Published in final edited form as:

Pharmacogenomics. 2008 April ; 9(4): 453–462. doi:10.2217/14622416.9.4.453.

Race, Ethnicity and Social Class and the Complex Etiologies of Asthma

Katherine A Drake^{1,†}, Joshua M Galanter², and Esteban Gonzalez Burchard^{1,2,3}

¹ Department of Biopharmaceutical Sciences, University of California, San Francisco

² Department of Medicine, University of California, San Francisco

³ Institute of Human Genetics, University of California, San Francisco

Summary

Asthma is a common but complex respiratory disease caused by the interaction of genetic and environmental factors. Significant racial and ethnic disparities in prevalence, mortality, and drug response have been described. These disparities may be explained by racial and ethnic-specific variation in genetic, environmental, social and psychological risk factors. In addition, race, ethnicity, and social class are important proxies for unmeasured factors that influence health outcomes. Herein, we review salient differences in the etiologies of asthma by race, ethnicity and social class, and argue for their continued use as variables in asthma research.

Keywords

Asthma; race; ethnicity; social class; interactions

Introduction

Asthma is a common and complex respiratory disease that results from the interaction of genetic, environmental, social and psychological factors. In addition to the complex pathogenesis of asthma, the clinical expression is heterogeneous and may be subdivided into allergic, non-allergic, exercise-induced, and aspirin-sensitive asthma. The heterogeneous clinical expression can make the diagnosis of asthma difficult and may lead to misclassification. These factors may confound asthma research resulting in inaccurate reporting of asthma prevalence and morbidity. Despite these limitations, there are well-documented disparities among racial and ethnic groups with respect to asthma prevalence, mortality and drug response [1–7].

In the United States, the prevalence of asthma is highest in Puerto Ricans, African Americans, Filipinos and Native Hawaiians [4,8,9]. However, the high prevalence is not universal in Hispanic and Asian subgroups; it is lowest in Mexicans and Koreans [8]. Mortality rates follow similar trends [3,10] and response to albuterol, the most commonly prescribed treatment for asthma, is lower in Puerto Ricans than in African Americans and Mexicans [1,5]. Unfortunately, with respect to asthma, racial and ethnic minorities have been largely understudied and often distinctions and heterogeneity within racial and ethnic groups are ignored.

[†]Correspondence and reprint requests: Katherine A Drake, UCSF/Lung Biology Center, University of California, San Francisco, San Francisco, California 94143-2911; e-mail: katherine.drake@ucsf.edu.

Recently, genetic studies of asthma and other complex diseases have flourished. However, the majority of asthma candidate gene studies and genome-wide linkage analyses have been performed on populations of European descent. Only three genome-wide linkage screens for asthma have included racial or ethnic minorities; one study included African American and Latino populations, one was performed on a Costa Rican population and another was conducted on an Asian population [11–14]. The only whole-genome association study of asthma thus far investigated two European populations [15]. Asthma prevalence and the percentage of genetic association studies conducted on each population are compared in Table 1.

Understanding the complex etiologies of asthma as they relate to diverse populations will become increasingly important from the perspective of public health. Over the next four decades, there will be significant demographic shifts in all Western countries. For example, in the U.S., the white non-Hispanic population is expected to decline from 69.4% of the population in 2000 to 50.1% in 2050 [16,17]. Latinos, who recently surpassed African Americans as the largest minority population, are expected to grow from 14.8% of the population in 2006 to 24.4% in 2050. African Americans and Asians are expected to grow from 12.7% and 3.8% in 2000 to 14.6% and 8.0% in 2050, respectively.

In addition to the public health benefits, there are methodological advantages to studying diverse populations. The study of a broad range of populations may help untangle complex genetic, environmental, social and psychological interactions that contribute to asthma and asthma disparities. This review will highlight the importance of including race, ethnicity and social class in biomedical research. These variables serve as proxies for unmeasured confounders and have an important impact on asthma etiology.

Defining Race and Ethnicity

Defining race and ethnicity for biomedical research is complex, contextual, and each plausible definition has its own limitations. The complexities associated with defining race and ethnicity are outside the scope of this review and have been described elsewhere [18–20]. Definitions of race and ethnicity are affected by both the racial and ethnic categories and the reporting method used. Thus, racial and ethnic categories are not necessarily consistent across studies. Racial and ethnic categories may be defined by the U.S. Census categories, but these imprecise definitions may limit within-group heterogeneity in asthma phenotypes [18]. Methods for dividing participants into racial and ethnic categories include self-report, observer-report and genetic estimates of individual ancestry [19]. Specific methods for reporting race and ethnicity may mask heterogeneity in risk factors associated with asthma. Given the difficulties associated with precisely defining race and ethnicity, researchers should clearly state how they categorize race and ethnicity and should recognize the limitations of their methods.

