Genetics and Asthma Disease Susceptibility in the US Latino Population

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OUTLINE

ABSTRACT

The US Latino population is heterogeneous with diversity in environmental exposures and socioeconomic status. Moreover, the US Hispanic population derives from numerous countries previously under Spanish rule, and many Hispanics have complex proportions of European, Native American, and African ancestry. Disparities in asthma severity and control are due to complex interactions between environmental exposures, socioeconomic factors, and genetic variations. In addition, diseases within the Latino community may also differ by country of origin. Although US Census data show low asthma rates in the Hispanic population as a whole, there is a lot of variability in the prevalence and morbidity of asthma, with a prevalence of 5.0% in Mexican Americans versus 17.0% in Puerto Ricans. The diversity and population admixture make the study of the genetics of asthma complex in Latino populations. However, an understanding of the genetics of asthma in all populations, including the Latino population, can enhance risk identification, help us to target pharmacological therapy, and guide environmental regulations, all of which can promote a reduction in health disparities. The inclusion of markers of ancestral diversity and the incorporation of techniques to adjust for stratification now make these studies feasible in complex populations, including the Latino population. To date, studies using linkage analyses, genome-wide associations, or candidate gene analyses have identified an association of asthma or asthma-related phenotypes with candidate genes, including interleukin 13, β-2 adrenergic receptor, a disintegrin and metalloproteinase 33, orosomucoid 1-like 3, and thymic stromal lymphopoietin. As reviewed here, although these genes have been identified in diverse populations, limited studies have been performed in Latino populations, and they have had variable replication. There is a need for the development of registries with well-phenotyped pediatric and adult Latino populations and subgroups for inclusion in the rapidly expanding field of genetic studies, and these studies need to be used to reduce health disparities. ***Mt Sinai J Med 77:140–148, 2010.*** *© 2010 Mount Sinai School of Medicine*

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Large-scale surveys conducted by the Centers for Disease Control and Prevention and the National Center for Health Statistics have estimated that 16.4 million adults (7.3%) and 7.0 million children (9.4%) in the United States currently have asthma, with a total lifetime asthma diagnosis prevalence of 7.7%.[1] These statistics vary geographically within the United States, with urban areas reporting higher rates of asthma, including a 12% self-reported lifetime prevalence of asthma among adults in New York City.[2] Although asthma is common in urban environments and is associated with socioeconomic status, the prevalence and severity of asthma also vary by race/ethnicity. In 2005–2007, the time period reported in the National Center for Health Statistics study, the rates of lifetime asthma diagnosis, current asthma, and asthma attacks were highest among American Indians/Alaska natives and blacks or African Americans in both

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adults and children.[1] Hispanic adults and children had lower rates of lifetime asthma diagnosis, current asthma, and asthma attacks in comparison with non-Hispanic whites and non-Hispanic blacks, with an overall prevalence of 5.4%.[3] However, it is now clear that the Hispanic population in the United States is heterogeneous, and better characterization of this population will help improve our understanding of asthma in this population. In the US Census data, the term *Hispanic* refers to peoples with roots in Spain or in areas that were previously under Spanish control, including Mexico, much of Central and South America, and some Caribbean islands.[4] As shown in data from the 2000 US Census, the 35.2 million Hispanics in the US population derive from a wide range of countries and geographic areas: 59.3% of Hispanics in the United States were from Mexico; 22.3% traced their ancestry to Puerto Rico, Central America, South America, or Cuba; and 18.3% came from other areas.[5] Importantly, 47.9% of Hispanics characterized their race as white, and 42.2% characterized their race as other. The country of origin is relevant for asthma prevalence because it varies throughout Latin America, with Mexico having the lowest childhood prevalence and Costa Rica having the highest.[6]

