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Pharmacogenetics of drug-metabolizing enzymes in US Hispanics

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Abstract

Although the Hispanic population is continuously growing in the United States, they are underrepresented in pharmacogenetic studies. This review addresses the need for compiling available pharmacogenetic data in US Hispanics, discussing the prevalence of clinically relevant polymorphisms in pharmacogenes encoding for drug-metabolizing enzymes. *CYP3A5**3 (0.245–0.867) showed the largest frequency in a US Hispanic population. A higher prevalence of *CYP2C9**3, *CYP2C19**4, and *UGT2B7* IVS1+985 A>Gwas observed in US Hispanic vs. non-Hispanic populations. We found interethnic and intraethnic variability in frequencies of genetic polymorphisms for metabolizing enzymes, which highlights the need to define the ancestries of participants in pharmacogenetic studies. New approaches should be integrated in experimental designs to gain knowledge about the clinical relevance of the unique combination of genetic

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variants occurring in this admixed population. Ethnic subgroups in the US Hispanic population may harbor variants that might be part of multiple causative loci or in linkage-disequilibrium with functional variants. Pharmacogenetic studies in Hispanics should not be limited to ascertain commonly studied polymorphisms that were originally identified in their parental populations. The success of the Personalized Medicine paradigm will depend on recognizing genetic diversity between and within US Hispanics and the uniqueness of their genetic backgrounds.

Keywords

admixture; CYP450; drug-metabolizing enzymes; genotypes; Hispanics; pharmacogenetics; Puerto Ricans

Introduction

On February 20, 2013, the Food and Drug Administration (FDA) expedited a new Boxed Warning – the strongest warning to restrict the use of codeine-containing medications in children as postoperative pain management. This warning resulted from reported adverse drug reactions such as life-threatening respiratory depression and three deaths of children that metabolized codeine faster, achieving lethal concentrations of morphine [1]. It is known that genetic polymorphisms affect a drug's response by three mechanisms: (a) altering the metabolism of the drug, (b) producing unexpected effects (i.e., hemolysis), and (c) altering the drug target [2]. The mentioned reports of codeine use in children are an example of how genetic polymorphisms in drug-metabolizing enzymes result in serious and even lethal drug responses. Adverse drug events were found to account for 2.5% of emergency department visits [3]. A meta-analysis study found that 59% of drugs cited in reports of adverse drug events were metabolized by at least one enzyme with a known genetic polymorphism associated with lower enzyme activity [4]. Even when the FDA had labeled about 150 xenobiotics with pharmacogenetic information, the potential cost-effectiveness of genetic tests to avoid adverse drug events remains unclear and controversial [5]. The presence of individuals with different genetic backgrounds in clinical trials that attempted to determine the cost-effectiveness of genetic tests in pharmacotherapy might be an explanation for such controversial results.

Overrepresentation of European descendant populations in pharmacogenetic studies and the extrapolation of those findings to other populations are factors that undermine the strong evidence that supports the incorporation of precision medicine [6]. The majority of the case control studies that search for associations between a certain phenotype and genetic polymorphisms (i.e., Genome Wide Association Studies) are often conducted in Caucasians and are therefore limited to account for the effect on associations of multihybrid admixtures and unique stratification observed in Hispanics. Admixture is defined as "a common type of gene flow in human populations that occurs when individuals from two or more parental populations that have been isolated for several generations form a new hybrid population". Admixture can be a confounding variable that may result in false associations due to differences in genetic backgrounds across individuals within a cohort [7]. Admixed populations may differ from other populations in frequency, distribution, and combination of

allelic variants in the genome [8]. Hispanics in the United States are a case of admixture, with mainly a trichotomous ancestral contribution of the following distant parental populations: Europeans, Native Americans, and West-Africans [7, 9, 10]. Using principal component analysis of autosomal genotype data in Hispanics and other putative ancestral populations, a tri-hybrid admixture pattern was confirmed by Bryc and coworkers [11]. Indeed, the two principal components shown in Figure 1 illustrate that Native American, European, and African ancestries enriched the genomic diversity of Hispanics. The fitting of ellipses to the covariance matrix reveals different ancestry depictions (mixtures) per Hispanic/Latino population. The analysis on the X chromosome markers showed a similar pattern, although with greater variance (data not shown) [11].