Genetic Risk Factors for Asthma

Over 118 genes have been associated with asthma. However, no gene that has been studied in multiple racial and ethnic populations has shown a positive association in every group [22, 23]. This may suggest that genetic risk factors can vary with race and ethnicity. For example, variation in *ADAM33* was associated with asthma in four populations of European descent, one African-American population and one Hispanic population [23–26]. However, *ADAM33* was not associated with asthma in Mexican, Puerto Rican, Korean, European, or Costa Rican populations [27–29]. A large, mixed-ethnicity study found no individual single nucleotide polymorphisms (SNPs) associated with asthma in African Americans or U.S. whites, and two SNPs with only a marginal association in Hispanics [30]. Furthermore, in a study that demonstrated an association between asthma and *ADAM33* in multiple populations, different SNPs were associated with asthma in each population [24]. Likewise, the Arg16Gly polymorphism in the beta₂-adrenergic receptor (*ADRB2*) has been associated with

bronchodilator response to albuterol in three mixed U.S. populations, one Korean population and one Puerto Rican population [31–35], but not in Mexican or African American populations [32,36].

There are several possible explanations for inconsistent results in genetic association studies. First, the contribution of a risk allele in any given population depends upon its allele frequency in that population. Stephens *et al.* found that only 21% of SNPs examined in 313 human genes were present across the four racial groups they investigated, while 15% of SNPs were specific to one race [37]. Although there are no examples yet of private SNPs associated with asthma, SNP 84GG in *GBA* is a private SNP associated with Gaucher's disease: it has a 12% frequency in Ashkenazi Jews with Gaucher's disease but is very rare among non-Ashkenazi Gaucher's patients [38]. Even pan-racial polymorphisms differ in allele frequencies, which may explain population-specific associations.

In addition, the genetic predisposition to disease (genotypic relative risk) that is associated with a risk allele may vary across populations. Presumably, this variation in genotypic relative risk may be due to interactions with unmeasured factors that are unique to specific populations. For example, homozygosity at the Alzheimer's-associated *APO-ε4* allele confers different relative risks across racial groups. While the frequency of this allele is highest in African Americans and lowest in Japanese populations, homozygosity for *APO-ε4* confers a 33-fold increased risk among Japanese and only a 6-fold increased risk in African Americans [39]. Interaction between the *APO-ε4* allele and other genetic loci or population-specific environmental risk factors likely modifies the magnitude of its effect. Investigators need to consider similar interactions in order to understand differences in associations across populations for complex diseases such as asthma.

Genetic Admixture, Ancestry, and Asthma

Racial ancestry can be a valuable tool for the discovery of novel associations and interactions, particularly in admixed populations. Admixed populations such as African Americans and Latinos are descendents of multiple ancestral populations. Their specific ancestral background can be estimated using ancestry informative markers (AIMs). AIMs have been used to demonstrate that African American ancestry is on average 20% European and 80% African, while Latino populations are descendents of European, Native American, and African ancestors [40,41]. The average proportion of these three ancestral populations varies between Latino subgroups and among individuals within the same subgroup. The variation in ancestry may help to explain differences in asthma phenotypes among ethnic subgroups. Our research team found that in Mexican Americans, European ancestry was associated with more severe asthma, as measured by FEV₁, a quantitative measure of lung function. A decrease of 1.7% baseline FEV₁ was observed per 10% increase in European ancestry [6]. However, it is important to note that although ancestry is associated with asthma phenotypes, it may be acting as a proxy for genetic, environmental or social factors and may not be directly causal.

If there is a true association between ancestry and asthma-related phenotypes, as described above, then the association may provide supporting evidence for the use of admixture mapping to identify genes associated with these phenotypes. Admixture mapping is a method that uses AIMs that are evenly spaced throughout the genome in admixed populations to localize disease-causing genetic variants that differ in frequency across populations [42]. The approach assumes that a higher proportion of ancestry from the population that has greater risk for the disease will be found near a disease-causing locus. This approach has been used to identify loci that contribute to multiple sclerosis, hypertension and circulating levels of inflammatory markers [42–44].

Several gene-gene interactions affect asthma [45–48]. These interactions may be modified by ancestry. A murine model of airway hyperresponsiveness (AHR) found an interaction between two loci that caused an increase in naive AHR [49]. The effect of these interacting loci was more pronounced in one murine strain than in another, suggesting that genetic background modifies the risk contributed by a given allele. In humans, admixed populations have been used to investigate the effect of different ancestral backgrounds upon the risk conferred by particular ancestral alleles. A European allele of the *LTA4H* gene, which is associated with myocardial infarction (MI), confers a three-fold higher risk for MI in African Americans than in European Americans. These results may suggest that African ancestry modifies risk for MI caused by this allele [50]. In addition to gene-gene interactions, ancestral background may modify the effect of known genetic associations.

Methodological Advantages of Studying Genetics in Racially and Ethnically Diverse Populations

There are important methodological advantages to studying genetics in diverse populations because of differences in linkage disequilibrium (LD) patterns. Many genetic variants (mostly SNPs) linked to a disease may not be the causative genetic factor, and data from a broad range of populations with varying LD patterns can overcome this limitation. An associated SNP may be in linkage disequilibrium (LD) with the causative SNP such that both SNPs are contained in the same “genetic block” and are associated with the disease, even if only one of them is pathogenically involved in disease. Studying the same SNP in multiple populations with varying linkage disequilibrium patterns may differentiate between the causative SNP and linked polymorphisms. This has been demonstrated for other heritable traits. For example, three different amino acid substitutions in the phenylthiocarbamide (PTC) bitter taste gene were associated with taste blindness [51]. Although most populations had strong to complete LD between these SNPs, studies of Africans separated the effects of individual SNPs because of the reduced LD in this group. Similarly, Mignot *et al.* identified DQB1*0602 as the functional HLA allele associated with susceptibility to narcolepsy by studying Africans, who were the only population in which LD between the DQB1*0602 and DR2 alleles was incomplete [52].

