Molecular mechanisms in allergy and clinical immunology
(Supported by an unrestricted educational grant from Genentech, Inc. and Novartis Pharmaceuticals Corporation)

Series editors: William T. Shearer, MD, PhD, Lanny J. Rosenwasser, MD, and Bruce S. Bochner, MD

Genetic epidemiology of health disparities in allergy and clinical immunology

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The striking racial and ethnic disparities in disease prevalence for common disorders, such as allergic asthma, cannot be explained entirely by environmental, social, cultural, or economic factors, and genetic factors should not be ignored. Unfortunately, genetic studies in underserved minorities are hampered by disagreements over the biologic construct of race and logistic issues, including admixture of different races and ethnicities. Current observations suggest that the frequency of high-risk variants in candidate genes can differ between African Americans, Puerto Ricans, and Mexican Americans, and this might contribute to the differences in disease prevalence. Maintenance of certain allelic variants in the population over time might reflect selective pressures in previous generations. For example, significant associations between markers in certain candidate genes (eg, *STAT6*, *ADRB2*, and *IFNGR1*) for traits such as high total IgE levels observed in resistance to extracellular parasitic disease in one population and atopic asthma in another supports the common disease/common variant model for disease. Herein is a discussion of how genetic variants might explain, at least in part, the marked disparities observed in risk to allergic asthma. (J Allergy Clin Immunol 2006;117:243-54.)

Key words: *Asthma, allergy, genetics, disparities, ethnicity*

Abbreviations used
CF: Cystic fibrosis
CFTR: Cystic fibrosis transmembrane conductance regulator
CTLA4: Cytotoxic T lymphocyte–associated 4
LD: Linkage disequilibrium
NOS: Nitric oxide synthase
SNP: Single nucleotide polymorphism

Despite the explosion of data on the role of genetics in the pathophysiology of both common and uncommon diseases, identifying the precise genes that confer susceptibility to many complex disorders, including allergic asthma, remains a daunting task. Identification of these genes has been hampered by variability in the clinical phenotype, genetic heterogeneity among human populations, and a failure to consider important environmental influences (ie, gene-environment interactions). Conversely, the quest for causal variants has been met with considerable success for a number of the monogenic disorders, such as cystic fibrosis (CF) and sickle cell anemia, wherein a major gene is known and confounding factors, although not entirely absent, have much less effect. For example, the ΔF508 variant in the CF transmembrane conductance regulator (*CFTR*) gene is the most common cause of CF in most populations,[1] the most common fatal recessive disorder among populations of European descent. This variant is believed to have emerged more than 52,000 years ago during the Paleolithic period from a single origin followed by diffusion along a southeast-northwest gradient across Europe, resulting in higher frequencies of the mutation in northern Europe and lower frequencies toward the south.[2] The heterozygote state is believed to confer some protection against cholera-induced secretory diarrhea because altered CFTR expression results in modified Cl^- secretion; *CFTR* knockout murine models support this.[3] The exceptionally high CF heterozygosity frequency (1 in 20) of the *CFTR* mutation supports the notion of heterozygote advantage and could reflect selective pressure from cholera epidemics in early European history.

In contrast, sickle cell disease, a common autosomal recessive disorder, caused a variant in the β-globin gene (*HbS*) believed to have spread as a protective mechanism against malaria, which would explain the high frequency of this variant in African and Mediterranean populations.[4] A life-threatening complication of sickle cell disease is acute chest syndrome, affecting some 1 in 1085 patients with sickle cell disease.[5] Both a promoter variant

From The Johns Hopkins Asthma and Allergy Center.
Supported by the Allergy and Asthma Foundation of America Young Investigator Award and National Institutes of Health grants A150024 and HL066583. KCB was supported in part by the Mary Beryl Patch Turnbull Scholar Program.
Received for publication November 16, 2005; revised November 29, 2005; accepted for publication November 29, 2005.
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0091-6749/$32.00

doi:10.1016/j.jaci.2005.11.030

(T-786C) in the endothelial nitric oxide synthase (*NOS*) gene,[6] or *NOS3*, and a polymorphism in the *NOS1* gene[7] have been shown to be associated with acute chest syndrome. Interestingly, it has also been shown that heterozygous carriers of a point mutation in the promoter of the *NOS2* are protected against severe malaria,[8] suggesting an overall selective advantage for variants in these genes as well. Striking differences in frequencies of variants in nitric oxide genes have been observed when comparing populations originating in regions endemic for malaria (eg, African descent) with European populations (*NOS1* CA repeat in exon 29 and intronic AAT repeat,[9] *NOS3* Glu298Asp polymorphism,[10] *NOS3*(G894T) polymorphism,[11] and 393 endothelial cell *NOS* allele[12]). Collectively, genetic studies of monogenic lung disorders suggest that (1) the presence of high-risk variants can differ substantially among ethnic groups, contributing to the marked differences in disease prevalence among ethnic groups, and (2) the maintenance of these variants in the population over time might be due to a selective advantage for the variant in previous generations.

ETHNICITY AND RACE AS CONSTRUCTS: IS THERE BIOLOGIC RELEVANCE?

