Gene by Environment Interaction in Asthma

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Asthma is a chronic inflammatory disease of the airways that is highly prevalent in the Western world. It is a genetically complex disease caused by multiple genetic and environmental factors, which may interact. Genetic research has recently incorporated environmental factors to investigate gene by environment interaction, and the first examples of gene by environment interaction in asthma have been reported. Linkage analyses indicate that one or more genes on chromosome 5q interact with environmental tobacco smoke in infancy in asthma development. Several candidate genes have been consistently shown to interact with the environment. These include the innate immunity genes *CD14* and *Toll-like receptor 4*, and microbial exposures, as well as the detoxifying gene family glutathione-S-transferase and environmental tobacco smoke exposure and air pollutants. Gene by environment interaction is important in asthma pathogenesis, and future studies should take the interaction of both factors into account.

Introduction

Asthma is a chronic inflammatory disorder of the airways, characterized by airway hyperresponsiveness and widespread but variable airway obstruction that is often reversible [1]. Asthma is a prevalent, chronic disease leading to substantial morbidity and health care costs [2]. During the last decades of the 20th century, asthma prevalence increased in Western populations [2]. This rise in asthma prevalence is most likely caused by changes in the environment, because it is very unlikely that the genetic background of the population has changed over the past decades.

It is generally accepted that asthma is a genetically complex disease caused by multiple genes and multiple environmental factors (Fig. 1) [3]. Many environmental factors may contribute to the development of asthma, such as indoor and outdoor pollution, allergen exposure, tobacco smoke, contact with microbial products, and infections [4]. Genetic research has recently incorporated environmental factors to investigate gene by environment interaction. This has already resulted in striking examples of how the environment interacts with genetic susceptibility in asthma development. In this paper, recent progress in research on gene by environment interaction in asthma is described.

Genetics of Asthma: Current Status

Genes for asthma and atopy have been identified by two different approaches: the candidate gene approach and "positional cloning."

The candidate gene approach takes account of existing knowledge on asthma. Genes are screened for polymorphic gene variants (single nucleotide polymorphisms [SNPs]), and the frequency of these variants is examined in cases with asthma and controls. To date, eight genes have been replicated with various phenotypes of asthma and atopy in five or more study populations [5•,6••]. These genes encode the Th2 cytokines interleukin (IL)-4 and IL-13, and their receptor IL4Rα; the β2-adrenoceptor; the β-chain of the high-affinity immunoglobulin (Ig)E-receptor; HLA-DRB1; tumor necrosis factor-α; and lymphotoxin-α. Twenty-three additional genes have been replicated in two to four populations [6••]. Although replications provide strong evidence for the role of these genes in asthma development, several issues remain unresolved. First, replication is found with different phenotypes. This may be consistent with a pleiotropic gene effect (ie, a gene associated with high IgE in one sample and with reduced lung function in another). Second, replication is found with different SNPs in the same gene or with different alleles of the same SNP. Third, it is unknown how many replication attempts in asthma genetics remain unpublished. Statistically, many studies are underpowered to exclude the role of a gene in a population, and publication bias may be present. Finally, age and gender effects may also modify results in asthma genetic studies [7].

