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Pharmacogenetics: Implications of race and ethnicity on defining genetic profiles for personalized medicine

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Pharmacogenetics is being used to develop personalized therapies specific to subjects from different ethnic or racial groups. To date, pharmacogenetic studies have been primarily performed in trial cohorts consisting of non-Hispanic white subjects of European descent. A "bottleneck" or collapse of genetic diversity associated with the first human colonization of Europe during the Upper Paleolithic period, followed by the recent mixing of African, European, and Native American ancestries, has resulted in different ethnic groups with varying degrees of genetic diversity. Differences in genetic ancestry might introduce genetic variation, which has the potential to alter the therapeutic efficacy of commonly used asthma therapies, such as β_2-adrenergic receptor agonists (β-agonists). Pharmacogenetic studies of admixed ethnic groups have been limited to small candidate gene association studies, of which the best example is the gene coding for the receptor target of β-agonist therapy, the β_2-adrenergic receptor (*ADRB2*). Large consortium-based sequencing studies are using next-generation whole-genome sequencing to provide a diverse genome map of different admixed populations, which can be used for future pharmacogenetic studies. These studies will include candidate gene studies, genome-wide association studies, and whole-genome admixture-based approaches that account for ancestral genetic structure, complex haplotypes, gene-gene interactions, and rare variants to detect and replicate novel pharmacogenetic loci. (J Allergy Clin Immunol 2014;133:16-26.)

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Abbreviations used

ADRB1:	β_1-Adrenergic receptor
ADRB2:	β_2-Adrenergic receptor
BADGER:	Best Add-on Therapy Giving Effective Response Trial
BARGE:	Beta Agonist Response by Genotype Trial
CAAPA:	Consortium on Asthma among African-ancestry Populations in the Americas
GALA:	Genetics of Asthma in Latino Americans
GLCCI1:	Glucocorticoid-induced transcript 1 gene
GRK5:	G protein receptor kinase 5
GWAS:	Genome-wide association study
ICS:	Inhaled corticosteroid
LABA:	Long-acting β-agonist
LARGE:	Long-acting Beta Agonist Response by Genotype
NHLBI:	National Heart, Lung, and Blood Institute
NIH:	National Institutes of Health
PEFR:	Peak expiratory flow rate
SABA:	Short-acting β-agonist
SMART:	Salmeterol Multicenter Asthma Research Trial
SNP:	Single nucleotide polymorphism
SPATS2L:	Spermatogenesis-associated, serine-rich 2-like gene

It is well known that frequencies and even severities of disease can differ between ***races***. Two simple examples include sickle cell anemia, which is caused by a mutation that arose in Africa, whereas the mutations that cause cystic fibrosis primarily arose in subjects of European white descent. A key question is whether a person's ethnic or ancestral background determines individual response to a medication? There is robust evidence from clinical trials for different medical conditions showing that subjects from different ***ethnic groups*** experience variable responses to specific therapeutic agents. For instance, there is a class of antihypertensive drugs, β_1-adrenergic receptor blockers or β-blockers, which might be less effective in a subgroup of African American subjects for the management of congestive heart failure.[1,2] This reduced efficacy might be related to variants in 2 genes related to the G protein–coupled pathway of the β_1-adrenergic receptor (*ADRB1*) and G protein receptor kinase 5 (*GRK5*) genes. These gene variants are overrepresented in African ancestral populations and result in changes in the amino acid code: a code change from arginine to a glycine in amino acid position 389 on *ADRB1* ($Arg^{389}Gly$) and $Gln^{41}Leu$ on *GRK5*.[3] The Arg^{389} allele in *ADRB1* and the Leu^{41} allele in *GRK5* have both been associated with a reduction in mortality in human subjects with heart failure and coronary ischemia treated with a β-blocker in different pharmacogenetic studies.[3,4] These examples of variable drug responses in patients with cardiovascular disease illustrate the challenge of having personalized approaches not only through recognizing ethnic or racial subgroups, which show variable therapeutic drug responses, but also identifying

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Terms in boldface and italics are defined in the glossary on page 17.

them through pharmacogenetic biomarkers related to a common genetic ancestral origin.

Pharmacogenetics is the study of the role of genetic variability in determining interindividual (between-subject) variability in responses to a pharmacologic therapy. Pharmacogenetics represents a gene-environment interaction whereby variation in a gene interacts with an exposure to a drug (the "environment") to alter a measurable ***phenotype*** related to drug efficacy or toxicity. The ultimate goal of pharmacogenetic research is the development of personalized medicine through genetic markers (individual genetic profiles), which would accurately predict which subjects with a particular condition would respond to a specific medical therapy, not respond to a therapy, or experience adverse effects.