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This heterogeneity in asthma prevalence, symptoms, and severity in the Hispanic population has been seen in many studies, and indeed, on closer analysis of the 2000 US Census data, although Hispanics as a whole had a low asthma prevalence, there was great variation in the rates, with a prevalence of 5.0% in Mexican Americans and a prevalence of 17.0% in Puerto Ricans.[1]

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In the United States, 90% of the US Mexican population lives in the Southwest, and 68% of the US Puerto Rican population lives in the Northeast; the question could be raised whether the differences in asthma prevalence among Hispanics of varied ancestry are due to environmental exposures and confounders.[7] Studies within urban areas, however, suggest that environmental exposure incompletely explains this variation. In New York City, asthma prevalence is highest among Puerto Rican children,[8,9] and this increase in prevalence persists even after adjustments for the neighborhood and income level.[10] Puerto Rican adults in the New York City Community Health Survey have a higher asthma prevalence than other Hispanic subgroups and Hispanics born outside the United States, and the increased prevalence is only partially explained by age, sex, socioeconomic status, or other potential confounders.[11] In Chicago, the overall prevalence of asthma in children is 12.9%; however, there is variation between neighborhoods, and some but not all of the variation is explained by race.[12] An analysis of the National Health Interview Survey data for children in all 50 states of the United States shows that Puerto Rican children have the highest burden of asthma, whereas Mexican children have the lowest.[13] In contrast to other Hispanic subgroups in which birth outside the United States is associated with a lower risk for asthma, the prevalence for asthma in the Puerto Rican population is increased in island-born children.[13] The high prevalence of asthma in specific Hispanic subgroups reinforces the need to study asthma in these groups. Moreover, the heterogeneity of asthma prevalence in Hispanic subgroups suggests that epidemiological and genetic studies need to incorporate ancestral information as well as environmental exposures.

GENETIC STUDIES AND ASTHMA DISPARITIES

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The association between Puerto Rican ethnicity and asthma prevalence and morbidity suggests that multiple factors, including genetic ones, may participate in the association. How these additional factors, including genetics, can promote the reduction in health disparities has been outlined in an excellent review.[14] As discussed in the review, rare variants, or susceptibility alleles with low frequency (≤2%) in the general population, may be found only in certain ethnic groups, and this reinforces the need to study diverse populations. Identification of these variants can provide specific insight into a disease in the selected ethnic population and may also provide insight into the biology of the disease. Second, disease susceptibility alleles that are common in some ethnic groups may be more or less common in other groups. Ample examples of this exist for genetic diseases such as cystic fibrosis, Tay-Sachs disease, and factor V Leiden, and screening for the presence of disease may be helped by an understanding of the allelic frequencies of variants in different populations. Third, genetic variants may affect therapy, and an understanding of the interactions between these genetic variants and specific therapeutic interventions as well as their prevalence in a population may have significant treatment implications. Finally, disease risk may be altered by the interaction between genetic variants and environmental interactions. Understanding this may be critical for disease prevention and may influence legislation for disease reduction. The Clean Air Act is an important example in which this potential exists.[15] Under the Clean Air Act, the Environmental Protection Agency sets National Ambient Air Quality Standards for 6 pollutants (carbon monoxide, lead, nitrogen dioxide, ozone, sulfur oxides, and particulate matter). Standards are based on the need to protect public health and the protection of sensitive human subpopulations. The definition of *sensitive human subpopulation* has been argued to include those identified by genomics (Interim Policy on Genomics, US Environmental Protection Agency, 2002). Thus, there is a potential role for genetic information to be included in the process for developing air quality standards.