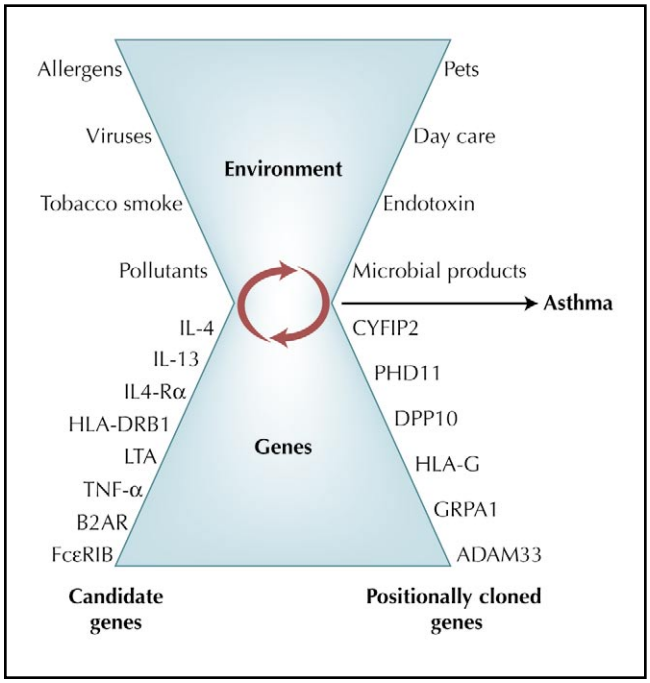

Figure 1: Gene by environment interaction in asthma

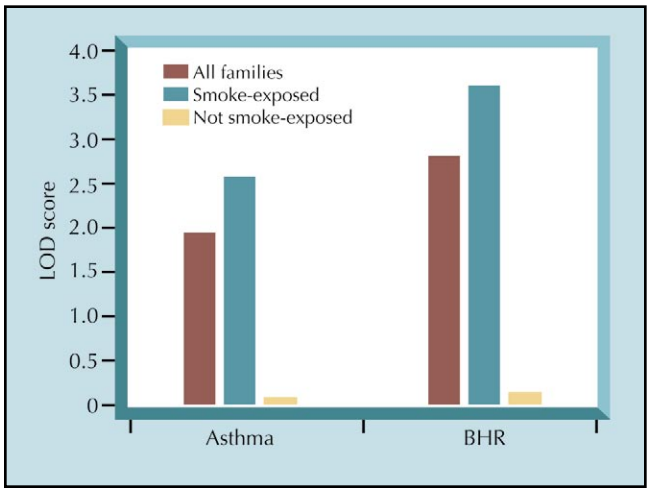

Figure 2. Linkage of asthma and bronchial hyperresponsiveness (BHR) in 200 Dutch families ascertained through a proband with asthma. Environmental tobacco smoke exposure was assessed by taking the smoking history of the proband: > or ≤ 5-pack years. Of the 200 families: 96 smoke-exposed families and 104 not-exposed families. LOD—logarithm of the odds. (*Adapted from* Meyers et al. [19•].)

Gene by environment interaction may explain some of these issues. Some SNPs are associated in one population with a certain exposure, but not in another without the exposure. Moreover, one allele of an SNP may be associated with protection from disease in one environment, but with increased disease risk in another. These examples are discussed later in this paper.

Positional cloning is the process of gene identification in a chromosomal region that has been identified by linkage analysis within families. Subsequent detailed analysis of the chromosomal region may reveal novel genes that had not been previously implicated in asthma pathogenesis. In 2002, the first success of this approach in asthma genetics was reported with the identification of a disintegrin and matrix metalloprotease 33 (*ADAM33*) as an asthma susceptibility gene on chromosome 20p [8•]. Subsequent studies have confirmed this observation, and a recent meta-analysis showed that two SNPs in *ADAM33* are significantly associated with asthma across eight populations [9]. Other novel identified genes, such as those encoding dipeptidylpeptidase 10 [10], PHD finger protein 11 [11], HLA-G [12], and cytoplasmic fragile X mental retardation protein (FMRP)-interacting protein 2 gene [13] await the results of replication studies. If these genes are confirmed in other populations, as recently shown for the gene encoding G-protein coupled receptor A [14,15], new insights into the pathogenesis of asthma will be obtained in the near future. Environmental factors interacting with these novel genes have not been identified to date. In fact, genetic research could provide new information about the environment, because novel environmental factors may be identified through interaction with these novel cloned genes [16••].