Environmental Risk Factors for Asthma

Several environmental factors, such as family size, daycare use, and exposure to second hand tobacco smoke (SHS), have been associated with asthma [10]. Family size and daycare use are thought to be associated with asthma because of early childhood exposure to infections. The association of environmental risk factors with asthma may be explained by the “hygiene hypothesis,” which states that developing immune systems need exposure to certain infectious agents, symbiotic bacteria, and other environmental factors in order to develop in a balanced and well-regulated manner [53,54]. Thus specific environmental factors may be protective against asthma, while other environmental factors may directly cause or exacerbate asthma.

Environmental factors associated with asthma vary by race, ethnicity and social class. For example, it is well known that SHS increases the risk for asthma and asthma severity [10]. SHS exposure also varies by race and ethnicity: smoking rates are highest in American Indians, followed by Puerto Ricans, European Americans, African Americans and Mexicans. Smoking rates increased in the 1990s in African American and Hispanic adolescents [55]. Amongst Latinos, smoking rates differ by place of birth, acculturation and socioeconomic status [1,56, 57]. There are well-documented racial and ethnic differences in nicotine uptake and metabolism, which may influence the observed differences in the quantity of cigarettes smoked per day and therefore SHS exposure of other household members [58–60].

Racial and ethnic differences in effect magnitude have been demonstrated for environmental exposures associated with asthma. Freeman and colleagues administered an asthma symptom and household exposure factor questionnaire to 4,634 school children in Passaic, New Jersey [61]. Passaic is a unique community in that it has a wide range of Latino ethnic groups representing the Caribbean, Mexico, Central and South America. This diversity offers an opportunity to compare asthma and exposure for a variety of Latino ethnic groups within the same urban and predominantly poor community. Although exposures were similar for all groups, environmental factors associated with asthma differed by ethnic group. For example, damp and moldy conditions were associated with asthma in Puerto Ricans but not Mexicans and Dominicans. These results suggest that other ethnic-specific factors interact with environmental exposures to modify the risk for asthma and asthma-related phenotypes.

Gene-Environment Interactions and Asthma

Environmental factors can also modify the disease risk, which is associated with a given genetic risk factor. Specifically, the association between a genetic risk factor and a particular disease may only manifest in the presence of a permissive environmental exposure. Despite initially contradictory and confusing results when environmental interactions were not considered, it is now well accepted that the *CD14* C-159T allele interacts with levels of endotoxin exposure [62]. At low levels of endotoxin exposure, the TT genotype at SNP C-159T is associated with protection from asthma, while the CC genotype is associated with protection at high levels of endotoxin exposure [63–66]. Two important racial and ethnic-specific factors may influence the relevance of this interaction in different populations. First, the frequency of the T allele varies from 32% in populations of African descent to 53% in Mexican Americans [11]. Second, cultural factors such as exposure to SHS, dog ownership and certain types of farming are associated with high levels of endotoxin exposure and vary by race and ethnicity [10]. Thus, race and ethnicity can affect genetic and environmental factors resulting in complex gene-environment interactions that modify asthma risk.

Social and Psychosocial Risk Factors for Asthma

Social factors, such as socioeconomic status and exposure to violence, and psychological factors, such as depression, stress and anxiety, have been associated with asthma [10,67]. Exposure to both social and psychological risk factors varies by race, ethnicity and social class. One study demonstrated that Puerto Ricans who self-identify as black have lower mean household income and are more likely to live below the poverty level than those who self-identify as white [68]. In addition, racial reporting was a significant predictor of hourly wages for Puerto Rican men in New York City, even after adjusting for potential confounding factors [69]. Similarly, among Mexican Americans those with dark skin and American Indian-physical appearance are more likely to be discriminated against, receive less education and hold occupations with lower prestige than their light skin and European-appearing counterparts [70]. This relationship was also observed with respect to earnings [71]. Thus, asthma researchers cannot ignore social and psychological factors that vary by race, ethnicity and social class.

There is a complex interplay between race and ethnicity and socioeconomic status with respect to asthma-associated risk factors. Togias *et al.* demonstrated that socioeconomic status influences allergy in African Americans: African Americans in the lowest income quartile had higher rates of cockroach sensitization than African Americans in higher income brackets. In contrast, there was no association between cockroach sensitization and income level among European Americans [72]. In addition, our group recently demonstrated that ancestry interacts with SES to modify the risk of asthma [2]. In Puerto Rican asthmatics of low SES, higher European ancestry was associated with asthma, whereas in Puerto Rican asthmatics of high

SES, higher African ancestry was associated with asthma (Figure 1) [2]. In this example, ancestry and SES, which may be surrogates for other biological, social, psychological or environmental factors, interact to influence asthma risk. These studies underscore the complex nature of class-specific environmental exposures, which are known risk factors for asthma and allergy.

