

# Pharmacogenetics, Personalized Medicine, and Race

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Citation: Hunt, S. (2008) Pharmacogenetics, personalized medicine, and race. *Nature Education* 1(1)

Could your ethnic background determine the drug treatments you receive? Believe it or not, race is sometimes considered when predicting how patients will respond to different medications.

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Metabolic pathways — the chains of chemical reactions that occur in each cell in the body — are affected by a wide range of DNA mutations, including single nucleotide polymorphisms (SNPs); gene deletions, duplications, and insertions; mutations in the regulatory elements of genes; and variations in gene copy number. The identification of gene variants (alleles) that influence drug metabolism is one of the goals of pharmacogenetics, a field of study focused on understanding the genetic basis for differences in drug response among individuals.

The appeal of pharmacogenetics lies in the possibility of personalized medicine. This sort of care has always been the goal of the doctor-patient relationship, with physicians considering a patient's family history and lifestyle when prescribing treatment. Access to information about an individual's genetic makeup would provide yet another source of personalized data and would therefore enable doctors to better define the nature of a disease and find the most effective treatment for a particular patient. With the help of pharmacogenetic studies, physicians will be able to administer treatment regimens that are personalized and adapted to each person's genetic makeup. Accordingly, two people with the same diagnosis might receive different therapies or drug dosages. This might in turn reduce health care costs, because physicians would be able to prescribe more targeted drugs and pharmaceutical companies would be able to develop and market drugs to specific groups of patients.

Codeine is one example of a drug whose metabolism is greatly influenced by genetics. In order for codeine to exert an effect, it first has to be converted into morphine by the body's enzymes. This chemical reaction occurs in the liver and is catalyzed by the cytochrome P450 enzyme, CYP2D6. However, up to 10% of individuals have a mutation in the CYP2D6 gene that abolishes enzyme activity (Wilson *et al.*, 2001; Zanger *et al.*, 2003). Thus, codeine may have very little or no impact on these patients. People with this mutation cannot convert codeine to morphine and thereby cannot benefit from the analgesic effects of the drug. Identification of the CYP2D6 mutation before therapy would allow physicians to prescribe a different pain control regimen, instead of resorting to trial and error.

Finding mutations that affect drug response is not unlike finding mutations that cause disease. Fifty years of clinical studies have repeatedly confirmed that the physiological response to specific chemicals can be inherited (Meyer, 2004). In fact, teasing out the underlying foundations of the genetic variation responsible for these different responses was one of the cornerstones used to build support for the unprecedented effort and expense that was needed to fully sequence the human genome. As researchers look at the entire spectrum of genes and genetic loci that affect an individual's metabolic responses, they are finding that groups of people — often defined according to racial categories — differ in their response to various drugs. However, understanding the basis for these differences has been a challenge.

## Race and Pharmacogenetics

Ethnicity and race are both concepts used as a way of categorizing people of shared ancestry and physical traits (Sankar *et al.*, 2007). However, ethnicity also connotes shared cultural, linguistic, behavioral, or religious characteristics. Thus, ethnicity and race are tied to both our genetics and our environment. This complexity makes it much more difficult for researchers to identify the specific connections between pharmacogenetics and race/ethnicity.

In a recent study, Tang *et al.* (2005) analyzed genetic data from 3,636 people who identified themselves as belonging to one of four major racial and ethnic groups in the United States (Caucasian, African American, East Asian, and Hispanic). Analysis of the data produced four major genetic clusters, which showed near-perfect correspondence with the four self-reported race/ethnicity categories. Tang and colleagues thus concluded that using self-identified race as a way to divide populations in clinical studies is valuable, because that definition encompasses genetic variations.

However, despite the findings of Tang *et al.*, two studies published in the *New England Journal of Medicine* provide a good example of the problems that can arise when race is used to make conclusions in clinical studies. These two studies focused on treatments for cardiovascular disease (CVD) — a class of diseases that involve the heart or blood vessels; such conditions include high blood pressure, coronary heart disease (heart attack and angina), congestive heart failure, stroke, and congenital heart defects, among others. CVD kills nearly 2,400 Americans each day, and the mortality rate is highest among African Americans. For instance, in 2004, 454 out of every 100,000 African American males died because of CVD, compared to 335 out of every 100,000 Caucasian males, according to the American Heart Association. Similarly, the death rate from CVD was 333.6 per 100,000 for African American females, compared to 238 per 100,000 for Caucasian females. These striking differences in morbidity and mortality, which were apparently linked to race, prompted scientists to ask whether there was a possibility that different standard treatments for CVD had different impacts in different races. Did standard treatments work better in Caucasians than in African Americans?