Given the negative and in many cases devastating use of the social construct of race in our recent past,[13] the use of the term in biomedical research has been met with a wide range of consternation and has generated a plethora of editorials variously calling for the judicious use of the concept as a legitimate tool for identifying disease-associated genes[14,15] to the stance that race is biologically meaningless.[16] At the very least, most experts in the field agree that race as a social construct represents a continuum rather than a term with clear-cut boundaries, a point that has been illustrated by large-scale genotyping among diverse biogeographic populations.[17] (For in-depth reviews on this topic, see supplement in *Nature Genetics*.[18]) However, whether we adopt the constructs of race, ethnicity, or self-defined group identity according to our ancestors' geographic origins (eg, ''biogeography''), there is no denying that health disparities, including asthma, exist among certain racial-ethnic groups in the United States. Consider, for example, the striking racial and ethnic disparities in disease prevalence for many of the common disorders characterized by inflammation, altered immunologic responses, or both, including hypertension,[19] non–insulin-dependent diabetes mellitus,[20] and obesity.[21] Although ethnic differences in disease incidence and prevalence have traditionally been dismissed as a mix of environmental, social, cultural, or economic factors in cause, genetic factors cannot be ignored.

As illustrated by Tishkoff and Kidd,[22] the 5 races referred to by entities such as the US Census Bureau (http://www.census.gov/population/www/socdemo/race/racefactcb.html) and the National Institutes of Health (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-01-053.html) reflect the 5 geographic regions: Africa, Europe, East Asia, Oceania-Pacific, and the Americas. There is typically good agreement between assignment to these 5 populations on the basis of genetic marker data and self-reported ancestry.[23] However, on the basis of the biogeographic distribution of our genetic variation, there are actually few sound arguments for lumping individuals into these specific racial categories. In the past several decades, the long-standing ''Multiregional Origin model'' to explain evolution of modern human origins, which alleged that parallel evolution of *Homo sapiens* from *Homo erectus* took place within geographically dispersed populations as *H erectus* migrated out of Africa more than 1,000,000 years ago,[24] has been replaced by the Recent African Origin model (Out of Africa hypothesis[25,26]). The Recent African Origin model argues that *H sapiens* evolved in Africa some 100,000 to 200,000 years ago (probably from an East African gene pool), after which its anatomically modern members migrated and replaced archaic human groups throughout Europe and Asia, and only within the past 100,000 years has racial differentiation occurred.

Historical evidence for recent expansions across Europe, Asia, the Americas, and the Pacific (dating back from 60−3 thousand years ago) correlates well with patterns of allele frequency variation,[27] with higher levels of sustained genetic diversity in the more ancient African populations and less diversity in the younger, non-African populations.[28] The end result of this process is a gradation of genetic differentiation across groups of *H sapiens*,[29] with no clear-cut boundaries defining races. In light of a more accurate time frame for evolution of our species, the amount of genetic diversity across the human genome is, perhaps not surprisingly, rather low. *H sapiens* as a species share approximately 99.6% to 99.8% of genetic material with each other, and only a fraction of the total genome (eg, approximately 10 million of 3 billion nucleotides) accounts for variability among populations.[22] Put another way, human genomes vary roughly one every thousand bases (kilobase). Additionally, genetic diversity is highest among individuals within populations (85%), and variation between groups or populations only accounts for approximately 15%.[30]

GENOMIC AND POPULATION STRUCTURE AND THE EFFECT ON GENETIC EPIDEMIOLOGIC STUDIES

To understand the potential role of genetic diversity in phenotype frequency, or disparities in disease, consideration of the structure of the human genome should be taken into account. An offspring inherits a copy of genetic material from each parent, and during gamete formation, recombination events shuffle chromosome segments but in a manner in which large portions of DNA travel together.[30] Within these broad segments are multiple polymorphic sites (alleles) that are physically linked. Combinations of these neighboring alleles, descended from single ancestral chromosomes, comprise preserved haplotypes. Linkage disequilibrium (LD) is the nonrandom association of

alleles at nearby genes (or haplotypes). Thus naturally occurring recombination events shape our genetic diversity by gradually eroding ancestral patterns of LD, resulting in new combinations of alleles into haplotypes. Measures of LD remain a useful tool for testing for association between a disease phenotype and genetic markers, and these are based on the departure of observed haplotype frequencies from what is expected under random assortment of alleles at different loci: the 2 most commonly used measures of pairwise LD are D′ and r^2, the correlation coefficient between alleles at different markers. In this pairwise approach, if one or more markers occur at a frequency significantly higher or lower in an affected group compared with an unaffected group, one can assume that either the marker itself is associated with the phenotype or that the marker is in LD with the unobserved causal variant.