The relative contribution of each parental population is different among Hispanics: European and Native American contribution in autosomal genes is higher in Mexicans when compared to Caribbean Hispanics, while African contribution is higher in Caribbean Hispanics than in Mexicans. In admixed populations, the relative contribution of the parental populations will determine the distribution of the relevant variants [7]. As a result, Hispanics present a large variation in ancestry proportions among different ethnic groups and among individuals in a country [9, 11].

Another concern of extrapolating the findings of pharmacogenetic studies in European descendants to admixed populations is the role that linkage disequilibrium plays in population genetics [12]. Some polymorphisms associated to a certain phenotype in drug response may not be the causal variant but rather are in linkage disequilibrium with one or more causal or functional variants that occur specifically in a given population (i.e., *rs12777823* in African-Americans and *VKORC1*-1639G>A in Asians, both associated to warfarin's response). Since Hispanics are the result of three distant parental populations (including an enrichment of African genetic variants), a new combination of the haplotype block architecture is expected, giving rise to a unique linkage disequilibrium structure with new putative markers or association signals in this population. Linkage disequilibrium can also be affected by the ancestral contributions. Bryc and colleagues [11] found that linkage disequilibrium decays faster in Hispanic/Latinos with greater African ancestry.

The US Census Bureau reported that, by July 2012, 53 million Hispanics are living in the United States, corresponding to 16% of the total population in this country. The most represented ethnicities among Hispanics are Mexicans (65%), Puerto Ricans (9.4%), Salvadorans (3.8%), and Cubans (3.6%). Hispanics are the nation's largest ethnic minority [13]. Although Hispanics are a continuing growing population in the United States, they are underrepresented in pharmacogenetic studies. Ongoing international efforts such as the 1000 Genomes Project and the HapMap Project are incorporating admixed populations due to the need of gaining knowledge of human genetic variations globally. These projects, in conjunction with the existing literature, are resources for studying genetic variations affecting human health and drug response across different populations in the world, including Hispanics. This review aims to evaluate the recent literature available about genetic polymorphism of drug-metabolizing enzymes (phase I and II) in Hispanics living in the United States, mainly in Mexicans, Puerto Ricans, and Cubans, and also to evaluate existing data available from the 1000 Genomes Project.

Phase I drug-metabolizing enzymes: cytochromes P450s

Cytochromes (CYP) P450 are a superfamily of proteins involved mainly in metabolism of xenobiotics (i.e., drugs) and endogenous compounds (including retinoic acid, prostaglandins, and eicosanoids) as well as the synthesis of endogenous compounds (steroid hormones) [14]. These enzymes have the capacity to interact with a large range of chemically different compounds. The CYP450s catalyze phase I reactions: oxidation, reduction, and hydrolysis, resulting in the introduction of functional groups (−OH, −COOH, −SH, −O−, or NH2) to the substrate. They are localized in the cytosolic face of the endoplasmic reticulum. CYP450s are expressed mainly in the liver, although some expression occurs in the gastrointestinal tract, lungs, kidney, and the central nervous system. The expression and function of CYPs are influenced by diet, environmental exposure, age, disease, genetic polymorphisms, and other factors [14, 15]. Mainly one or a few members of the CYP450s metabolize many drugs at pharmacologically relevant concentrations, even given the overlapping substrate specificity in these enzymes [15]. The superfamily of CYP450s is classified in families and subfamilies based on their amino acid sequence similarity. Twelve CYPs belonging to three families (families 1–3) have been identified to metabolize xenobiotics in humans, from which members of the subfamilies CYP2C, CY2D, and CYP3A are the most important for drug metabolism [14].

CYP2C9

CYP450, family 2, subfamily C, polypeptide 9 (*CYP2C9*) is a gene (ID:1559) within the CYP2C cluster of approximately 390 kilobases (Kb) in the chromosome 10q23.3 [16]. This locus also contains the *CYP2C8*, *CYP2C18*, and *CYP2C19* genes [15]. *CYP2C* family members are responsible for 20% of the metabolism of clinically important drugs [17]. Among the members of the *CYP2C* family, *CYP2C9* has the highest expression levels [15]. *CYP2C9* is 50 Kb in size, codes for a 490-amino-acid protein (GI:527178914), and is thought to interact with weakly acidic ligands. It has been speculated that CYP2C9 protein may have more than one binding site [18]. CYP2C9 interacts with arachidonic acid to produce hydroxyeicosatetraenoic acid and epoxyeicosatrienoic acid [19]. This enzyme metabolizes drugs such as warfarin, phenytoin, losartan, glyburide, and most nonsteroidal anti-inflammatory drugs (NSAIDs) [15].