Social and psychological risk factors are closely related because social factors can increase psychological stress. Psychological factors may alter a person's allostatic load, the physiological sequelae of chronic exposure to stress. Although the exact processes are unclear, the pathophysiologic sequelae are thought to be mediated through neuroendocrine and/or immunologic pathways [73]. The influence of allostatic load on disease outcomes has been demonstrated for coronary heart disease (CHD). For example, the Whitehall study demonstrated that the risk of CHD increased as social class decreased among classes of British civil servants. CHD in the lowest social class of British civil servants was 3-fold higher compared to the highest class, after adjusting for known CHD risk factors [74]. In addition, British civil servants who experienced negative interactions in their closest relationship, such as conflict in their marriage, were more likely to develop CHD than those who did not, even after adjusting for differences in demographic, social, biological and psychological confounders [75]. Racial discrimination can also influence health outcomes by increasing allostatic load. In African Americans, perceived racial discrimination was associated with risk of hypertension, carotid plaque and low-birth-weight deliveries [76]. Chronic psychological stress, which may be exacerbated by social class or perceived discrimination, can "get under your skin" and alter health outcomes. However, the mechanism by which both social and psychological risk factors influence physiological processes is unclear.

Recently, Chen and colleagues investigated the mechanism by which neighborhood and family level social and psychological factors influence asthma [77]. They found that lower levels of family support affected asthma symptoms and pulmonary function through biological pathways, such as allergic inflammation, whereas community factors influenced asthma symptoms through behavioral pathways, such as higher smoking rates. Although the population in this study was mixed and mostly of European descent, it provides an excellent basis for the examination of the influence of social factors and changes in allostatic load on disease. Genetic, environmental, social and psychological risk factors likely operate at the individual, family and community level. However, further research on biopsychosocial models of asthma and other complex diseases is needed. Research across a broad range of populations will refine the mechanisms through which these risk factors interact and translate into disparities in disease outcomes.

Immigration, Acculturation and Risk of Asthma

Immigration and acculturation can also affect risk for asthma. The increased risk associated with these factors is likely attributable to complex changes in physical and social environments, and can vary by race, ethnicity and ancestry. Studies in Chinese, Dominican, and Mexican populations have demonstrated lower asthma rates in foreign-born children and adults than in their U.S.-born counterparts [4,78–80]. Recently, Eldeirawi and colleagues demonstrated that acculturation, defined using an acculturation scale based on language preferences of participants, had a stronger effect on the risk of asthma than country of birth among Mexican youth [81]. In addition, Klinnert *et al.* demonstrated that Latino children with low-acculturated parents, defined by language preference and country of birth, exhibited a lower prevalence of asthma than their highly acculturated counterparts [82]. Collectively, these studies suggest that environmental and social risk factors associated with acculturation to the U.S. contribute to asthma risk.

Immigration of certain racial and ethnic populations to the U.S. correlates with strong language differences that can affect health care. There is evidence that asthma-related words such as 'wheeze' do not translate well into other languages [83]. Greenfield *et al.* found that 35.6% of Cantonese-speaking immigrants who watched a video of wheezing said that their conception of wheezing differed from what they saw in the video [84]. Differences in the meaning of asthma-related words in different languages may confound diagnosis of asthma and contribute to variation in the reporting of asthma.

The effect of immigration and acculturation may be population-specific. Lara *et al.* found no difference in asthma rates between Puerto Ricans born in Puerto Rico and in the continental U.S. [4]. This may reflect the fact that Puerto Ricans are born as U.S. citizens and thus may already be acculturated or may suggest that immigration has population-specific effects. Moreover, levels of acculturation vary by race and ethnicity [85,86]. Third generation Asian immigrants to the U.S. are more likely than third generation Latino immigrants to speak only English. Among Latino immigrants, Dominicans are less likely to speak only English in the third generation. In contrast, Filipino and Japanese immigrants are more likely to speak only English in the second generation than other immigrants. Unfortunately, studies of immigration and acculturation may be complicated by selection bias for particular sub-populations. We recently demonstrated that the proportion of Native American ancestry, which was associated with less severe asthma, is higher among Mexican asthmatics living in Mexico City than in those who were born in Mexico and immigrated to the U.S. [87]. The factors that determine which sub-populations migrate to the U.S. are complex and likely reflect socioeconomic as well as political forces. Nonetheless, changes in environmental and social exposures mediated by immigration and acculturation and dependent on race and ethnicity are important contributors to asthma risk.

Commentary

Much progress has been made in elucidating genetic causes of asthma through linkage studies, candidate gene studies, and studies of gene-environment interactions. 118 genes have been linked to asthma so far, with at least 54 replicated in 2 or more populations [23]. In addition, the introduction of affordable whole-genome association studies holds promise for discovery of asthma candidate genes. For example, *ORMDL3*, a gene of unknown function, was recently discovered through a combination of a whole-genome association study and expression analysis in lymphoblastoid cell lines of asthmatic children [15]. Promising analytical methods, such as admixture mapping, may elucidate genetic differences that account for disease disparities. In addition, novel methods for measuring environmental, social and psychological factors are being developed.

While modern genetic techniques and careful data collection will continue to advance genetic and epidemiologic studies of asthma, the insight gained from examining individual factors is limited. Already, the number of factors known to contribute to asthma is large and growing. A holistic view of this complex disease will not be possible without understanding the interactions between these factors and the pathways through which they work. Careful collection of genetic and environmental, as well as social and psychological data is necessary to assess their interaction. In this setting, the use of race as a surrogate for complex genetic, environmental and psychosocial factors can be beneficial. This will enable effective strategies for the amelioration of health disparities.