Recombination events do not occur at a uniform rate within the human genome, and in fact, the genome is organized into a block-like structure of strong LD interspersed with recombination hotspots.[31] Of interest is the fact that in an analysis of more than 1 million single nucleotide polymorphisms (SNPs) genotyped in 269 DNA samples from 4 populations as part of the international HapMap Project (http://www.hapmap.org/), common recombination hotspots, or blocks of LD with low haplotype diversity, are observed across groups, highlighting our similarities.[32] Nevertheless, natural selection can exert a powerful influence on individual genes or even on LD patterns, and LD among alleles might arise as a result of mutation, random genetic drift, migration, or selection in response to environmental forces, all of which can result in different patterns of LD across biogeographic groups and, importantly, can result in associations over large regions and increases in the frequency of a particular variant within a given population. This might be particularly important for genes showing the so-called signature for selection, such as those associated with resistance to malarial infection (eg, *G6PD*, *HBE1*, *Duffy* [FY]).[22] For example, LD between the *FY* (or Duffy) locus on chromosome 1 and markers up to 22 cM away (which would normally be considered only loosely linked) has been reported among African Americans[33] and greatly exceeds the usual distance for measurable LD (approximately 2000-5000 kb, or thousand base pairs) in older populations, such as those from Africa. The *FY* locus confers a strong selective advantage against malaria,[34] and the protective variant occurs in the majority of African individuals.[35] Thus it appears that positive selection has created a block of LD extending far greater than normal among Africans.

Younger populations typically express less genetic diversity than more ancient ones (eg, African) at the level of individual markers, and they have larger regions of strong LD because of fewer recombination events over less time. For this reason, younger and especially isolated founder populations can be especially useful in finding genes associated with complex traits because LD spans greater physical distances and fewer genetic markers will have to be typed to detect association between markers and disease. (Note: A *founder* is referred to as one of a few members of a group who move into a new and typically isolated environment and then multiply to create a new population for which there is the potential for a loss of genetic variation compared with the parent population or the population from which the founders derived.) To demonstrate the power of LD in illustrating our genetic diversity, consider the juxtaposition of LD between a 12-generation founder population originally founded by 3 unrelated northern Europeans[36] and an African Caribbean group of founders characterized by European and African admixture similar to that observed among African Americans.[37] By genotyping a dense panel of SNPs in a large chromosomal region in both groups, one can visualize the striking differences in LD between these 2 very different groups. For example, in Fig 1, a very large block of LD is conserved among founders in the relatively young European American isolate compared with decay of LD for these same markers among unrelated individuals from a large, family-based sample of African Caribbeans in Barbados.

Although subpopulations defined by genetic distance typically parallel geographic separation, genetic variation also reflects sociocultural barriers (eg, interethnic marriage).[22] This is especially the case for minorities in the United States, whose unique population history has been characterized by a mixture of European ancestry with West Africans, indigenous groups (northern and southern Native Americans, as in the case of Mestizos in Central and South America), and a multitude of peoples from other distinct geographic regions, known as *admixture*. The effect of admixture is compounded when the disease of interest is more prevalent in one particular subgroup within a given population because alleles that are more common in this minority subgroup can appear to be associated with the disease, even if unlinked to the disease-causing locus. This phenomenon is variously referred to as *confounding* or *population stratification*.

Several approaches exist to deal with the problem. The most widely accepted approach is to use several unlinked markers in which allele frequencies differing substantially between ancestral populations are genotyped to detect, quantify, and correct for hidden population structure that could lead to stratification in case-control designs when relying on self-reported ethnic membership.[17,38,39] If substantial population stratification exists, not only can there be a spurious association between disease status and a genetic marker, but unlinked markers should also show significant evidence of such association as well. However, if a panel of unlinked SNP markers, referred to as *ancestry informative markers*, is genotyped in the same set of patients and control subjects, association statistics for these unlinked markers can be used to adjust for spurious associations caused by stratification.

COMMON VARIANTS FOR COMMON DISEASES?

In an effort to understand the role of genetics in the disproportionate distribution of some common complex

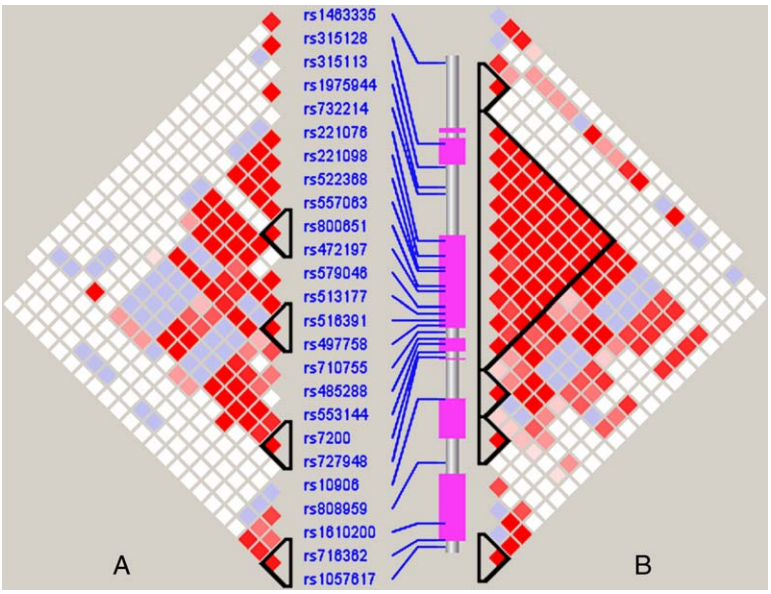

FIG 1. Comparison of pairwise LD estimates in 2 populations. LD was estimated between each of 25 SNP markers genotyped on chromosome 12q (67953342−68500427; NCBI build 35; Illumina panel 42) by using Haploview (Julian Maller, Developer/MIT). **A** represents LD between SNPs and founders from an African Caribbean population (estimated from 900 chromosomes), and **B** shows the same set of SNPs in European American founders from Tangier Island, Va (estimated from 354 chromosomes). *Squares* illustrate strong *(red)*, little or no *(white)*, and nonsignificant *(blue)* LD.