RATIONALE FOR PHARMACOGENETICS IN THE MANAGEMENT OF ASTHMA IN DIFFERENT ETHNIC GROUPS

Asthma is a complex, chronic inflammatory disease of the airways that results from the interaction of multiple genetic and environmental factors. Asthma is a heterogeneous disease with variability in its phenotype expression and variability in interindividual therapeutic responses to different pharmacologic therapies.[5-7] Variability in therapeutic responses might result from the interaction of multiple genes from different biologic pathways and even shared environmental influences.[8-10] Persons with shared ancestry and physical traits are most commonly categorized by ethnic or racial groups; however, this designation also implies common genetic ancestral backgrounds, which might affect therapeutic responses.[11]

To date, pharmacogenetic studies have been primarily performed in trial cohorts consisting of non-Hispanic asthmatic subjects of European descent; however, a small number of studies have also evaluated study cohorts of recently admixed ethnic groups, such as African American or Hispanic subjects. There are inherent challenges related to the genetic study of recently admixed ethnic or racial subgroups from varying ancestries. These challenges have been primarily related to sample size, complex ancestral population structures, and genotype data primarily based on a genetic background from populations of European descent. In this review article we will summarize the genetic and epidemiologic basis for the variable genetic backgrounds observed between different recently admixed ethnic groups, outline the rationale for pharmacogenetic research in these ethnic groups, discuss the contribution of pharmacogenetic studies in identifying ethnic group–specific genetic variants for therapeutic responses in asthmatic subjects, and outline how admixture-based analytic methods and next-generation sequencing will contribute to future pharmacogenetic studies.

WHY GENETIC DIVERSITY VARIES BETWEEN SUBJECTS OF DIFFERENT ANCESTRIES

Information about the demographic history of our species can be evaluated through the distribution of gene variants located throughout the human genome. Initially, most publicly available databases contained mostly common gene variants, such as ***single nucleotide polymorphisms*** (SNPs) based on the Human Genome Project.[12,13] The early ascertainment strategies of the Human Genome Project favored the identification of common variants, which were of particular interest based on the "common disease–common allele hypothesis," which states that multiple common gene variation with mild-to-modest effects influences susceptibility to complex common phenotypes (Fig 1).[14-18]

GLOSSARY

ETHNIC GROUPS: A socially defined category of persons based on shared social experience (eg, language, dressing style, and cuisine) or ancestry. The only ethnic category queried in the US Census is whether respondents are of Hispanic or Latino origin.

EXOSITE: The β_2-adrenergic receptor has 7 transmembrane spanning domains (TMDs). Conventional β-agonists have critical contact points at TMDs 3, 5, and 6. The long duration of salmeterol's action involves its side chain binding to TMDs. In contrast to most beta agonists, salmeterol binding to a nontraditional site on the fourth TMD is termed an exosite. Exosite binding is critical to the long duration of action of salmeterol by anchoring the drug to the receptor to provide for repetitive binding events. Such binding to a nontraditional receptor-binding site is termed exosite binding because it lies outside the critical contact points.

FIRST MODERN HUMANS: Also referred to as anatomically modern humans and members of *Homo sapiens*, with an appearance consistent with the range of phenotypes in modern humans. The subspecies *Homo sapiens sapiens* constitutes anatomically modern humans. Features include a less prominent brow ridge, a more vertical forehead, and a more prominent chin compared with their predecessors.

LINKAGE DISEQUILIBRIUM (LD): In population genetics LD is the nonrandom association of alleles at 2 or more genetic loci derived from similar or different ancestral chromosomes. LD occurs along varying genomic distances and is defined as the following. *Admixture LD* arises when 2 ancestral populations with divergent allele frequencies mix, is weak at all distances, and decays slowly. *Background LD* is used for conventional association mapping, is strong at short distances, and decays rapidly. *Mixture LD* occurs between unlinked markers because of varying ancestral proportions among subjects.

PHENOTYPE: The observable properties of an organism that are produced by the interaction of the genotype and environment.

POPULATION GENETIC EQUILIBRIUM: The frequency of an allele in a population does not change from generation to generation. It is a theoretic state taking into account ideal conditions. The most common conditions arise from Hardy-Weinberg equilibrium and include random mating, equal survival, no migration, no mutation, no inbreeding, large population sizes, and gene frequencies equal in male and female subjects.

RACE: A category of self-identification used as a data item by government. Self-reported race takes into account both ancestry and social and cultural characteristics. The 5 official US government racial categories are as follows: white, black or African American, Asian, American Indian/Alaska Native, and Pacific Islander. The US Census Bureau allows respondents to mark more than one race, if desired. Race is defined medically as a category of humankind that shares certain distinctive physical traits.

SINGLE NUCLEOTIDE POLYMORPHISM: One of 2 or more variants of a particular single base pair of DNA.

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