COMPLEXITY OF STUDYING GENETICS, RACE AND ETHNICITY, AND HEALTH DISPARITIES IN THE LATINO POPULATION

The study of genetics in the Latino population is not a trivial matter. The expression of genetic variants is modified by huge environmental effects of pollution, allergen exposure, social stressors, and comorbid conditions. The relative importance and use of race/ethnicity in biomedical research and genetics are controversial, and the importance is debated.[16]

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Moreover, there is not complete agreement on the definitions of *ethnicity* and *race*.[17] The concepts of race and ethnicity include connotations that reflect culture, history, socioeconomics, linguistics, and political status, although race has been considered to be characterized by the primary continent of origin.[17–20] Recent studies that assess the relationship of self-reported race and genetic ancestry with allergic sensitization in a non-Latino population provide conflicting data about the importance of the use of race/ethnicity; in one study, self-reported African American race was associated with allergic sensitization, asthma, and high total serum immunoglobulin E (IgE) levels,[21] whereas in another study, the association with allergic sensitization was not significant after researchers accounted for the location of residence.[22]

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The Hispanic community is an admixed population, and the allelic frequency differences among different race/ethnic groups can interfere with association studies and lead to false-positive results. The current Hispanic population is a result of combinations of individuals from Europe, Africa, and the Americas that

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resulted from intermating of migrant and indigenous populations.[5] This intermingling resulted in admixed populations and a combination of genomes that evolved independently on different continents.[23] Self-report of race and ancestry has been used extensively to assess race and ethnicity; however, self-report may be a poor proxy for underlying genetic relatedness,[16,24–26] and as recently described for an African American population, self-report may not predict ancestral clusters or reveal the extent of admixture.[27] In general, Puerto Ricans and Cubans have a greater proportion of African ancestry but a lower proportion of Native American ancestry than Mexican Americans.

The need to compensate for population stratification in genetic studies can be reduced if studies use family-based controls rather than case-control methods. Family-based control studies are often analyzed with transmission disequilibrium tests; however, this approach may not always be feasible because it requires first-degree relatives and usually genotyping of the proband and both parents. It is often difficult to recruit families, and in studies of adults or diseases with adult onset, it may be difficult to obtain parents. Thus, case-control studies are commonly used for genome-wide association (GWA) studies, candidate gene studies, and replication studies of GWA findings because of their cost effectiveness. However, in these studies, the possibility exists that allele frequency differences between cases and controls are unrelated to the genetics of the disease phenotype and instead are due to differences in the population genetic structure and substructure. Thus, false associations of particular single-nucleotide polymorphisms (SNPs) or markers can be identified, and each SNP may be affected by ancestry to a different extent, with some SNPS showing very different allele frequencies in different continental or ethnic groups and others showing little difference.

An approach to overcoming the problem of population substructure in genetic analyses makes use of DNA-based estimates of ancestry and appropriate statistical techniques that can add information to stratify populations and provide the ability to control for genetic differences that are unrelated to disease risk.[28–31] Ancestry informative markers (AIMs) are sets of polymorphisms for a locus that exhibit different frequencies between populations from different geographic regions. Preferably, AIMs are widely spaced across the genome so that there is no linkage disequilibrium among them within each subpopulation. Admixture mapping or mapping by admixture linkage disequilibrium takes advantage of sets of markers that are relatively evenly spaced across the genome. Several approaches, including structured association tests (Structure)[32] and principal component analyses,[33,34] have been proposed to adjust population stratifications in genetic association studies. Structure performs tests that are conditional on the group membership, which is determined with a Bayesian clustering algorithm that fits the data to the number of cluster groups that is specified. The association test is for the null hypothesis that there is no dependence of allele frequencies on phenotypes within each group. Principal component analysis infers a continuous axis of orthogonal linear transformations of AIMs that maximize the genetic variation but does not depend on the assignment of individuals to specific subpopulations. The number of SNPs is reduced to smaller numbers of dimensions that group patterns together on the basis of observed data. Ancestry-adjusted genotypes and phenotypes can then be calculated with Eigenstrat to compute the association statistic.[34] This algorithm can be difficult to perform with large numbers of SNPS and large populations. Plink, another commonly used program, can be used for large data sets[35] through the use of identical-by-state distance to do hierarchical clustering and subsequent Cochran-Mantel-Haenszel tests of association.