traits across subgroups within a population, it is necessary to consider yet another layer of complexity. There is increasing evidence that a susceptibility marker (or markers) for one particular trait might also influence risk to another trait. Previous studies have revealed several genes outside the major histocompatibility complex that influence risk to various human autoimmune and inflammatory diseases. Becker et al[40] demonstrated that collective results of genome-wide screens for various autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, psoriasis, and Crohn's disease, are clustered within 19 distinct loci. The common disease/common variant hypothesis[41] has been put forth as one explanation for why many contemporary complex diseases are so common and why disease-associated variants occur at such high frequency in the population. One possibility is that the functional effects of certain alleles manifest in multiple disorders, presumably because they are involved in basic underlying immune regulatory pathways. If true, this implies much of the genetic variation associated with disease is conserved and shared across human groups, suggesting observed disparities are due more to environmental factors rather than genetic differences.

In allergy and clinical immunology genetics, examples supporting this hypothesis abound. As a single example, variants in the gene encoding cytotoxic T lymphocyte–associated 4 (*CTLA4*) have been shown to play a role in different autoimmune diseases. *CTLA4* variants have been associated with insulin-dependent diabetes mellitus,[42] Graves disease,[43] Hashimoto thyroiditis,[44] celiac disease,[45] and systemic lupus erythematosus.[46] Recently, an association was noted between an exon 1 (+49) polymorphism of the *CTLA4* gene and scleroderma among African Americans but not among European Americans.[47] Associations have also been observed between novel *CTLA4* variants and asthma.[48] Interestingly, in a study to analyze the LD structure and haplotype diversity in the *CTLA4* gene among a population dataset of nearly 1300 individuals from 44 different populations, strong LD was observed with a relatively homogeneous pattern both within and between continents, suggesting limited population-specific selection pressures for the variants.[49] However, the haplotype composition did vary significantly differently between geographic groups, most likely a result of demographic processes specific to the various groups, including founder effects, expansions, and migrations.

ETHNIC DISPARITIES IN ALLERGY AND CLINICAL IMMUNOLOGIC DISEASES: A ROLE FOR GENETICS?

Curiously, differences in linkage and association between the common complex traits, such as allergies and other diseases of clinical immunology, and conventional genetic markers have been observed according to ethnicity. As described by Joseph et al[50] in this issue, asthma morbidity and mortality is disproportionately high and continues to increase among African Americans and low-income-housing residents.[51,52] Puerto Ricans represent the ethnic group with an even higher asthma prevalence, morbidity, and mortality[53] and the poorest therapeutic response,[54] which cannot be explained entirely by the excess occurrence of certain factors known to be associated

with asthma risk. Several studies have demonstrated that although Puerto Rico has an exceptionally high prevalence of asthma,[55,56] the prevalence is similarly high among Puerto Ricans in the mainland United States (eg, >15%) compared with other groups, including other Hispanic Americans.[54] A higher than expected asthma prevalence among Puerto Ricans living both in the mainland and on the island suggests a possible role for genetics.

The National Heart, Lung, and Blood Institute–funded Collaborative Study on the Genetics of Asthma was one of the first genome-wide screens for asthma and included families representing 3 US ethnic groups: European American, African American, and Hispanic American.[57] From this study, evidence for linkage to 6 novel regions and asthma was demonstrated; curiously, however, the best evidence for African Americans (5p15, 17p11.1-q11.2), European Americans (11p15, 19q13), and Hispanics (2q33, 21q21) did not overlap, suggesting that environmental differences, ethnicity, or both were involved. Regretfully, of the dozen or so genome-wide screens that have been performed for asthma, the Collaborative Study on the Genetics of Asthma is the only study to have included underserved minorities; all others have been focused on European-descended populations, and only one has been performed on an Asian group (Fig 2). More recently, the multicenter internationally collaborative Genetics of Asthma in Latino Americans study focusing on asthma and asthma severity among Puerto Ricans and Mexicans has demonstrated that even within a collective ethnic group (''Hispanic Caucasian'' according to National Heart, Lung, and Blood Institute guidelines), ethnic-specific pharmacogenetic differences exist between genotype and asthma severity and bronchodilator response.[58]

With the rapid progress and technologic advances in the field of molecular genetics, supporting evidence for a role of genetics in the observed ethnic disparities in complex diseases has appeared in the form of substantial variations in frequencies of risk variants in candidate genes according to self-reported ancestry and biogeography for hypertension,[59] myocardial infarction,[12] Crohn's disease,[60] asthma,[58] and colon cancer.[61] In other words, a substantial number of genetic markers associated with inflammatory and immunologic diseases have shown large frequency differences among ethnically distinct populations.