Gene by Environment Interaction in Linkage Studies

Environmental tobacco smoke (ETS) exposure in utero and/or in early childhood is associated with asthma [17]. Two family studies investigated the effect of ETS exposure on linkage results of asthma and bronchial hyperresponsiveness (BHR). In a US collaborative study of 144 families ascertained through two affected siblings, genomewide linkage results on asthma were compared in children exposed and not exposed to ETS in infancy. Three regions (1p, 5q, and 9q) were identified, with nominal evidence for linkage of asthma when stratified on the basis of ETS exposure ($P < 0.01$, logarithm of the odds [LOD] ≥ 1.18). The increase in LOD score was significantly different from the baseline LOD score in all asthmatics [18]. A genomewide linkage study of 200 Dutch families, ascertained through a proband with asthma, provided strong support for interaction of genes on chromosome 5q and ETS. Families were stratified based on the smoking history of the proband that reflected ETS exposure in infancy of the children. The families with the children exposed to passive smoking accounted for almost all evidence for linkage of BHR and asthma to 5q (Fig. 2) [19•]. In conclusion, these linkage analyses indicate that one or more genes on chromosome 5q interacts with environmental tobacco smoke in infancy in asthma development.

Gene by Environment Interaction in Candidate Gene Studies

Evidence for gene by environment interaction in asthma and atopy has been provided by several studies that have used a candidate gene approach and selected environmental factors. Examples are studies of genes interacting with cigarette smoke, microbial exposure, infections, and air pollution in asthma development (Table 1).

Genes Interacting with Tobacco Smoke

Genes that have been suggested to be involved in host susceptibility to cigarette smoke are *CD14*, *IL-13*, and *B2AR* on chromosome 5q and glutathione-S-transferase genes on chromosomes 1 and 22 (Table 1). The *CD14* gene encodes part of the endotoxin receptor complex. Cigarette smoke contains endotoxin, and passive smoking results in exposure levels of endotoxin that are 120 times higher than smoke-free air. *CD14* gene by environmental tobacco smoke (ETS) interaction was investigated in 659 Hispanic families from Puerto Rico and Mexico in which more than 40% of children were exposed to ETS. Three SNPs (*CD14/–810*, *–159*, and *+1437*) were correlated with asthma severity (lung function) and total serum IgE. In the ETS-exposed subjects, two SNPs were significantly associated with low forced expiratory volume in 1 second (FEV_1), and one SNP (*CD14/–159*) was associated with total serum IgE levels. None of these associations were observed in subjects not exposed to ETS. In conclusion, this study shows evidence for a role of *CD14* interacting with ETS, resulting in modification of FEV_1 and total serum IgE levels in asthmatic children [20].

The GST gene family comprises genes implicated in several detoxification pathways, such as the response to oxidative stress. This gene family consists of four members (designated A, M, P, and T), with each family member having several subtypes. In white populations, whole gene deletions of *GSTM1* and *GSTT1* are prevalent, called *GSTM1* and *GSTT1* null alleles. These loss-of-function mutations may result in impaired detoxification of toxic substances. A study in 2950 schoolchildren from the United States assessed the effects of *GSTM1* genotype, maternal smoking during pregnancy, and childhood ETS exposure on asthma and wheezing. Among children having the *GSTM1* null alleles, in utero exposure was associated with increased prevalence of asthma with current symptoms and persistent asthma. Among children with *GSTM1* wild-type genotypes, in utero exposure was not associated with asthma or wheezing [21]. These results were confirmed in a cross-sectional study of 3054 German schoolchildren. Current and past ETS exposure and respiratory symptoms were assessed by questionnaire, and children underwent pulmonary function, skin prick, and BHR testing. In utero smoking was significantly associated with lower lung-function measurements in children carrying the *GSTT1* null alleles. Moreover, current smoking (≥ 20 cigarettes per day) was associated with a higher frequency of self-reported asthma and current wheeze compared with the nonsmokers in carriers of the glutathione-S-transferase M1 null genotype [22•]. Thus, certain children are at increased risk for developing asthma and BHR when exposed to ETS in early life.

Genes Interacting with Air Pollution

Air pollutants include diesel exhaust particles with particulate matters less than 10 μm or 2.5 μm. These diesel exhaust particles are thought to exert their detrimental effects through generation of reactive oxygen species. The glutathione-S-transferase genes protect from oxidant stress. Thus, carriers of the glutathione-S-transferase genes that result in loss of function may be at increased risk for respiratory morbidity when exposed to air pollution.