The use of AIMs has recently been applied to Hispanic populations, and variations in the ancestral composition of European Americans, Mexican Americans, disparate populations within the Native American population, Puerto Ricans, African Americans, and Southeast Asians have been demonstrated.[29,31,36–39] Studies using AIMs suggest that population admixture among Latinos has important implications when disease association is being assessed in case-control studies.[37] Analyses between these populations suggest that there are differences in the severity of asthma among Mexican Americans and Puerto Ricans and that there is an association between greater European ancestry in these populations and more severe asthma.[39]

GENETICS OF ASTHMA

Asthma is a complex genetic disorder that does not follow classic Mendelian inheritance; instead, each genetic factor contributes at most a modest amount to the total variation in the trait. Moreover, trait definition and phenotypic variation complicate the study of asthma. With the completion of the human genome sequence in 2005 and the development of techniques to assess thousands of SNPs, multiple techniques, including GWA studies, have been used to identify hundreds of genetic loci in which common genetic

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variations occur that are reproducibly associated with polygenic traits.[40] However, the analysis of these variations is complex, and the use of these variations to understand disease and disease biology is in its early stages for asthma as well as other diseases.[40,41] Extensive linkage analyses (positional cloning) and GWA studies, in which the entire genome is interrogated, as well as candidate gene association studies, in which a priori hypotheses are tested, have been performed for asthma, and several excellent reviews discussing both the successes and problems of the different approaches have recently been published.[42–45]

Studies using linkage analysis, a hypothesis-free approach to genetic associations, have identified 6 genes: a disintegrin and metalloproteinase 33 (*ADAM33*; chromosome 20p13), a metalloprotease; dipeptidyl peptidase 10 (chromosome 2q14), a regulatory molecule involved in protein targeting; plant homeodomain finger protein 11 (chromosome 13q14), a gene involved in messenger RNA transcription; G protein–coupled receptor for asthma (chromosome 7p14); human leukocyte antigen G (chromosome 6p21), a major histocompatibility complex antigen; and *GYFIP2* (chromosome 5q33), a G protein modulator.[42] Additional positional cloning studies have recently identified associations with genes predominantly expressed on epithelial cells: interleukin 1 receptor–associated kinase M (chromosome 12q14), a gene that encodes a protein regulating nuclear factor kappa B and the Toll-like receptor/interleukin 1 receptor pathway[46]; and opsin 3 (chromosome 1q43), a gene whose function remains unknown.[47] The role and function of many of these genes remain to be clarified.

GWA studies, in which large representative (tagged) marker panels of SNPs (100,000–1,000,000) are analyzed across the genome, are becoming more common as the technical ability and the density of markers available for study increase. The orosomucoid 1-like 3 (*ORMDL3*) gene (chromosome 17q21) was the first gene to be identified with childhood asthma through a GWA study.[48] The collaborative study also allowed for replication in additional British and German populations. Subsequent replication in a French-Canadian Caucasian population was also performed.[49] The gene that encodes YKL-40 (chitinase 3-like 1), a chitinase-like protein, has also been identified in a GWA study as a susceptibility gene for asthma, measures of lung function, and serum levels of YKL-40.[50]

Genetic association studies using case-control techniques for biologically plausible genes have identified numerous candidate SNPs and genes. The hundreds of genes identified with this approach have recently been reviewed.[44,45,51] Relatively few candidate gene associations have been replicated in multiple independent studies, and those that have been replicated repeatedly include the β-2 adrenergic receptor (*ADRB2*) gene, which is located in the cytokine gene cluster on chromosome 5q31-33, the interleukin 4 receptor, and the human leukocyte antigen DRB1 gene (chromosome 6).