In 2001, Yancy *et al.* showed that a drug called carvedilol, which blocks the function of beta-adrenergic receptors, a type of hormone receptor in the body, worked equally well as a treatment for both African American and Caucasian patients with heart failure. However, in a second study (Exner *et al.*, 2001), another drug called enalapril, which blocks the action of a protein known as angiotensin-converting enzyme (ACE), was shown to be more effective in Caucasian patients with a particular heart defect than in African Americans. As a result of this study, there was a reported decrease in the

offering of ACE inhibitors to treat hypertension in African American patients.

Despite this finding, subsequent studies have shown that when adequate dosing and appropriate combinations are used, ACE inhibitor therapy provides effective blood pressure control in both groups of patients (Saunders & Gavin, 2007). There have also been inconsistencies in results from studies looking at the effects of drugs that block beta-adrenergic receptors (beta blockers). For instance, in 2008, a mutation in G-protein-coupled receptor kinase 5 (GRK5) was found in 40% of African Americans. This mutation protects individuals suffering from heart failure from death and thus has an effect similar to beta-blocker drugs following heart failure (Liggett *et al.*, 2008). The authors concluded that this finding suggests "a reason for conflicting results of beta-blocker clinical trials in this **population**."

In addition to inconsistent findings among clinical studies that group individuals according to self-defined racial groups, some researchers have voiced fears that such studies could support views that biological differences underlie the social definitions of race. The association of these differences to the social construct of race could potentially usher in a new era of racial discrimination (Sankar *et al.*, 2004). These concerns have prompted scientists to think more broadly about how study design can be improved to find genetic variations related to drug response without dragging social issues of race into the equation.

## Redefining Race in Genetic Study Design

In 2001, Wilson *et al.* tried to address the intersection of genetic variation, drug response, and race by assigning people to different groups depending on shared genetic regions — leaving race and ethnicity out of the equation entirely. In this study, researchers looked at variations in **microsatellites**, or sequences of two, three, or four nucleotides repeated 10 to 100 times along the DNA that show great variation in repeat length among individuals. Specifically, the researchers examined 16 microsatellites on **chromosome 1** and 23 on the **X chromosome** in a heterogeneous group of individuals. Study participants were then assigned to four subclusters according to their microsatellite alleles, which roughly corresponded to four geographic areas: Western Eurasia, Sub-Saharan Africa, China, and New Guinea (Table 1).


Notably, the data in Table 1 show that 62% of the Ethiopians included in the study were found in the same cluster as most of the Jews, Norwegians, and Armenians, indicating that placement of these individuals in an African American cluster would be at odds with their genetic grouping.

Moreover, 21% of Afro-Caribbeans were clustered with the West Eurasians, whereas people from China and New Guinea were almost entirely in separate clusters, revealing that the ethnic label of "Asian" is also an inaccurate description.

Because different populations have different frequencies of various alleles involved in drug metabolism, Wilson *et al.* next examined variations in genes encoding these enzymes, including CYP2D6, across the clusters they identified with their **microsatellite** analysis. They found that the genetic groupings (based on the microsatellite analysis) appeared to be more informative regarding differences in drug metabolism than the groupings based on skin color or self-defined ethnic groups.


While the Wilson *et al.* study supports the premise that understanding an individual's genetic makeup is the key to creating personalized drugs with greater efficacy and safety, it must not be forgotten that environment, diet, age, lifestyle, and state of health all influence a person's response to medicine as well.

Population	A	B	C	D
Bantu	0.04	0.02	0.93	0.02
Ashkenazi	0.96	0.01	0.01	0.02
Ethiopia	0.62	0.08	0.24	0.06
Norway	0.96	0.02	0.01	0.01
Armenia	0.90	0.04	0.02	0.05
China	0.09	0.05	0.01	0.84
Papua New Guinea	0.02	0.95	0.01	0.02
Afro-Caribbean	0.21	0.03	0.73	0.03

 **Table 1: Proportion of membership of each sampled population in structure-defined subclusters**

These results indicate that a reasonably high number of loci should be used to obtain consistency in clustering; one approach would be to use one marker from each chromosome arm.

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Population genetic structure of variable drug response. *Nature Genetics* **29**, 267. Used with permission. All rights reserved. 

**Figure Detail**

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