As a point of illustration, examples of allelic variants that have been associated with either the presence of disease or for which the putative susceptibility allele occurs at a greater frequency among individuals of African descent compared with non-Africans include (1) the 237G allele of the β chain of the high-affinity IgE receptor (*FCER1B*),[62] (2) the −589T allele of *IL4*,[63] (3) the Ile50 allele of the *IL-4* receptor α gene,[64] (4) the P46L (c.224C>T) variant in the gene encoding member 1A of the TNF receptor superfamily,[65] (5) the −174 G/G genotype in the proinflammatory cytokine *IL6* gene,[66] and (6) the −401A allele of *RANTES*.[67] The *CCR5* receptor (a common receptor for *RANTES*, macrophage inflammatory protein 1α, and macrophage inflammatory protein 1β) is preferentially expressed in T_H1 cells and has been identified as a coentry factor for macrophage-tropic HIV strains. A 32-bp deletion in this *CCR5* gene was shown to protect from macrophage-tropic HIV infection in homozygous individuals.[68,69] More than 10% of Europeans are carriers for this 32-bp deletion, whereas this mutation is absent in African populations.[70]

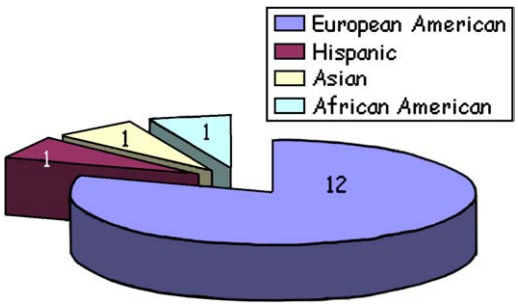

FIG 2. Summary of genome-wide linkage screens for asthma according to ethnicity, illustrating an overrepresentation of studies in populations of European descent.

Substantial differences in minor allele frequencies of variants across ethnic groups are evident for a number of the asthma candidate genes examined thus far, several of which are illustrated in Table I.[54,67,71-73] Of note is that in some cases the wild-type allele confers risk of the trait rather than the variant; for example, the variant T allele at position −260 in the *CD14* gene has been associated with lower total IgE levels[71,74-76] and less severe asthma.[72] The *CD14*(C-260T) polymorphism is functional, as described by LeVan et al,[77] who showed that the T allele exhibits increased transcriptional activity resulting from decreased affinity for Sp3, thus favoring binding of activating Sp1/Sp2 and, consequently, higher soluble *CD14* levels. As demonstrated in Table I, the protective functional *CD14*-260 variant occurs at a much higher frequency among European Americans compared with founders of African descent, which begs the question of why this is the case. As part of the substantial initiative to explore whether differences in asthma prevalence between Puerto Ricans and Mexicans could be explained by genetic susceptibility, the multicenter international Genetics of Asthma in Latino Americans study[58] has generated some of the only data on frequencies of candidate variants in Hispanic participants, and as highlighted in Table I, ethnic-specific differences between 2 major subgroups, Puerto Rican and Mexican American Hispanics, with regard to allelic frequencies for several asthma candidate genes are evident. Collectively, these data suggest that certain allelic variants in candidate genes for immunologic and inflammatory diseases can be more common (or rare) in persons of non-European descent.

THE EFFECT OF THE ENVIRONMENT

As illustrated previously, a major selective force that can affect our genetic diversity is what is referred to as

TABLE I. Ethnic differences in allelic frequencies of asthma candidate genes

Gene	SNP	Minor allelic frequencies (%)			
		African descent*	European descent†	Puerto Rican‡	Mexican American§
ADRB2	rs1042713 (Arg16Gly)	50.8	60.0	55.8	55.0
	rs1042714 (Gln27Glu)	12.3	27.8	27.1	16.8
CD14	rs2569190 (C-260T)	31.9[72]	46.0[71]	44.8	53.1
IL4	rs2243250 (C-590T)	35.2	18.3[73]	32.8	47.5
RANTES	rs2107538 A-403G	56.0	85.0[67]	ND	ND

ADRB2, β_2-Adrenergic receptor; *CD14*, monocyte differentiation antigen *CD14*; *RANTES*, regulated on activation, normally T-expressed, and presumably secreted; *ND*, not done.

*Represents minor allelic frequencies (MAFs) from 450 founders from Barbados for all variants except *IL4* C-590T, for which the MAF is based on 147 African American healthy control subjects from the Baltimore–Washington, DC, metropolitan area.

†Represents MAFs for the 2 *ADRB2* variants from 446 European American founders from Tangier Island, Virginia.

‡Represents MAFs from 770 self-reporting Puerto Rican parents of asthmatic subjects participating in the Genetics of Asthma in Latino Americans (GALA) study.[54]

§Represents MAFs from 602 self-reporting Mexican American parents of asthmatic subjects participating in the GALA study.[54]

host counteradaptations to pathogens or, simply, defense against disease; the example of the Duffy locus as a protective measure against malaria is a classic example, and not surprisingly, the distribution of the Duffy locus parallels the world's distribution of *Plasmodium vivax* (http://www.who.int/ctd/html/malariageo.html). Other forces that can affect our genetic makeup are our biocultural adaptations. Consider another classic example of selection as a result of adaptation: the distribution of a lactase persistence polymorphism. Some 8000 years ago, recent in the history of *H sapiens*, certain groups of human subjects developed a dependence on milk from domestic cows as a valuable food source. This adaptation is caused by, at least in part, a causal nucleotide change in the *apo A-IV* gene (*apo A-IV-2*), which confers the persistence of lactase activity into adulthood, which otherwise decreases during infancy after the weaning phase.[78] The distribution of the lactase persistence polymorphism is highest in northwestern Europe, especially among northern Europeans, and decreases in a south and west direction.[79] Individuals who do not have the variant, such as the Nuer people on the banks of the Nile River in southern Sudan or the Herero people of southwestern Africa, might be characterized as lactose intolerant, but manifestation of a disease state (eg, gastrointestinal symptoms) would only occur if they were to change their eating habits and consume milk as part of their diet.