Genetic studies of asthma are difficult because of the modest size of the genetic effects, which necessitates large sample sizes. Linkage analyses and GWA studies require sample sizes of thousands of individuals for successful identification of small effects and the need to compensate for multiple testing to enhance the ability to distinguish true positives from false-positive errors. In addition, for all of these genetic studies, replication of associated loci or candidate genes in independent populations is critical; however, replication has been variable between independent studies and in diverse populations for asthma genes.[52] This variability in replication has been attributed in part to differences in phenotypes and definitions of asthma-associated phenotypes, coverage of common genetic variants by SNPs, and population differences.

SELECTED ASTHMA GENES IN THE LATINO POPULATION

A limited number of genes associated with asthma risk have been identified in diverse Hispanic populations (Table 1). Regions on chromosome 5q, including regions 5q23 and 5q31-33, are some of the first well-replicated regions linked to asthma or asthma-associated phenotypes, and the association with this region has been reported in multiple candidate gene association studies in numerous populations, including Dutch, Amish, American Caucasian, Hutterite, and British.[44,45] The importance of this region or candidate genes for asthma in this region in Hispanic populations is less well documented. A recent GWA and admixture mapping

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Table 1. *Asthma-Related Genes Studied in Hispanic Populations.*

Gene	Gene Map Locus	Biological Process	Hypothesized Role	References
IL-13	5q31	Th2 effector	Asthma risk, eosinophils, IgE	53–56
ADRB2	5q32-34	Bronchial smooth muscle function	Airway remodeling, lung function, asthma severity	57
ADAM33	20p13	Proteolysis, cell adhesion–mediated signaling	Asthma risk, lung function, airway remodeling	61–64
ORMDL3	17q21.1	Protein folding, calcium signaling	Childhood asthma risk	69, 71
TSLP	5q23	Epithelial cell Th2 regulation	Gender-specific IgE regulation	76

Abbreviations: ADAM33, a disintegrin and metalloproteinase 33; ADRB2, β-2 adrenergic receptor; IgE, immunoglobulin E; IL-13, interleukin 13; ORMDL3, orosomucoid 1-like 3; Th2, T helper 2; TSLP, thymic stromal lymphopoietin.

analysis for asthma in a very small Puerto Rican sample failed to identify any association with asthma in this region, although a subsequent overlap analysis suggested an association in 5q23.3 as well as 13q.13.3.[53] Many genes in this 5q area, including the gene for interleukin 13 (IL-13), are in the cytokine cluster associated with Th2 cell differentiation and effector functions. IL-13 is a central effector cytokine and mediates many of the features of Th2 cell–mediated responses in the lung, including IgE synthesis. A study of a Costa Rican population initially failed to identify an association with IL-13 and asthma[54]; however, a subsequent study of Costa Rican children, using a larger sample size and a replication group, suggested that some IL-13 SNPS were associated with an increased eosinophil count, increased total serum IgE levels, and asthma exacerbation.[55] Our preliminary data, coming from a case-control association study for IL-13 that controlled for ancestral diversity through the use of AIMs in a predominantly Latino, admixed urban population, also identified an association with the frequently reported IL-13 variant.[56] These data suggest that findings in IL-13 variants may be robust even within different Latino populations, but additional studies with large populations are needed.

The *ADRB2* gene has been classified as a gene involved in lung function, airway remodeling, and disease severity.[44] Variants in 7 SNPS in the *ADRB2* gene were analyzed in the Genetics of Asthma in Latino Americans study with Puerto Rican and Mexican families of asthmatics[57] Although 2 SNPS were associated with the baseline forced expiratory volume in 1 second and bronchodilator responsiveness among the Puerto Rican families, a different SNP was marginally associated with bronchodilator responsiveness in the Mexican families. These studies again suggest differences between Latino populations and the need for additional studies.