This hypothesis was tested in a cross-sectional study of school children in Taiwan. Children were selected from three areas characterized by low, moderate, and high air pollution levels. A nested case control study was done with a subset of this sample: 61 children with asthma versus 95 nonasthmatic controls stratified by area of air pollution. *GSTP1 Ile 105* homozygotes were at significantly higher risk for asthma in areas of high air pollution compared to carriers of the *Val 105* alleles. This association was not observed in areas of low or moderate air pollution [23]. This is consistent with the idea that loss of function of the *GSTP1* gene may be associated with increased susceptibility to the effects of air pollution in asthma development. Further experimental evidence for a role of glutathione-S-transferase genes in severity of atopic symptoms was provided by a randomized placebo-controlled study of patients sensitive to ragweed. These patients were challenged in the nose with ragweed allergen with and without diesel exhaust particles in a crossover design. The allergic response in the nose to this challenge was compared in subjects with *GSTM1*, *T1*, and *P1* wild-type and null alleles. Subjects with *GSTM1* null and *GSTP1 150 Ile* alleles showed increased nasal responses to the ragweed allergen in the presence of diesel exhaust particles compared with carriers of the *GSTP1* wild-type or *GSTP1 150 Val* [24•]. This experiment, therefore, suggests that *GSTM1* and *GSTP1* genotypes modify the effect of diesel exhaust particles on allergic inflammation [24•]. Together with other data indicating that alleles in the glutathione-S-transferase genes are associated with asthma and BHR, this suggests that the interaction with the glutathione-S-transferase gene family is a relevant pathway in asthma and atopy development [25].

Innate Immunity Genes Interacting with Microbial Products

Innate immunity genes encode pattern recognition receptors that recognize specific molecules on the surface of

Table 1. Examples of gene by environment interaction in asthma and atopy in epidemiologic studies

Gene family	Gene	Environment	Population	Phenotype	Effect
Innate immunity	*CD14*	Endotoxin	Central Europe [34]	Specific IgE, total IgE	*CD14/-159* TT increased risk for specific IgE in children exposed to high endotoxin levels or contact with stable animals.
		Contact with stable animals and pets			*CD14/-159* TT showed trend toward protection from specific IgE levels in children with contact to pets.
		Exposure to dog in first 6 months of life	US children [35]	Atopic dermatitis (doctor's diagnosis)	*CD14/-159* TT exposed to dogs had a lower prevalence of atopic dermatitis compared to TT homozygotes not exposed to dogs.
		Endotoxin	Barbados families [36•]	Asthma (doctor's diagnosis), severity, total and specific IgE	*CD14/-159* TT appeared protective for asthma when exposed to low endotoxin levels; *CD14/-159* TT exposed to high endotoxin levels were at increased risk for asthma
		ETS	Puerto Rico and Mexico [20]	FEV_1, total IgE	In *CD14/-159* TT children exposed to ETS, increased total serum IgE levels and reduced FEV_1 values were observed
	TLR 2	Growing up on a farm	Central Europe [39]	Asthma, (doctor's diagnosis) and symptoms	Protection from asthma in farmers' children, but not in non-farmers' children. Endotoxin did not explain this effect.
	TLR 4	Endotoxin	Central Europe [39]	Specific IgE	Highly exposed farmers' children with *TLR4/4434* had lower prevalence of specific IgE compared to low-exposed children.
		Endotoxin	Germany, adults [38]	Asthma	Homozygotes for the wild-type *TLR4* alleles were at increased risk for asthma when exposed to increased endotoxin levels, whereas carriers of the polymorphism showed a nonsignificant trend for reduced prevalence of asthma
	MBL-2	*Chlamydia pneumoniae* infections (serology)	Hungary, children [45]	Asthma (questionnaire)	Children infected with *C. pneumoniae* carrying the *MBL* gene variants (loss of function) had increased asthma risk compared to infected children with normal *MBL-2* genotype.
Response to infections	*TIM-1*	Hepatitis A infection (serology)	US subjects [41•]	IgE	In seropositive subjects, the 6 amino acid insertion was associated with a lower prevalence of atopy; this effect was not observed in seronegative subjects.
	NOS3, IL4RA and FcεRIB	Day care in the first 6 months of life	US children [46]	Phenotypes related to atopy (Th2 cytokine responses)	Three genes had association with multiple phenotypes related to atopy (Th2 cytokine responses) and had at least one interaction with the exposure to day care in the first 6 months.
Response to allergens	*IL-4*	Der p1 allergen levels	German children [47]	Specific IgE to house dust mite	Risk estimates for sensitization to mite allergen in children homozygous for *–590 T* allele differed by mite exposure levels

