tests	589	50	*GPRA*	27 SNPs	NS	No ETS interaction

Gilliland 2006 (29)	Controlled human study	ETS + ragweed	Nasal wash total IgE	19	NA	*GSTP1*	Ile105Val	$P = 0.03$—	GSTM1 null > ragweed IgE response
	Allergic adults, United States		Nasal wash ragweed IgE			*GSTM1*	Deletion	$P = 0.03$—	GSTP1Ile > histamine reponse
	United States		Nasal wash histamine					$P = 0.02$—	GSTM1null & GSTP1Ile > ragweed IgE response
			Nasal wash IL-4, IFNγ					$P = 0.06$—	GSTM1null & GSTP1Ile > histamine response

[a]Abbreviations: BDR, bronchodilator response; BHR, bronchial hyperresponsiveness; ETS, environmental tobacco smoke; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IFN, interferon; IgE, immunoglobulin E; IL, interleukin 4; NA, not applicable for this type of study; NG, not given in the publication; NO, nitric oxide; NS, not statistically significant; PEF, peak expiratory flow; PFTs, pulmonary function tests; SNP, single nucleotide polymorphism.

[b]Where information was available, only subjects with genotype and exposure data are included in the case or total *N*. Where the study examined a case group, the number of that case type is *N*. For studies of continuous outcomes the total *N* is given. Where additional case groups were analyzed and too numerous to list, numbers are given for case groups where interactions were reported by the authors.

[c]NS indicates *P* value for interaction was given but did not reach statistical significance at a level of 0.05.

Table 2 Studies of interactions between specific genetic polymorphisms and ambient air pollutants[a]

First author, year	Study type, population	Outcome(s)	Case *N*, or Total *N* if no cases[b]	Exposure metric	% exposed	Gene	Polymorphism	*P* for interaction[c]	Interaction findings
Corradi 2002 (15)	Controlled exposure Adults Italy	EBC: H_2O_2, TBARS, LTB4 EBC: 8-isoprostanes Blood: PMN-ROS, IL6, IL8 Blood: TBARS, 8-OHdG	22	0.1 ppm Ozone (2 hours)	NA	*NQO1* *GSTM1*	Por187Ser Deletion	Not given	↑ with O3 only in GSTM1null & NQO1Pro for: EBC: TBARS, LTB-4, 8-isoprostanes Blood: 8-OHdG DNA adducts
Bergamashi 2001 (3)	Controlled exposure Adults Italy	PFTs: FEV1, FVC, PEF MEF25, 50, 75 CC16	24	32 to 103 ppb Ozone (2 hours)	NA	*NQO1* *GSTM1*	Pro187Ser Deletion	Not given	↓ PFTs with O3 in GSTM1null & NQO1Por r^2 between FEV1 + O3 ↑ for GST1null & NQO1Pro r^2 between CC16 + O3 ↑ for GST1null & NQO1Pro
David 2003 (16)	Case triad Children, Mexico	Asthma	218	Life-time residence in Mexico City	100	*NOQ1* *GSTM1*	Pro187Ser Deletion	Not given	↓ asthma risk for NQO1 variant only among GSTM1 null

Romieu 2004 (69)	Randomized controlled trial of antioxidants Asthmatic children Mexico	PFTs-FEF25-75 repeated measures	158 total	Ozone: 50 ppb difference in 1 hour maximum	NA	*GSTM1*	Deletion	$P = 0.14$	↑ drop in FEF25-75 with ozone in GSTM1 null Antioxidant supplements negate FEF25-75 drop Antioxidant benefit mostly in GSTM1 null
Lee 2004 (46)	Cross-sectional School children Taiwan	Asthma	61	Outdoor air pollution (low, medium, high)	70	*GSTP1*	Ile105Val	$P < 0.035$	Ile/Ile→ ↑ wheeze, but not in low pollution areas
Yang 2005 (90)	Controlled exposure Adults Germany	PFTs-FEV1, FVC	51 total	200 to 400 ppb ozone (2–4 hours)	NA	*TNF* *LTA* *SOD2* *GPX1* *TLR4*	−308 + 3 others +252 Val16Ala Pro197Leu Asp299Gly	$P < 0.003$ NS NS NS NS	↓ FEV1 with ozone only in TNF-308G/G TNF/LTA haplotype results support -308 finding No effect modification by other genes
Li 2006 (51)	Cohort, California, United States Children	Ever asthma Ever wheezing	403 886	Ozone annual average of 1 hr averages >50 ppb	59	*TNF* *GSTM1*	TNF-308 Deletion	$P < 0.04$ No 3-way	↓ wheeze with TNF-308G/G only in low ozone ↓ wheeze with TNF-308G/G in low ozone only with GSTM1null