ADAM33, a disintegrin and metalloproteinase gene located on chromosome 20, was the first asthma susceptibility gene to be identified through linkage studies and positional cloning.[58] Subsequent studies suggested a potential role for this gene in airway remodeling and revealed that *ADAM33* is expressed by lung fibroblasts and bronchial smooth muscle cells, although not by bronchial epithelial cells or immune cells.[59] *ADAM33* variants have been associated with an accelerated decline in the forced expiratory volume in 1 second.[60] Although the association of *ADAM33* variants and asthma has been replicated in many different ethnic populations,[43] the association of *ADAM33* and asthma in Latino populations has been less clear. One study using diverse populations, which included 112 Hispanic cases, suggested that variations in *ADAM33* were associated with asthma in all populations, although differences were noted between populations, and no causative variation could be identified in all populations.[61] A weak association with *ADAM33* variants and asthma was noted in children in the Childhood Asthma Management Program, a study that included only 39 children of Hispanic ethnicity.[62] An association between asthma and *ADAM33* variants was not found in Puerto Rican or Mexican adults,[63] nor was an association identified in Costa Rican children.[64] These studies differ in the techniques used for analysis, the size of the population studied, and the ancestry of the Latino populations. However, they suggest that the association of *ADAM33* with asthma remains inconsistent in the Latino population.

The *ORMDL3* gene was the first gene to be identified with a GWA study in white British and German patients.[48] *ORMDL3* transcription levels are correlated with several genetic markers near the *ORMDL3* gene, and although the function of *ORMDL3* remains incompletely understood, the gene product may participate in protein folding, calcium signaling, and cellular stress.[65] Polymorphisms in the *ORMDL3* gene have been associated with childhood asthma in multiple ethnic populations.[66–68] Two studies suggest an association with Latino populations. A recent study reported an association of *ORMDL3* gene variants and asthma in Mexican children.[69] In another, an

association was identified in a Mexican population, but only a weak association was found in Puerto Rican children.[70] The possibility that smoke exposure modifies the risk for *ORMDL3* variants and asthma raises an intriguing question about environmental interactions.[71]

Our interest has focused on the ability of airway epithelial cells to regulate airway immune responses, particularly in response to environmental injury by pollutants. Thymic stromal lymphopoietin (TSLP) is an epithelial cell–derived cytokine that regulates the Th2 response,[72–74] and we have described its production in response to exposure to diesel exhaust particles.[75] Thus, the gene for TSLP, located on chromosome 5, is a biologically plausible candidate gene for the study of gene and environment interactions. A locus on 5q23 was associated with cockroach-specific IgE in Costa Rican children in a genome-wide linkage analysis when it was analyzed with sex-stratified linkage analysis.[76] The TSLP gene was identified in this region, and the proposal was made that a variant in TSLP may have female-specific effects on allergic phenotypes. Further replication studies are needed to confirm this association in additional populations, but the biological importance of TSLP makes the study provocative.

CONCLUSION

In summary, the high prevalence of asthma in specific Latino subpopulations makes it imperative to study asthma in Hispanics. The study of asthma and asthma genetics is made complex in these populations by the diversity and heterogeneity of the Hispanic population in the United States. The inclusion of markers of ancestral diversity and the incorporation of techniques to adjust for stratification now make these studies more feasible and will enable an understanding of the underlying biology of asthma, genetic risks for asthma, and gene and environmental interactions. These studies have the potential to enhance risk identification, target pharmacological therapy, guide environmental regulations, and thus reduce health disparities. New technical advances that now allow for the study of asthma and asthma-associated phenotypes at a rapid pace using linkage analyses and GWA studies as well as candidate gene studies require large populations. Although large populations of European descent exist for genetic studies of asthma, fewer well-phenotyped populations are available for studies of Latino populations. There is a need for the development of registries with large pediatric and adult Latino populations for inclusion in the rapidly expanding field of genetic and environmental studies. These studies will promote the ultimate goal of improving our understanding of the biology and treatment of asthma in all populations and thus reduce health disparities.

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DISCLOSURES

Potential conflict of interest: Nothing to report.

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