BHR—bronchial hyperresponsiveness; ETS—environmental tobacco smoke; IgE—immunoglobulin E; SNP—single nucelotide polymorphism.

Table 1. Examples of gene by environment interaction in asthma and atopy in epidemiologic studies *(continued)*

Gene family	Gene	Environment	Population	Phenotype	Effect
Response to cigarette smoke	*B2AR*	Active smoking	China [48]	Asthma	*B2AR* homozygotes for *Arg16* who ever smoked were at increased risk for asthma compared to *Gly 16* never smokers
	IL4RA *IL13*	Maternal smoking	Germany [47, 49]	Specific IgE to cat Total IgE	*IL4R Arg 551* allele at increased risk for cat sensitization when the mother smoked. Maternal smoking increased effects of two Il13 SNPs on total serum IgE.
	GSTM1	In utero smoking / ETS	US children [21]	Asthma, wheezing	Children with null alleles reported higher prevalences of symptoms when exposed in utero to tobacco smoke
	GSTM1 *GSTT1*	ETS In utero smoking	German children [22•]	Asthma, wheezing (symptoms)	Children with *GSTM1* null alleles exposed to ETS were at increased risk for current asthma (symptoms). Children with *GSTT1* null alleles exposed to in utero smoking had lower lung function values compared to carriers of the wild-type not exposed to smoke.
Response to air pollution	*GSTP1*	Air pollution	Taiwanese children [23]	Asthma (BHR and symptoms)	Homozygotes of *GSTP1 Ile 105* had increased asthma risk in areas of high air pollution compared to carriers of one or two *GSTP1 Val 105* allele(s).
Response to sedentary life style	*B2AR*	Sedentary life style	Nurses' health study [50]	Asthma	Increased risk for asthma in women with *Gly 16* allele and sedentary life style.

BHR—bronchial hyperresponsiveness; ETS—environmental tobacco smoke; IgE—immunoglobulin E; SNP—single nucelotide polymorphism.

microbes. Examples of these pattern-recognition receptors are CD14 and the toll-like receptor (TLR) family. CD14 is part of the receptor complex for endotoxin together with TLR4. Endotoxin is a major component of the cell wall of gram-negative bacteria. CD14 does not have a transmembrane domain, but contributes to the affinity of the interaction between the microbial products and TLRs by formation of a receptor complex. TLR2 is part of a receptor complex that is responsive to a range of microbial products, such as gram-positive bacteria, mycoplasma, mycobacteria, and yeast. TLR4 more selectively forms the receptor for endotoxin [26]. Downstream effects of CD14/TLR-receptor activation include the release of cytokines, such as IL-10 and IL-12, and the activation of regulatory T cells [26]. These mechanisms are potentially important in directing the adaptive immune response.

Genetic variants in innate immunity genes have been investigated in relation to microbial exposures. It has been hypothesized that contact with microbial products, such as endotoxin, or infections, modifies the immune response in early life and subsequent asthma development [27]. This "hygiene hypothesis" is supported by lower prevalence rates of asthma and allergies in children living on farms compared to children from rural populations not living on farms [28]. In addition, protective effects on atopy have been observed in children with more siblings, early entry to day care, and with dogs in their house [27].