(*Continued*)

Table 2 (*Continued*)

First author, year	Study type, population	Outcome(s)	Case *N*, or Total *N* if no cases[b]	Exposure metric	% exposed	Gene	Polymorphism	*P* for interaction[c]	Interaction findings
	Multiethnic	Current wheezing	493			*GSTP1*	Ile105Val		↓ wheeze with TNF-308G/G in low ozone only with GSTP1ile/ile
		Meds for wheezing	296						No ozone interaction with GSTM1 or GSTP1 alone
Romieu 2006 (68)	Panel study	Breathing difficulties	151 total	ozone-20 ppb difference in 1 hour maximum	NR	*GSTM1*	Deletion	$P < 0.05$	↑ ozone effects in GSTM1 null/ GSTP1*Val/Val*
	Asthmatic children, Mexico	Bronchodilator use				*GSTP1*	Ile105Val		
Gilliland 2004 (30)	Controlled exposure	Nasal wash total IgE	19 total	Nasal challenge with	NA	*GSTM1*	deletion	$P < 0.05$	Greater ↑ ragweed IgE, histamine in GSTM1 null
	Allergic adults, United States	Nasal wash raweed IgE		Diesel exhaust particles		*GSTP1*	Ile105Val	$P < 0.05$	Greater ↑ ragweed IgE, histamine in GSTP1Ile/ile
	United States	Nasal wash histamine		+ ragweed allergen		*M1/P1*	Combined	$P < 0.05$	Greater ↑ ragweed IgE, histamine in GSTM1null/ GSTP1Ile/Ile
		Nasal wash Il-4,IFNG				*GSTT1*	Deletion	NS	
Salam 2007 (72)	Cohort, California, United States	Lifetime asthma	422	Close (<75 m) to major road	23	*EPHX1*	Tyr113His	$P < 0.05$	↑ OR for EPHX high activity greater in exposed

	Children Multiethnic	Late-onset asthma Early persistent asthma Current asthma	276 217 308			*EPHX1* *GSTP1* *GSTM1* *GSTT1*	His139Arg Ile105Val deletion deletion	$P < 0.05$	↑ OR for EPHX high activity+ P1Val/Val in exposed $P < 0.05$ for some outcomes
Islam 2008 (39)	Cohort, California, United States Children Whites (non-Hispanic)	New-onset asthma	103	Long-term ozone > median also examined PM10, PM2.5, and NO2	50	*HMOX-1* *CAT* *CAT* *MNSOD*	[GT]n repeat –262C>T –844C>T Ala-9Val	$P < 0.003$	OR for HMOX-1 s-allele stronger in low ozone
Chen 2007 (8)	Cohort, California, United States College students No respiratory illness	PFTs: FEV1, FVC, FEF25-75	210 total	Ozone (lifetime in high ozone areas of California)	100	*GSTM1* *NQO1* *GSTP1*	Deletion Pro187Ser Ile105Val	$P < 0.05$ $P < 0.15$	Ozone related ↓ in FEF25-75 ↑ in GSTM1null/ NQO1Pro in ♀ Ozone-related ↓ in FEF25-75 ↑ in GSTP1Val in ♂
Hong 2007 (36)	Panel Children Korea	PFTs: PEF	43 total	PM10, PM2.5 Pb, Mn in PM	100	*GSTM1* *GSTT1*	Deletion Deletion	Not given	No effect of GSTM1 null or GSTT1 null on PEF