Outlook

To date, much attention has been devoted to the idea of elucidating as many factors that contribute to asthma as possible, with the prospect of developing personalized medicine based

on genotype and specific exposures. Though exciting, this is still impractical for complex diseases like asthma, because of the many contributing and interacting factors that modify disease risk (Figure 2) [88]. Contemplating the number of possible causes that have been identified thus far and the number of possible multi-level interactions between them is a daunting task. The use of variables such as race, ethnicity and social class as surrogates for unmeasured factors, however, may enable investigators to identify interactions that have practical value for identifying and treating asthma in high-risk groups. Even if it were practical to fully genotype an individual, identify all known environmental exposures and account for the interactions between genetics and the environment, race, ethnicity and social class will continue to serve as valuable proxies for unknown factors. As such, these variables will remain important and independent contributors to health and disease. Despite suggestions that race and ethnicity should not be reported in biomedical research and are purely social constructs [89,90], the need for their reporting and investigation as predictive variables is clear: as long as researchers are using our current methods for measurement of genetic, environmental and psychosocial variables, race and ethnicity will not become a moot point.

References

1. Burchard EG, Avila PC, Nazario S, et al. Lower bronchodilator responsiveness in Puerto Rican than in Mexican subjects with asthma. *Am J Respir Crit Care Med* 2004;169:386–92. [PubMed: 14617512]
2. Choudhry S, Burchard EG, Borrell LN, et al. Ancestry-environment interactions and asthma risk among Puerto Ricans. *Am J Respir Crit Care Med* 2006;174:1088–93. [PubMed: 16973984]
3. Homa DM, Mannino DM, Lara M. Asthma mortality in U.S. Hispanics of Mexican, Puerto Rican, and Cuban heritage, 1990–1995. *Am J Respir Crit Care Med* 2000;161:504–9. [PubMed: 10673193]
4. Lara M, Akinbami L, Flores G, Morgenstern H. Heterogeneity of childhood asthma among Hispanic children: Puerto Rican children bear a disproportionate burden. *Pediatrics* 2006;117:43–53. [PubMed: 16396859]
5. Naqvi M, Thyne S, Choudhry S, et al. Ethnic-specific differences in bronchodilator responsiveness among african americans, puerto ricans, and mexicans with asthma. *J Asthma* 2007;44:639–48. [PubMed: 17943575]
6. Salari K, Choudhry S, Tang H, et al. Genetic admixture and asthma-related phenotypes in Mexican American and Puerto Rican asthmatics. *Genet Epidemiol* 2005;29:76–86. [PubMed: 15918156]
- 7* . Barnes KC, Grant AV, Hansel NN, Gao P, Dunston GM. African Americans with asthma: genetic insights. *Proc Am Thorac Soc* 2007;4:58–68. [PubMed: 17202293] A discussion of genetic techniques for studying admixed populations, with emphasis on populations of African descent
8. Davis AM, Kreutzer R, Lipsett M, King G, Shaikh N. Asthma prevalence in Hispanic and Asian American ethnic subgroups: results from the California Healthy Kids Survey. *Pediatrics* 2006;118:e363–70. [PubMed: 16882779]
9. Johnson DB, Oyama N, LeMarchand L, L Wilkens. Native Hawaiians mortality, morbidity, and lifestyle: comparing data from 1982, 1990, and 2000. *Pac Health Dialog* 2004;11:120–30. [PubMed: 16281689]
10. Gold DR, R Wright. Population disparities in asthma. *Annu Rev Public Health* 2005;26:89–113. [PubMed: 15760282]
11. Barnes KC. Genetic epidemiology of health disparities in allergy and clinical immunology. *J Allergy Clin Immunol* 2006;117:243–54. [PubMed: 16461122] quiz 255–6
12. CSGA. A genome-wide search for asthma susceptibility loci in ethnically diverse populations. The Collaborative Study on the Genetics of Asthma (CSGA). *Nat Genet* 1997;15:389–92. [PubMed: 9090385]
13. Hersh CP, Soto-Quiros ME, Avila L, et al. Genome-wide linkage analysis of pulmonary function in families of children with asthma in Costa Rica. *Thorax* 2007;62:224–30. [PubMed: 17099076]
14. Shek LP, Tay AH, Chew FT, Goh DL, Lee BW. Genetic susceptibility to asthma and atopy among Chinese in Singapore--linkage to markers on chromosome 5q31–33. *Allergy* 2001;56:749–53. [PubMed: 11488668]