CD14

The *CD14* gene has several SNPs, the most important one being the *CD14/–159* C-T SNP (also called *CD14/–260*) localized in the promoter region. This SNP affects the transcription rate of the *CD14* gene [29]. Genetic studies on the association of *CD14/–159* with asthma and atopy have produced conflicting results [30]. In some studies, the *CD14/–159* C allele is associated with atopic phenotypes, whereas in other studies the T allele is [31]. Additionally, in other populations, the *CD14* gene was not associated with atopy at all [32]. Vercelli [33••] explained these apparent contradictory results by proposing the "endotoxin switch." Different levels of endotoxin exposure would trigger different host responses, resulting in either Th1 or Th2 type responses. The *CD14* genotype may shift this endotoxin response curve [33••]. This hypothesis was supported by a study of 624 children living in rural communities in central Europe. The *CD14* gene was investigated in relation to exposure to farm life (stable animals) and endotoxin exposure in their mattresses. In this study, outcome variables were total and specific IgE, and no data on asthma were provided. In the complete sample of 624 children, *CD14/–159* genotype was not associated with total and specific IgE. However, this changed when the exposure was taken into account. *CD14/–159* T allele was a risk factor for the development of specific IgE in children exposed to the highest tertile of endotoxin exposure. Moreover, the *CD14/–159* T allele was also a risk factor for raised total and specific IgE levels in children with regular contact to stable animals. In contrast, in children with regular contact with pets, but not stable animals, the T allele showed a trend toward protection against raised specific IgE levels [34]. Another study assessed this potential pet by *CD14* gene interaction, because dog ownership could be a proxy variable of microbial exposure. The interaction of dog ownership with *CD14/–159* genotype on atopy development was investigated in 285 US children prospectively followed up until the age of 1 year. Children exposed to dogs in the first 6 months of life reported a lower prevalence of atopic dermatitis. Moreover, the *CD14/–159* TT homozygotes exposed to dogs had a lower prevalence of atopic dermatitis compared to *CD14/–159* TT homozygotes not exposed to dogs [35]. Other atopic variables and cytokine responses did not show significant evidence for interaction, and a direct assessment of the environmental exposures was not available in this study. Additionally, a genetic study from Barbados investigated asthma (severity) and atopy development in relation to endotoxin levels in living room dust samples. Among subjects exposed to low endotoxin levels, *CD14/–159* TT genotypes appeared protected for asthma, whereas the subjects exposed to high endotoxin levels were at increased risk for asthma. Similar trends were observed for asthma severity scores and total serum IgE levels [36•].

Although the number of subjects with the *CD14/–159* TT genotype and the exposure is limited, these studies provide empirical support for a dose-dependent gene by environmental interaction in asthma development. This is the first example in asthma of a genotype to confer risk to disease in a certain environment, but protect from it in another environment.

Toll-like receptor 4

TLR4 forms a receptor complex for endotoxin together with CD14. The *TLR4* gene has two missense mutations in the extracellular domain of the receptor: D299G and T339I. Healthy volunteers carrying one or two of these missense mutations showed bronchial hyporesponsiveness to endotoxin inhalations [37]. The allele frequency of two variants is relatively low (< 10%) in Western populations. In a cross-sectional study of the European Respiratory Community Health Survey in Germany, 334 adult subjects were investigated on asthma and atopy development in relation to endotoxin exposure in house dust. Subjects with the *TLR4* wild-type exposed to elevated levels of endotoxin (second tertile and third tertile) had increased risk of physician-diagnosed asthma, compared to those with low exposure (first tertile). In contrast, carriers of the *TLR4* mutant alleles exposed to elevated endotoxin levels (second and third tertile) had a decreased risk for BHR and elevated total and specific IgE levels compared with those exposed to endotoxin in the first tertile, indicating a protective effect [38]. Moreover, in children from Cen-

tral Europe, a *TLR4* SNP also showed an interaction with endotoxin exposure. Highly exposed farmers' children with *TLR4/4434* had significantly lower prevalence of specific IgE compared with low-exposed children. Thus, these genetic variants appear to protect from disease development in a risk (ie, high endotoxin) environment [39].