[a]Abbreviations: 8-OHdG, 8-Hydroxy-2′-deoxyguanosine; CC16, serum clara cell protein; EBC, exhaled breath condensate; FEF, forced expiratory flow; FEF25-75, forced midexpiratory flow rate or the average expiratory flow over the middle half of forced vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; IFN, interferon; IgE, immunoglobulin E; IL, interleukin; LTB-4, leukotriene B-4; MEF, maximal expiratory flow; Mn, manganese; NA, not applicable (for this type of study); PEF, peak expiratory flow; PFTs, pulmonary function tests; PM.25, particulate matter less than 2.5 microns; PM10 particulate matter less than 10 microns; Pb, lead; PMN-ROS, reactive oxygen species generation from neutrophils (PMNs); NA, not applicable for this type of study; NS, not statistically significant; TBARS, thiobarbituric reactive substances.

[b]Where information was available, only subjects with genotype and exposure data are included in the case or total *N*. Where the study examined a case group the number of that case type is *N*. For studies of continuous outcomes the total *N* is given. Where additional case groups were analyzed and too numerous to list, numbers are given for case groups where interactions were reported by the authors.

[c]NS indicates that the *P* value for interaction was given but did not reach statistical significance at a level of 0.05.

Table 3 Studies of interaction between specific genetic polymorphisms and farm life and/or measured exposure to pathogen associated molecular patterns[a]

First author, year	Study type, population	Outcome(s)	*N*, cases or total *N*[b]	Exposure metric	% exposed	Gene	Polymorphism	*P* for interaction[c]	Interactions findings
Arbour 2000 (1)	Controlled exposure	FEV1	83 total	Endotoxin (LPS)	NA	*TLR4*	Asp299Gly	$P = 0.037$	Greater ↓ in FEV1 with LPS for carriers of either variant allele than for wt/wt
	Adult, United States						Thr399Ile		
Levan 2008 (47)	Controlled exposure	WBC: 0, 6, 24 hours	88 total	Endotoxin (LPS)	NA	*CD14*	–159C/T	<0.05	WBC at 6, 24 hours haplotype, but no SNP findings
	Adult, Belgium	CRP: 0, 6, 24 hours					–1359G/T	<0.05	↑ sCD14 at 0 hours associated with all 3 SNPs
		LBP: 0, 24 hours					–1619A/G		sCD14 at 24 hours, no associations
		sCD14: 0, 24 hours							
Eder 2004 (21)	Cross-sectional	Asthma diagnosis	609 = total *N*	Living on farm	38	*TLR2*	*TLR2* – 16934	<0.07, <0.05-	*TLR2*-16934AA →↑ asthma, atopy, sx -farm only,
	Farm/non farm	Current asthma	*N* not given for the outcomes	Dust endotoxin >27.4 EU/mg	50	*TLR4*	TLR2 + 596		but no difference by endotoxin exposure
	Children	Atopy					*TLR4* + 4434	$P = 0.014$	TLR4+4434AA →↓ atopy in high endotoxin but
	Austria, Germany	Current hay fever					*TLR2* + 1349		↑ atopy in lower endotoxin

Eder 2005 (22)	Cross-sectional	Total IgE	544 total	Endotoxin in dust	60	*CD14*	–260C/T	0.07	CC →↓ atopy only in 3rd tertile of endotoxin
	Farm/non farm	Atopy by specific IgE	112	Contact with farm animals			(also known as –159)	0.018	CC →↓ atopy if contact with farm animal, but
	Children			Contacts with pets					CC →↑ atopy if only pet contact
	Austria, Germany								
Eder 2006 (20)	Cross-sectional	Hay fever	55	Living on farm	38	*CARD4*	–21596T	<0.05	Farm→↓ pollen,cat atopy, hay fever & and topic
	Farm/non farm	Pollen atopy	99	Dust endotoxin >27.4	50				Wheeze only in TT genotype
	Children	Cat atopy	18	Dust muramic acid	Not given			<0.05, 0.08	Endotoxin→↓ pollen, cat atopy only in CC/CT
	Austria, Germany	Atopic wheeze	37						No muramic acid interactions
Bieli 2007 (5)	Cross sectional	Asthma	173	Drank farm milk	45	*CD14*	−4191	0.004	↓ asthma with farm milk differed by −4191
	Farm/non farm	Current wheeze	167				−2839		Significant only in 1 of 2 studies
	Children	Allergic rhinitis	148				–260 (also known as 159)	0.059	↓ pollen atopy with farm milk differed by −4191
	Europe-2 studies	≥1 specific IgE+ of 7	318				–1721		Significant only in 1 of 2 studies
		+IgE to pollen	190						
		+IgE to dust mite	179						
		Gene expression	222 (total)						