15. Moffatt MF, Kabesch M, Liang L, et al. Genetic variants regulating ORMDL3 expression contribute to the risk of childhood asthma. *Nature* 2007;448:470–3. [PubMed: 17611496]
16. US Census Bureau: Census 2000. (2000)
17. US Census Bureau. US interim projections by age, sex, race, and Hispanic origin. 2004
18. Burchard EG, Ziv E, Coyle N, et al. The importance of race and ethnic background in biomedical research and clinical practice. *N Engl J Med* 2003;348:1170–5. [PubMed: 12646676]
19. Risch N, Burchard E, Ziv E, Tang H. Categorization of humans in biomedical research: genes, race and disease. *Genome Biol* 2002;3comment 2007
20. Lin SS, Kelsey JL. Use of race and ethnicity in epidemiologic research: concepts, methodological issues, and suggestions for research. *Epidemiol Rev* 2000;22:187–202. [PubMed: 11218371]
21. Hickman CB. The devil and the one drop rule: racial categories, African Americans, and the U.S. census. *Michigan Law Review* 1997;95:1161–1265.
22. Ober C. Perspectives on the past decade of asthma genetics. *J Allergy Clin Immunol* 2005;116:274–8. [PubMed: 16083779]
- 23** . Ober C, Hoffjan S. Asthma genetics 2006: the long and winding road to gene discovery . *Genes Immun* 2006;7:95–100. [PubMed: 16395390]A comprehensive review of all asthma genetic association studies through 2005
24. Howard TD, Postma DS, Jongepier H, et al. Association of a disintegrin and metalloprotease 33 (ADAM33) gene with asthma in ethnically diverse populations. *J Allergy Clin Immunol* 2003;112:717–22. [PubMed: 14564349]
25. Van Eerdewegh P, Little RD, Dupuis J, et al. Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature* 2002;418:426–30. [PubMed: 12110844]
26. Werner M, Herbon N, Gohlke H, et al. Asthma is associated with single-nucleotide polymorphisms in ADAM33. *Clin Exp Allergy* 2004;34:26–31. [PubMed: 14720258]
27. Hersh CP, Raby BA, Soto-Quiros ME, et al. Comprehensive testing of positionally cloned asthma genes in two populations. *Am J Respir Crit Care Med* 2007;176:849–57. [PubMed: 17702965]
28. Lind DL, Choudhry S, Ung N, et al. ADAM33 is not associated with asthma in Puerto Rican or Mexican populations. *Am J Respir Crit Care Med* 2003;168:1312–6. [PubMed: 12958057]
29. Lee JH, Park HS, Park SW, et al. ADAM33 polymorphism: association with bronchial hyper-responsiveness in Korean asthmatics. *Clin Exp Allergy* 2004;34:860–5. [PubMed: 15196271]
30. Raby BA, Silverman EK, Kwiatkowski DJ, Lange C, Lazarus R, Weiss ST. ADAM33 polymorphisms and phenotype associations in childhood asthma. *J Allergy Clin Immunol* 2004;113:1071–8. [PubMed: 15208587]
31. Cho SH, Oh SY, Bahn JW, et al. Association between bronchodilating response to short-acting beta-agonist and non-synonymous single-nucleotide polymorphisms of beta-adrenoceptor gene. *Clin Exp Allergy* 2005;35:1162–7. [PubMed: 16164442]
32. Choudhry S, Ung N, Avila PC, et al. Pharmacogenetic differences in response to albuterol between Puerto Ricans and Mexicans with asthma. *Am J Respir Crit Care Med* 2005;171:563–70. [PubMed: 15557128]
33. Israel E, Chinchilli VM, Ford JG, et al. Use of regularly scheduled albuterol treatment in asthma: genotype-stratified, randomised, placebo-controlled cross-over trial. *Lancet* 2004;364:1505–12. [PubMed: 15500895]
34. Israel E, Drazen JM, Liggett SB, et al. Effect of polymorphism of the beta(2)-adrenergic receptor on response to regular use of albuterol in asthma. *Int Arch Allergy Immunol* 2001;124:183–6. [PubMed: 11306963]
35. Martinez FD, Graves PE, Baldini M, Solomon S, Erickson R. Association between genetic polymorphisms of the beta2-adrenoceptor and response to albuterol in children with and without a history of wheezing. *J Clin Invest* 1997;100:3184–8. [PubMed: 9399966]
36. Tsai HJ, Shaikh N, Kho JY, et al. Beta 2-adrenergic receptor polymorphisms: pharmacogenetic response to bronchodilator among African American asthmatics. *Hum Genet* 2006;119:547–57. [PubMed: 16596417]