Thus it is evident that just as the environment is a powerful factor selecting for genetic variation, the environment is also important in determining whether certain traits associated with variants are ever expressed. Simple examples of this phenomenon abound, and the range of the effect of the environment on the presence or absence of a particular genetic variant or variants is wide. For example, familial aggregation studies of the behavioral trait (or phenotype) absolute pitch demonstrate a very strong genetic influence on the ability to identify pitch of tones in the absence of a reference pitch, as evident by very high estimates of the sibling recurrence risk (or lambda sib), but expression of the phenotype (absolute pitch) is very much dependent on exposure to early music training.[80] In other words, if an individual with the genetic predisposition for absolute pitch does not have early music training, he or she is unlikely to realize this unique talent. Heritability estimates for asthma and atopy biomarkers and quantitative traits, such as bronchial hyperreactivity, FEV_1, and total and specific IgE levels, tend to be much lower,[81-84] as shown in Fig 3, supporting an even stronger role for the environment in disease expression.

Unfortunately, in the field of asthma and allergic disease epidemiology, our understanding of the seemingly limitless number of environmental exposures that can affect disease expression is daunting enough but is further compounded by issues such as the time of exposure in one's life and dose of exposure. For example, although there appears to be a rather clear relationship between allergen exposure and allergen sensitization, the dose-response relationship is specific for some allergens and not for others and in any case is most relevant for susceptible individuals (eg, those who are atopic or who have a family history of atopy). Much higher doses of allergen exposure are necessary for sensitization in individuals with no history of atopy,[85] and a substantial portion of the population exposed to very high concentrations of allergen will never become sensitized. Adding to the complexity is the fact that despite the worldwide ubiquity of indoor allergens, such as cockroach and house dust mite, and in many cases concomitant exposure to different allergens, the relative importance of specific allergens varies between regions. Peat et al[86] demonstrated that in Australia exposure to high concentrations of house dust mite is a risk factor for bronchial hyperreactivity in children living in a humid subtropical region, but *Alternaria* species sensitization was the major risk factor for bronchial hyperreactivity in a dry rural region. Other examples abound wherein there is primarily one dominant allergen, varying according to region (eg, mite in New Zealand,[87] and cat allergen in Los Alamos, NM[88]). Of further interest, the importance of certain allergens also appears to vary across ethnic groups, even when exposure levels are similar. For example, in a cross-sectional evaluation of risk factors for higher asthma severity in African American and

European American adolescents, Togias et al[89] demonstrated that despite the fact that cockroach allergen levels in dust samples collected from the adolescents' homes were highest in the lowest-income quartile in both ethnic groups, African Americans were more prone to experience cockroach sensitization than European Americans, suggesting that income and ethnic background interact with respect to increased risk for cockroach allergy and that African Americans constitute a susceptible group. If we consider the message illustrated above, that it is not sufficient to have genetic susceptibility alone but that environmental exposure is essential for expression or manifestation of disease, we begin to appreciate the formidable task of even identifying which environmental factors are at play and whether those factors are more important to one ethnic group compared with another.

A great deal of focus has been directed toward the role of domestic endotoxin or LPS (gram-negative bacteria) and allergic disease. Several groups have shown that the promoter C→T variant at position −260 in *CD14* is negatively associated with total serum IgE levels or other measures of atopy, primarily in populations of European or Asian descent. Recently it was shown that the C-260T allele protects against asthma severity in families of African descent, although the frequency of the T allele was considerably lower in this population compared with frequencies reported in populations of European descent, and the TT genotype was especially rare in families from Barbados, where asthma is very common.[72] Because the *CD14* receptor is the primary ligand for LPS, domestic endotoxin levels in homes were also measured and tested for gene-environment interaction. Interestingly, the TT genotype seemed to protect against asthma among individuals living in homes with low endotoxin concentrations compared with those in homes with high endotoxin levels, suggesting that the association between the *CD14* promoter polymorphism and asthma might depend on endotoxin exposure but only certain levels of endotoxin. Finally, the findings in this study are strikingly different than findings in settings focusing on populations of European descent, in which a strong inverse association of endotoxin exposure with atopic sensitization is observed overall.[90]

IS A RISK VARIANT IN ONE DISEASE PROTECTIVE IN ANOTHER?