(*Continued*)

Table 3 (*Continued*)

First author, year	Study type, population	Outcome(s)	*N*, cases or total *N*[b]	Exposure metric	% exposed	Gene	Polymorphism	*P* for interaction[c]	Interactions findings
Zambelli-Weiner 2005 (91)	Case-sibling	Asthma diagnosis	221 cases	Dust endotoxin	26	*CD14*	C-260C/T	NS	TT → ↑ asthma in high endotoxin, ↓ in low
	Barbados	Total IgE	422 total	>44,000 EU/m2					TT→ ↓ IgE, more so in low endotoxin
Leynaert 2006 (48)	Cross-sectional	Nasal allergy	216	Lived on farm during childhood	12	*CD14*	−159C/T	NS	↓ nasal allergy, atopy, high IgE for combined
	Adult	Atopy	197						Farm exposure and TT genotype
	France	Asthma ever Total IgE > 100 IU/ml	88 159						
Bruce 2008 (7)	Cross-sectional	Allergic symptoms	415	Current, regular	50	*NPSR1*	rs323922—	<0.005	Protective effect of exposure stronger
	children			contact with farm animals		(also known as *GPRA)*	rs324377—	<0.005	in one genotype than in another for several SNPs
	Europe						rs740347—	<0.05	No interaction with objective measure of atopy (data not shown)
							+4 other SNPs	NS	

Simpson 2006 (75)	Birth cohort	≥1 specific IgE+ of 7	145	Endotoxin in dust	100	*CD14*	−159C/T	0.09	↑ endotoxin → ↓ IgE atopy only in CC genotype
	United Kingdom	≥1 skin test+ of 7	110	Mite in dust				Not given	similar finding for skin test atopy
		Eczema	64	Both as continuous				Not given	+IgE to mite c/(↑mite+ ↓endotoxin) only in CC
		Wheeze, recent	91					0.05	↑ endotoxin → ↓ ezcema only in CC
		Atopic wheeze	42					Not given	↑ endotoxin →↑ recent wheeze only in CC above limited to nonatopic wheeze
		sCD14	442 total					Not given	
		+IgE to mite	62						
Gern 2004 (27)	Birth cohort	7 specific IgEs	285 total	Cat +/or dog at home	Coth: 12	*CD14*	−159C/T	0.0071	TT→ ↓ atopic dermatitis with dog
	United States	Atopic dermatitis (AD)	88 cases		Dog: 27				No other interactions
		Eosinophilia IFNγ, IL10, IL13, IL5			Cat: 18				
		Food allergy	34 cases						

[a]Abbreviations: CRP, C-reactive protein; IFN, interferon; IL, interleukin; LBP, LPS binding protein; LPS, lipopolysaccharide; NA, not applicable for this type of study; NS, not statistically significant; sCD14, serum soluble CD14; WBC, white blood cell count; wt/wt, wildtype/wildtype.

[b]Where information was available, only subjects with genotype and exposure data are included in the case or total N. Where the study examined a case group the number of that case type is the N. For studies of continuous outcomes the total N is given. Where additional case groups were analyzed and too numerous to list, numbers are given for case groups where interactions were reported by the authors.

[c]NS indicates P value for interaction was given but did not reach statistical significance at a level of 0.05.

asthma or related phenotypes (**Table 2**) (3, 8, 15, 16, 30, 36, 39, 46, 51, 68, 69, 72, 90).