- 37* . Stephens JC, Schneider JA, Tanguay DA, et al. Haplotype variation and linkage disequilibrium in 313 human genes. *Science* 2001;293:489–93. [PubMed: 11452081]A large-scale report of the distribution of SNPs across racial groups
38. Beutler E. Gaucher disease: multiple lessons from a single gene disorder. *Acta Paediatr Suppl* 2006;95:103–9. [PubMed: 16720474]
39. Farrer LA, Cupples LA, Haines JL, et al. Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA* 1997;278:1349–56. [PubMed: 9343467]
40. Choudhry S, Coyle NE, Tang H, et al. Population stratification confounds genetic association studies among Latinos. *Hum Genet* 2006;118:652–64. [PubMed: 16283388]
41. Parra EJ, Marcini A, Akey J, et al. Estimating African American admixture proportions by use of population-specific alleles. *Am J Hum Genet* 1998;63:1839–51. [PubMed: 9837836]
- 42* . Zhu X, Luke A, Cooper RS, et al. Admixture mapping for hypertension loci with genome-scan markers. *Nat Genet* 2005;37:177–81. [PubMed: 15665825]The first study that used admixture mapping to identify a disease locus
43. Oksenberg JR, Barcellos LF, Cree BA, et al. Mapping multiple sclerosis susceptibility to the HLA-DR locus in African Americans. *Am J Hum Genet* 2004;74:160–7. [PubMed: 14669136]
44. Reich D, Patterson N, Ramesh V, et al. Admixture mapping of an allele affecting interleukin 6 soluble receptor and interleukin 6 levels. *Am J Hum Genet* 2007;80:716–26. [PubMed: 17357077]
45. Barnes KC, Grant A, Gao P, et al. Polymorphisms in the novel gene acyloxyacyl hydroxylase (AOAH) are associated with asthma and associated phenotypes. *J Allergy Clin Immunol* 2006;118:70–7. [PubMed: 16815140]
46. Battle NC, Choudhry S, Tsai HJ, et al. Ethnicity-specific gene-gene interaction between IL-13 and IL-4Ralpha among African Americans with asthma. *Am J Respir Crit Care Med* 2007;175:881–7. [PubMed: 17303794]
47. Howard TD, Koppelman GH, Xu J, et al. Gene-gene interaction in asthma: IL4RA and IL13 in a Dutch population with asthma. *Am J Hum Genet* 2002;70:230–6. [PubMed: 11709756]
48. Kamada F, Mashimo Y, Inoue H, et al. The GSTP1 Gene Is a Susceptibility Gene for Childhood Asthma and the GSTM1 Gene Is a Modifier of the GSTP1 Gene. *Int Arch Allergy Immunol* 2007;144:275–286. [PubMed: 17643058]
49. Ackerman KG, Huang H, Grasemann H, et al. Interacting genetic loci cause airway hyperresponsiveness. *Physiol Genomics* 2005;21:105–11. [PubMed: 15657107]
50. Helgadottir A, Manolescu A, Helgason A, et al. A variant of the gene encoding leukotriene A4 hydrolase confers ethnicity-specific risk of myocardial infarction. *Nat Genet* 2006;38:68–74. [PubMed: 16282974]
51. Kim UK, Jorgenson E, Coon H, Leppert M, Risch N, D Drayna. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 2003;299:1221–5. [PubMed: 12595690]
52. Mignot E, Lin X, Arrigoni J, et al. DQB1*0602 and DQA1*0102 (DQ1) are better markers than DR2 for narcolepsy in Caucasian and black Americans. *Sleep* 1994;17:S60–7. [PubMed: 7701202]
53. Weiss ST. Eat dirt--the hygiene hypothesis and allergic diseases. *N Engl J Med* 2002;347:930–1. [PubMed: 12239263]
54. Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347:911–20. [PubMed: 12239261]
55. CDC. Tobacco use among US racial/ethnic minority groups- African Americans, American Indians and Alaska Natives, Asian Americans and Pacific Islanders, and Hispanics: A report of the surgeon general. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; Atlanta, GA: 1998.
56. CDC. National Health Interview Survey. 1998 2000
57. Perez-Stable EJ, Ramirez A, Villareal R, et al. Cigarette smoking behavior among US Latino men and women from different countries of origin. *Am J Public Health* 2001;91:1424–30. [PubMed: 11527775]

58. Haiman CA, Stram DO, Wilkens LR, et al. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006;354:333–42. [PubMed: 16436765]
59. Perez-Stable EJ, Herrera B, Jacob P 3rd, Benowitz NL. Nicotine metabolism and intake in black and white smokers. *JAMA* 1998;280:152–6. [PubMed: 9669788]
60. Wilson SE, Kahn RS, Khoury J, Lanphear BP. Racial differences in exposure to environmental tobacco smoke among children. *Environ Health Perspect* 2005;113:362–7. [PubMed: 15743729]
61. Freeman NC, Schneider D, McGarvey P. Household exposure factors, asthma, and school absenteeism in a predominantly Hispanic community. *J Expo Anal Environ Epidemiol* 2003;13:169–76. [PubMed: 12743611]
- 62** . Martinez FD. CD14, endotoxin, and asthma risk: actions and interactions. *Proc Am Thorac Soc* 2007;4:221–5. [PubMed: 17607003]A comprehensive description of the discovery of the gene-environment interaction between CD14 and endotoxin
63. Eder W, Klimecki W, Yu L, et al. Opposite effects of CD 14/-260 on serum IgE levels in children raised in different environments. *J Allergy Clin Immunol* 2005;116:601–7. [PubMed: 16159630]
64. Simpson A, John SL, Jury F, et al. Endotoxin exposure, CD14, and allergic disease: an interaction between genes and the environment. *Am J Respir Crit Care Med* 2006;174:386–92. [PubMed: 16614348]
65. Zambelli-Weiner A, Ehrlich E, Stockton ML, et al. Evaluation of the CD14/-260 polymorphism and house dust endotoxin exposure in the Barbados Asthma Genetics Study. *J Allergy Clin Immunol* 2005;115:1203–9. [PubMed: 15940135]
66. Williams LK, McPhee RA, Ownby DR, et al. Gene-environment interactions with CD14 C-260T and their relationship to total serum IgE levels in adults. *J Allergy Clin Immunol* 2006;118:851–7. [PubMed: 17030237]
67. Deshmukh VM, Toelle BG, Usherwood T, O'Grady B, Jenkins CR. Anxiety, panic and adult asthma: a cognitive-behavioral perspective. *Respir Med* 2007;101:194–202. [PubMed: 16781132]
68. Rodriguez CE. Racial classification among Puerto Rican men and women in New York. *Hispanic Journal of Behavioral Sciences* 1990;12:366–79.
69. Rodriguez, CE. The effect of race on Puerto Rican wages. In: ME, editor. *Hispanics in the Labor Force*. Plenum Press; New York, N.Y.: 1991. p. 77-98.
70. Arce CH. Phenotype and Life Chances among Chicanos. *Hispanic Journal of Behavioral Sciences* 1987;9:19.
71. Telles E. Phenotypic discrimination and income differences among Mexican Americans. *Social Sciences Quarterly* 1990;71:682–693.
72. Togias A, Horowitz E, Joyner D, Guydon L, Malveaux F. Evaluating the factors that relate to asthma severity in adolescents. *Int Arch Allergy Immunol* 1997;113:87–95. [PubMed: 9130491]
73. McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav* 2003;43:2–15. [PubMed: 12614627]
- 74* . Marmot MG, Shipley MJ, Rose G. Inequalities in death--specific explanations of a general pattern? *Lancet* 1984;1:1003–6. [PubMed: 6143919]A classic investigation of the effect of social class on disease
75. Vogli De R, Chandola T, Marmot MG. Negative aspects of close relationships and heart disease. *Arch Intern Med* 2007;167:1951–7. [PubMed: 17923594]
76. Mays VM, Cochran SD, Barnes NW. Race, race-based discrimination, and health outcomes among African Americans. *Annu Rev Psychol* 2007;58:201–25. [PubMed: 16953796]
- 77* . Chen E, Chim LS, Strunk RC, Miller GE. The role of the social environment in children and adolescents with asthma. *Am J Respir Crit Care Med* 2007;176:644–9. [PubMed: 17556714]A unique study investigating the mechanism by which social and psychological factors influence asthma
78. Brugge D, Lee AC, Woodin M, C Rioux. Native and foreign born as predictors of pediatric asthma in an Asian immigrant population: a cross sectional survey. *Environ Health* 2007;6:13. [PubMed: 17474985]
79. Dumanovsky T, Matte TD. Variation in adult asthma prevalence in Hispanic subpopulations in New York City. *J Asthma* 2007;44:297–303. [PubMed: 17530529]