As described above, the majority of human genetic variation occurs among individuals within the same populations, but a good deal of attention has been directed toward the variation across populations as a source for understanding the complexities of disease disparity. Human genetic variation is the end result of diverse forces in nature. Adaptation through natural selection is the net effect of local and selective environmental forces (eg, parasites, disease, diet, and climate), resulting in altered patterns of genetic variation only in certain populations. Well-documented examples of positive selection for

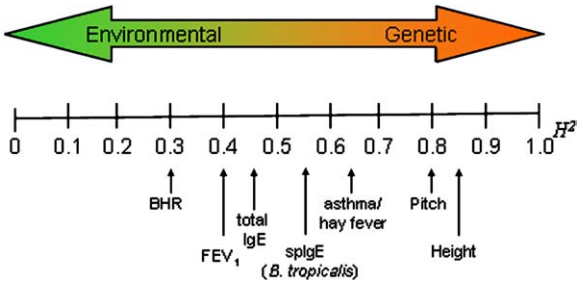

FIG 3. Relative influence of the environment versus genetics on trait development. Heritability estimates for disease-specific traits (bronchial hyperreactivity *[BHR]*, FEV_1, total serum IgE, specific IgE *[splgE]* to *Blomia tropicalis* allergen, and asthma–hay fever) are compared with traits with a strong genetic basis, including pitch and height. Adapted with permission from Hartl DL. A primer of population genetics. Sunderland (MA): Sinauer Associates, Inc; 2000 (with additional references[81-84]).

genetic variants are relatively few, and the best are restricted to infectious diseases (eg, resistance to malaria[91]) or nutritional adaptations (eg, lactose tolerance[78]), as described above. These functional variants are typically geographically restricted and often show a unique clinical distribution (eg, endemicity of parasites and nutritional and cultural constraints).

Our understanding of natural selection is very limited but growing as public information on SNPs and the identification of genome-wide signatures of natural selection become available. These might be useful in defining the genotype-phenotype correlation for genes controlling risk to complex diseases. Consider, for example, the pivotal role of CD14 in innate immunity as an LPS-binding receptor and initiator of an antimicrobial defense response. In focusing on the role of a functional variant in the *CD14* gene and susceptibility to sepsis, Gibot and others[92] demonstrated that the same C→T promoter polymorphism at bp −260 in *CD14* described above in the context of risk for allergic disease also increased the relative risk of death caused by septic shock and was significantly overrepresented among patients with septic shock compared with control subjects. As alluded to above, however, the sepsis risk T allele has been associated with lower serum total IgE levels in a number of populations and less severe asthma in a population of African descent.[72] Curiously, the frequency of the T variant in the population of African descent is nearly half that reported in non-African populations.[71,74,76,93] Looked at another way, the wild-type C allele (associated with higher total IgE levels and, arguably, not dying from sepsis) is more common among the African ancestry population compared with the non-African populations, suggesting that there might be some prior advantage to a phenotype resulting from the CC or CT genotype.

One possibility is based on a long-standing hypothesis that there is a selective advantage conferred by high IgE producers in regions endemic for extracellular parasitic disease because the production of very high concentrations of specific and nonspecific IgE in response to

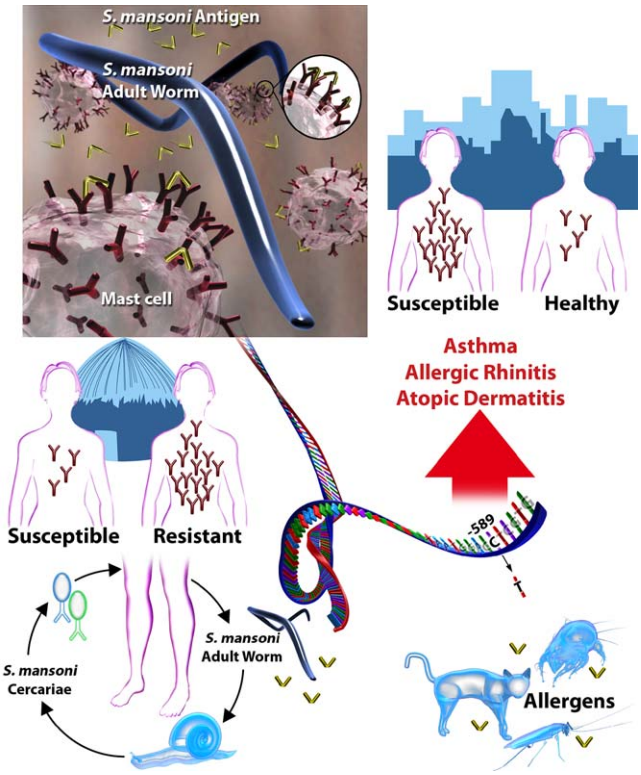

FIG 4. A proposed model for the common disease/common variant hypothesis and the inverse relationship between resistance to extracellular parasitic disease in traditional endemic environments and allergic disease in metropolitan nonendemic environments. Central to this hypothesis is a variant in a candidate gene (illustrated by the C→T substitution on the strand of DNA) that confers high IgE production, which is (1) protective when directed toward *Schistosoma mansoni* worm antigen *(yellow)*. The *lower left-hand illustration* depicts the water-borne *S mansoni* cercariae penetrating through the human host's skin, where IgE antibodies bound to activated mast cells are produced in response to shed worm antigens *(upper left-hand enlargement)*, bind to the worm antigen, facilitate an adaptive immune response against the worm, and lead to a resistant state. Susceptible hosts produce less worm-specific IgE. Conversely, (2) in nonendemic regions the human host with a genetic predisposition for production of high IgE levels overreacts to common allergens, such as those produced from cat, dust mite, or cockroach, resulting in conditions, such as asthma, allergic rhinitis, and atopic dermatitis. Healthy individuals do not mount a similar IgE-mediated response.