Genotype: genetic constitution of an organism as opposed to the physical appearance or phenotype. In the context of this article, for a single nucleotide polymorphism such as CD14–159C/T, there are three possible genotypes, CC, CT, TT

The number of different genes studied in relation to environmental tobacco smoke and ambient air pollution is relatively small. Much of the research has focused on a handful of common polymorphisms with well-described functional effects in genes thought to be involved in oxidative stress responses. The single most commonly examined is a highly prevalent deletion polymorphism of the glutathione S-transferase M1 gene (*GSTM1*). Deletion of both copies of the *GSTM1* gene, also referred to as homozygous deletion or the null genotype, abolishes GSTM1 activity (78). The high frequency of the *GSTM1* null genotype, ranging from 25% to 60% depending on the ethnic group, enables examination of this polymorphism in studies that were not originally powered to study interactions. At least 4 studies of ETS (**Table 1**) and 10 studies of air pollution (**Table 2**) have examined interaction with this polymorphism. The second most commonly studied gene in relation to either environmental tobacco smoke or ambient air pollution is glutathione S-transferase P1 (*GSTP1*). A functional polymorphism (Ile105Val) occurs at relatively high frequency (78). Most of the published studies looking at interactions with either or both *GSTM1* and *GSTP1* polymorphisms show a positive finding, but not always in the same direction for *GSTP1*. As new data accumulate, whether the *GSTM1* and/or *GSTP1* polymorphisms will be confirmed as modifiers of effects of exposure to environmental tobacco smoke or other inhaled oxidants remains to be seen.

The body of literature on interactions between genetic polymorphisms and exposure to bioallergens such as endotoxin, other PAMPs, or aeroallergens in relation to asthma and allergy is also limited (1, 5, 7, 20–22, 27, 47, 48, 75, 91) (**Table 3**). The number of genes studied remains very limited, focusing primarily on a common polymorphism in *CD14* (-159C/T, referred to as -260C/T in some studies), which correlates with soluble CD14 levels and functional coding SNPs in *TLR4*. Few have been examined in multiple study populations. Looking at the data on *CD14*, the results appear to be discordant with different directions of effect in different studies. This divergence in results across studies has been ascribed to true underlying differences in the biologic effects of the *CD14*159C/T SNP at varying endotoxin exposures (21, 55, 80). However, in our opinion, there is too little data to draw the conclusion that these differences in results reflect the underlying biology as opposed to random variation, given the small numbers of studies, low statistical power of the individual studies, multiple testing of various asthma outcomes, and likely publication bias. In a more recent study with data on multiple *CD14* SNPs, it was not the functional -159C/T SNP for which interactions were seen, but another SNP with unknown functional effects (5). Of note, several of the reports of *CD14* interactions with endotoxin or farm exposures come from the same study population(s) and/or involve overlapping investigators. Thus, although the data are interesting, we cannot conclude that there is a causal interaction between the *CD14*-159C/T polymorphism, or other SNPs, in relation to endotoxin or related exposures relevant to the hygiene hypothesis (**Table 3**).

The inability to draw definite conclusions about specific gene-environment interactions in asthma in the still-small body of literature to date is not surprising. The study of gene-environment interaction in relation to asthma is a field in its infancy. As occurs during the natural evolution of any field, early studies have limitations that are improved on in subsequent work.

The published studies are generally underpowered to evaluate the interactions presented. Sample size requirements increase markedly when studying interactions compared with main effects (76). Both genetic polymorphisms and ambient pollutants produce weak independent effects, and, given the complexity in response pathways, we should not expect very strong interaction effects with any single gene. Although the total sample size in some studies seems large (>2000 subjects), the number of cases, rather than the total study size, is