80. Holguin F, Mannino DM, Anto J, et al. Country of birth as a risk factor for asthma among Mexican Americans. *Am J Respir Crit Care Med* 2005;171:103–8. [PubMed: 15516539]
81. Eldeirawi KM, Persky VW. Associations of acculturation and country of birth with asthma and wheezing in Mexican American youths. *J Asthma* 2006;43:279–86. [PubMed: 16809241]
82. Klinnert MD, Price MR, Liu AH, Robinson JL. Unraveling the ecology of risks for early childhood asthma among ethnically diverse families in the southwest. *Am J Public Health* 2002;92:792–8. [PubMed: 11988449]
83. Netuveli G, Hurwitz B, Sheikh A. Lineages of language and the diagnosis of asthma. *J R Soc Med* 2007;100:19–24. [PubMed: 17197682]
84. Greenfield RO, Lee AC, Tang R, D Brugge. Screening for asthma in Cantonese-speaking immigrant children. *BMC Public Health* 2005;5:48. [PubMed: 15904513]
85. Alba R, Logan J, Lutz A, B Stults. Only English by the third generation? Loss and preservation of the mother tongue among the grandchildren of contemporary immigrants. *Demography* 2002;39:467–484. [PubMed: 12205753]
86. Alba, R. Language assimilation today: bilingualism persists more than in the past, but English still dominates. Lewis Mumford Center for Comparative Urban and Regional Research, University at Albany; 2004.
87. Gonzalez Burchard E, Borrell LN, Choudhry S, et al. Latino populations: a unique opportunity for the study of race, genetics, and social environment in epidemiological research. *Am J Public Health* 2005;95:2161–8. [PubMed: 16257940]
- 88*. Choudhry S, Seibold MA, Borrell LN, et al. Dissecting complex diseases in complex populations: asthma in latino americans. *Proc Am Thorac Soc* 2007;4:226–33. [PubMed: 17607004]A review of asthma in Latino populations and methods for studying admixed populations
89. Cooper RS, Kaufman JS, Ward R. Race and genomics. *N Engl J Med* 2003;348:1166–70. [PubMed: 12646675]
90. Bamshad M. Genetic influences on health: does race matter? *JAMA* 2005;294:937–46. [PubMed: 16118384]

Figure 1. Percent African ancestry in Puerto Rican asthma cases and controls stratified by socioeconomic status (SES). SES was obtained using clinic recruitment site address.

Figure 2.

There is evidence to suggest that there are genetic, environmental, social and economic risk factors independently and dependently influencing the development and severity of asthma.

Table 1

Percent of asthma prevalence and genetic association studies across racial and ethnic groups

Race/Ethnicity	Asthma Prevalence [4,8]	Genetic Association Studies* [7, 19]
Non-Hispanic white	13.0%	60.0%
African American	16.0%	5.0%
Hispanic		8.0%
Mexican	13.2%	
Puerto Rican	22.8%	
Central American	14.4%	
Cubans	23.0%	
Asian		28.0%
Filipinos	23.8%	
Koreans	10.9%	
Laotians	11.6%	

* The percentages in this column do not add up to 100% because some studies analyzed data for more than one racial/ethnic population.