helminth antigen is associated with a protective response against infections[94] and because individuals with a history of atopy have been shown to be protected from helminthic parasites because they mount a stronger IgE-mediated response to worm antigen and demonstrate a lower intensity of parasitic infection compared with nonatopic individuals with the same exposure (Fig 4).[95,96] Thus a situation emerges that suggests that a genetic adaptation in one context (eg, protective variant selected for environments endemic for parasitic disease) might be a risk variant in another setting (eg, contemporary setting in which antigens homologous to worm antigens, such as cockroach and dust mite,[97,98] abound).

From a study in the Chinese population, Gao et al[99] characterized a significant association between an asthma-associated genetic variant (G4219A) within the 3′ regulatory element of the gene encoding signal transducer and activator of transcription 6 and low intensity of infection by *Ascaris lumbricoides* ($P = .0002$).[100] Signal transducer and activator of transcription 6 is an important candidate because of its role in signaling for the differentiation of $CD4^+$ T cells to a T_H2 type of immune response, which is associated with immunity against intestinal nematode infections.[101] Similar associations for both ascariasis[102] and asthma[103,104] have also been observed for a common polymorphism in the gene encoding the β_2-adrenoreceptor (Arg16Gly). Focusing on factors associated with the development of periportal fibrosis as a complication of chronic schistosomiasis in a Sudanese population, Chevillard et al[105] tested for association of polymorphisms in the gene encoding *IFNG* because of observations that high IFN-γ levels are associated with a marked reduction in the risk of fibrosis.[106] Similarly, another group focusing on hepatic fibrosis in schistosomiasis, also in Sudan, observed a marker in the IFN-γ receptor 1 (*IFNGR1*) gene (rs1327475) on chromosome 6q22-q23,[107] in which strong evidence of linkage had previously been reported[108] and the gene for which modest association has been reported for total serum IgE levels in a British population.[109]

Consider also that the strongest evidence for linkage to schistosomiasis intensity of infection has been found for chromosome 5q31-q33,[110] the same locus for which some of the most compelling evidence for linkage to asthma and atopy had been reported. Other loci that overlap with evidence for linkage to asthma include 7q and 21q.[111] Specific variants in candidate genes for schistosomiasis have not been identified at the same pace as have asso ciations in other extracellular parasitic diseases, possibly because of the unique complexity and natural history of schistosomiasis, the fact that appropriate controls that best match the reference population have not been agreed on, and complexities associated with the natural history of the disease and definition of the phenotype. Schistosomiasis as a trait is typically defined quantitatively as the intensity of infection through a measure of egg count per gram of fecal matter (*Schistosoma mansoni*) or a measure of worm antigen in urine (*Schistosoma hematobium*). Kouriba et al[112] recently identified 2 SNPs (*IL13*-1055C [$P = .05$] and *IL13*-591A [$P = 0.01$]) in the *IL13* gene that conferred increased risk for high infection intensity in a population endemic for *S* hematobium.

Taken together, these findings support the notion that genetic determinants that originally arose as an adaptive mechanism in minimizing morbidity associated with parasitic infection, both intracellular and extracellular, are associated with a contemporary manifestation, such as asthma and allergic disease, conditions that are rarely observed in regions endemic for parasitic disease.

SUMMARY

Our understanding of the role of genetic variation as it might contribute to the health disparities in complex diseases, such as allergic asthma, is limited at best. No doubt greater strides have been accomplished in identifying key social, cultural, and economic factors that continue to contribute to the inequitable care, maintenance, and quality of life for asthmatic subjects who are underserved minorities in the United States. Perhaps much of the consternation surrounding genetic susceptibility in the context of sensitive social constructs, such as race and ethnicity, could be mitigated if we shift our paradigm from one of absolute boundaries of race represented by biogeography to one of a continuum. Indeed, accumulated knowledge from the fields of anthropology and molecular genetics illustrates a scenario whereby modern *H sapiens* only replaced the more ancient species in Africa some 100,000 to 200,000 years ago, experienced profound environmental influences (eg, infectious disease insults, dietary constraints) that conferred genetic adaptations, and then migrated to other regions whereby the genome was modified in the face of new selective forces and admixture of subgroups. As a result, allelic frequencies of polymorphisms in genes that might (or might not) play a role in susceptibility to allergic disease vary from group to group, as do the conserved regions (or haplotype blocks in the genome), but importantly 99.6% to 99.8% of our genetic material is shared. The significance of variants that are relatively common across groups and that appear to confer risk of, or resistance to, more than one disease is still poorly understood, as are the incomprehensible possibilities of gene-environment interactions.

I thank Audrey Grant, Shu Zhang, and William Shao for assistance in summarizing the asthma association and linkage disequilibrium data; Drs Shweta Choudhry and Esteban González Burchard for contribution of allelic frequency data from the Genetics of Asthma in Latino Americans study; Drs Terri Beaty and Maria Ilma A. S. Araújo for their critical review; and Pat Oldewurtel for technical assistance in the preparation of this manuscript.

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