the more important determinant of statistical power. Furthermore, studies often report interactions seen only in subsets of cases, not in the entire case group. The specific case group for which positive interactions were reported is smaller than 600 subjects in all studies; one study with 659 asthmatics found significant differences only for quantitative traits for which power will be greater, not for case status (11). To better illustrate the sample size limitations in the existing literature, we have tabulated the relevant number of cases whenever a dichotomous outcome has been studied for interaction, rather than the total study size (**Tables 1–3**). If the interaction was found only in one case subgroup, we list that number rather than the total number of cases. Because power for studying interactions depends on the joint distribution of exposure and genotype, the number of cases with both the exposure and the genotype of interest is limited in all published studies with these modest sample sizes (**Tables 1–3**). Given the limited power, not surprisingly, in several of these studies, statistical tests of interaction were either not done or were not significant. Instead, the authors reported "interaction" based on finding a statistically significant effect of genotype only in one exposure stratum or vice versa. Although we do not recommend slavish devotion to statistical tests of interaction, effect estimates will tend to fluctuate within small strata; therefore, statistical tests of interaction are important to help the reader evaluate the role of chance in explaining differences in associations across strata. Another issue in evaluating the published literature on gene-environment interactions in asthma is multiple comparisons. Although corrections for multiple comparisons are standard in the genetics literature, they are uncommon in the literature on gene-environment interaction in asthma. Because the multiple outcomes and exposure classifications have been tested for interaction in many reports, the possibility for finding statistically significant interactions at an arbitrary P value increases.

Publication bias is a serious but underappreciated issue, limiting conclusions from the available literature. Publication bias occurs because negative findings tend not to be published or even submitted for publication (12). Inadequate sample sizes are a major reason for lack of replication across studies (12). Small studies without significant findings are much more difficult to publish than are small positive studies. Thus the literature becomes replete with positive studies without the corresponding negative ones on the same associations. Publication bias is perhaps an even greater issue in studies of gene-environment interaction than in studies of main effects of genes because there are so many ways to cross-classify the data, and there is great enthusiasm for finding and publishing reports of interactions because there are so few well-established examples. As a testimony to the level of interest, there are nearly as many reviews of the literature on gene-environment interaction in relation to asthma and allergy as there are original data reports to review.

One issue in evaluating the epidemiologic literature is the proper consideration of ethnicity. When studies include multiethnic populations, interactions present in all or most ethnic groups are most convincing because the result would constitute an internal replication. Sometimes results for multiple ethnic groups are combined with adjustment for ethnicity. Although this action may be taken because of insufficient sample size in stratified analyses, it can lead to erroneous conclusions because frequencies of polymorphic alleles tend to vary greatly among ethnic groups as does the prevalence of exposures such as parental smoking. If there are differences in effect estimates within combined strata of genotype and exposure by ethnic group, simple adjustment for ethnicity could give erroneous conclusions of interaction.

FUTURE WORK

Knowledge of these problems with the modest existing literature is leading to new generations of studies that address them. Consortia of studies are being formed both for replication of results and for pooled analyses to increase sample size for evaluating interactions. Measures

of exposure to air pollution are being added to established cohort studies, and genetic collections are being added to existing studies or air pollution health effects to provide more and better data to study gene-environment interactions. Rapid decreases in price for genome-wide association genotyping will enable these larger studies and consortia to examine gene-environment interactions in a publication bias–free manner because all studies using the same commercial genome-wide association platform generate the same genotypes. Many groups are posting data on the Internet to enable other investigators to look for replication of results at lower levels of statistical significance. Should an interaction appear at a borderline level of statistical significance in several studies, pooling data may provide definitive conclusions.

Another approach to enhance power without enrolling more subjects is to refine the phenotype. Asthma is an especially messy disease phenotype (23, 81). One approach to refinement is to obtain repeated measures of quantitative phenotypes (86). We took this approach in a study of genetic modification of acute ozone effects (68, 69), although larger studies are clearly needed. Subclassifying asthma into qualitative phenotypes that may have different etiologies would help us interpret and replicate results across studies. For example, early endotoxin exposure may be protective against atopy but may increase risk of nonatopic wheezing, which is often diagnosed as asthma (19). Increased use of objective measures of asthma phenotypes will be helpful in the future.

The power of gene-environment interaction studies can also be enhanced without increasing sample size by improving exposure assessment (86). Repeated measures are one approach to improving precision of exposure assessment. Repeated measures over longer periods of time will also be important to determine why the effects of some exposures, such as endotoxin, differ over the life course. Future studies will likely include improved assessment of chronic exposures. To this end, the Exposure Biology Program of the Genes Environment and Health Initiative at the U.S. National Institutes of Health is funding environmental technology development to produce and validate new methods for monitoring environmental exposures that interact with genetic variation to produce human disease. This program also supports statistical methods development for analyzing gene-environment interactions in whole genome association studies.