Toll-like receptor 2

The association of *TLR2* with asthma was investigated in 239 farmers' and 387 nonfarmers' children from Central Europe. Atopy was defined by self-reported physicians' diagnosis of asthma and allergic rhinitis, and assessed by specific IgE measurements against a panel of aeroallergens. Endotoxin levels were measured in dust samples collected from the children's mattresses [31]. Three SNPs in *TLR2* were genotyped. Farmers' children carrying a T allele in *TLR2/–16934* were significantly less likely to have a diagnosis of asthma and current asthma symptoms than farmers' children with genotype AA. No such association was found in the nonfarming children. Thus, a protective effect in farmers' children of the *TLR2* genotype was observed. However, this protective effect was not present when children were stratified based on high and low endotoxin exposure, indicating that endotoxin may not be the environmental factor explaining this gene by environment interaction of the farming environment with TLR2 [39].

TIM-1

Serologic evidence of hepatitis A infection has previously been reported to be inversely associated with atopy in Italian conscripts [40]. The *TIM-1* (T-cell immunoglobulin domain and mucin domain) gene encodes the cell surface receptor used by hepatitis A virus to infect human cells and may play a role in stimulating the Th2 pathway. Therefore, the *TIM-1*–hepatitis A interaction is an attractive pathway for gene by environment interaction. The *TIM-1* gene contains a prevalent six amino acid insertion (157insMTTTVP). The interaction of hepatitis A infection (assessed by serum hepatitis A antibodies) and atopy (IgE levels) was studied in a US sample of cases and controls. In hepatitis A seronegative subjects, the six amino acid insertion was not associated with atopy. However, in seropositive subjects, the six amino acid insertion was associated with a lower prevalence of atopy. The authors propose that this might represent one mechanism through which infections may protect against atopy development [41•]. Further studies have indeed provided evidence that *TIM-1* SNPs are associated with various atopic phenotypes, although a specific interaction with hepatitis A infection was not reported [42].

Conclusions

Asthma is a complex genetic disease with multiple genetic and environmental factors that may interact. The analysis of gene by environment interaction has been recently introduced into genetic studies of asthma. Yet, several studies have provided replicated evidence for these interactions, such as the *CD14* and *TLR4* genes, microbial exposure (endotoxin), the glutathione-S-transferase gene family, ETS, and air pollutants. Characteristics of most of these investigations are a cross-sectional design with retrospective assessment of the environment and low sample sizes to investigate interactions. However, these studies illustrate the value of assessing environmental exposure in genetic studies and suggest that heterogeneity in the environment may be one reason for the difficulty in replication of genetic results [6••].

Several patterns of gene by environment interaction emerge from these studies. First, the environment can increase risk of disease in carriers of a certain (susceptibility) genotype. Second, a risk environment may not induce disease in carriers of a certain (protective) genotype. Finally, different levels of environmental exposures may increase or decrease risk depending on the genotype (dual effect). These examples illustrate the complexity of gene by environment interactions in asthma.

Future studies are planned that will include large sample sizes [43]. Increased power can also be reached by collaboration between groups and pooling of existing data. Now that a catalogue of prevalent SNPs in humans has been described [44•], attention should be directed at environmental exposures. A design that prospectively assesses environmental factors before the onset of symptoms is not limited by recall bias, which is a limitation of the current cross-sectional studies. The investigations described in this paper clearly illustrate that stratification on a uniformly exposed group may enhance the power to detect genetic effects considerably.

The detection of gene by environment interaction may lead to various public health consequences. It could help stratify disease risks and focus interventions to achieve population health benefits; it could identify new environmental factors for disease development or severity; and it could help our understanding of the natural history and severity of the disease [16••]. This understanding may be increased by functional studies into the mechanisms of these interactions, such as epigenetic effects, effects of dosing, and timing. It may be expected that the results of these investigations will increase our understanding of the complex etiology of asthma, and open up new possibilities for prevention and treatment.

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