Given the large number of genes that respond to environmental agents, the complex mechanisms of asthma pathogenesis, and the small magnitude of associations with individual genetic variants being found in genome-wide association studies of asthma and most other common diseases, consideration of gene-gene interactions or epistasis will be important. The need to consider much higher-order interactions further challenge statistical power. Methods for evaluating epistasis or gene-gene interactions in genome-wide association data are evolving (32, 60).

Higher-order interactions including other susceptibility factors may also merit consideration. We found some preliminary evidence of a gene-diet-environment interaction in relation to acute effects of ozone on repeated measures of pulmonary function in asthmatic children in Mexico City (69). Antioxidant supplementation, with vitamins C and E, appeared to modify the effect of *GSTM1* genotype on decrements in pulmonary function (FEF25-75) in relation to ozone exposure.

Published studies have focused on interactions between environmental exposure and DNA sequence variation. Environmental exposures may also interact with genetic predisposition via epigenetic mechanisms. Epigenetics refers to the study of processes that alter gene activity without changing the DNA sequence (40). Epigenetic changes to DNA can be inherited (24). The best-studied mechanism of epigenetic modification is DNA methylation, the covalent addition of a methyl group to a base, typically cytosine. Dietary intake of methyl donors (such as folate, vitamin B12, choline, and betaine) during pregnancy clearly influenced methylation in a mouse model (85). In this model, methylation at the *Agouti* gene

results in an easily detectable phenotype: change in coat color. In addition to diet, environmental exposures can also influence methylation. In mice, in utero exposure to bisphenol A, a ubiquitous environmental contaminant used in plastics manufacture, led to hypomethylation of DNA (18), which could be counteracted by dietary intake of methyl donors. Although the doses of bisphenol A used were high compared with human population exposures, the study demonstrates that common ambient environmental chemicals can influence DNA methylation and that diet may influence this process in a gene-diet-environment interaction.

Emerging evidence suggests that exposures during adulthood can influence methylation. In twins, methylation patterns varied more within older twin pairs compared with younger ones (25). However, prospective studies of changes in methylation over time will be necessary to conclude that these differences are due to aging or exposure occurring over the life course. We are aware of only one study linking ambient exposure to an environmental contaminant to methylation in human adults. In that study of 78 gas station attendants, 77 traffic police officers, and 58 office workers in Milan, Italy, ambient benzene concentrations were associated with reductions in global methylation (6). They also found differences in methylation by exposure at specific genes (*P15* and *MAGE-1*) relevant to leukemia, a disease clearly linked to benzene exposure (6).

Methylation can be measured in the peripheral blood DNA samples routinely collected in epidemiologic studies using a variety of methods either on a gene-specific or genome-wide basis. Because methylation can be tissue specific, it will also be important to examine changes in methylation in response to inhaled exposures in cells, nasal and/or airway, from the respiratory tract for studies of asthma-cells. Improvements in the sensitivity, throughput, and cost of methods to detect differences in global and gene-specific methylation will facilitate studies of the epigenetic effects of ambient environmental exposures in relation to asthma and other conditions (37). Studies of DNA methylation in relation to air pollution exposure are underway. Histone modification is another common mechanism of epigenetic modification that could be influenced by the environment (24), but methods for detection in population studies are not well developed.

There is little information on how the environment may interact with the epigenome to influence asthma. However, it has recently been reported that feeding pregnant mice a high methyl donor diet results in an allergic asthma phenotype in the offspring (35). This model identified 82 differentially methylated gene loci. One of the overmethylated genes, *RUNX3*, is known to regulate allergic asthma negatively.

CONCLUSIONS

The lack of firm findings of interaction between specific genes and exposures to environmental pollutants is not surprising, given the early stage of the field. Upcoming studies that have larger sample sizes, often through collaboration, better measures of exposure, more refined asthma phenotypes, and whole genome association genotyping will improve our understanding of gene-environment interactions in asthma. Epigenetic mechanisms for environmental interactions merit consideration.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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