CYP2C9 functional and clinical significance of the most common variant alleles

CYP2C9 is one of the most studied CYPs in pharmacogenetics since it metabolizes a broad spectrum of commonly used drugs. Common or wild-type allele is known as *CYP2C9**1 (http://www.cypalleles.ki.se/cyp2c9.htm) [20]. *CYP2C9**2 (*r s1799853*; 430C>T at exon 3) results in a change in arginine for cysteine in residue 144, which had been associated with slower metabolism of S-warfarin (i.e., average 40% reduction in warfarin metabolism), diclofenac, and lauric acid (i.e., 60%–70% of normal enzyme activity) [21]. It is thought that this variant affects the interaction of the enzyme with NADPH CYP450 oxide-reductase [22, 23]. *CYP2C9**2 has been associated with lower dose requirement of warfarin, phenytoin-induced neurotoxicity, and a greater decrease in blood pressure in patients treated with irbesartan [24–27]. *CYP2C9**3 (*rs1057910*; 1075A>C at exon 7) produces an isoleucine to leucine, and a change in codon 359 results in lower enzyme activity (i.e., 5% of normal

enzyme activity) [20, 22, 23, 28]. *CYP2C9*5* (*rs28371686*; 1080C>G), **6* (*rs9332131*; 818delA), **8* (*rs7900194*; 449G>A), and **11* (*rs28371685*; 1003C>T) occur predominantly in individuals of African descent. Their allele frequencies range from 0.01 to 0.06 in African-Americans. They have been associated with lower warfarin dose requirements in African-Americans [29].

It is known that common variants in the *CYP2C9* gene may decrease S-warfarin's metabolic rate and therefore alter a patient's sensitivity and dose requirements (i.e., approximately 16-fold interindividual variability in dose requirements). Notably, the *CYP2C9**2 and *3 variants (most frequent among Caucasians) account for 15%–20% of the warfarin dose variability in various populations worldwide [30–33]. *CYP2C9* genotypes are associated with decreased warfarin clearance, longer time to achieve stable anticoagulation therapy, 5–6 times higher likelihood of having initial International Normalized Ratio (INR) > 3 (indicative of overanticoagulation), and 4 times higher likelihood of developing major bleedings and intracranial hemorrhage during the initiation phase [34–36]. Likewise, patients carrying these single-nucleotide polymorphism (SNPs) may show a higher risk of developing acute gastrointestinal bleeding when using NSAIDs. On the basis of a meta-analysis of nine qualified studies, the FDA has approved reduced recommended warfarin dosage based on the presence of these variants [37].

We have recently found a significant association between *CYP2C9* genotypes and warfarin dose requirements in Puerto Ricans. Patients carrying at least one copy of either the *CYP2C9**2 or the *3 allele required a mean daily warfarin dose that was 26% less than that for patients with wild-type genotype. Moreover, carriers of functional *CYP2C9* polymorphisms, along with the target of warfarin, vitamin K epoxide reductase complex subunit 1 (VKORC1)-1639G>A variant, demonstrated a higher incidence rate of multiple adverse events (i.e., 5.2 vs. 1.0 cases per 100 patient-months; RR=4.8) as compared to those with wild-type genotype in a cohort of Puerto Rican patients on warfarin. A significant association was observed between multiple adverse events and the carrier status (HR=2.5; 95% CI, 1.0–6.3; p=0.04). However, no significant associations between genotypes and individual outcomes over the first 90 days of therapy were found [38].

The 2010 Medco-Mayo Warfarin Effectiveness study suggested that genetic test in *CYP2C9* and *VKORC1* significantly reduced (by approximately 30%) the hospitalization rate for bleeding or thromboembolic events in patients starting anticoagulation therapy when compared with controls [39]. Both a report by the Centers for Medicare and Medicaid Services and the randomized clinical effectiveness CoumaGen-II trial (NCT00927862) concluded that pharmacogenetic guidance was superior to current dosing approaches (fixed and clinical) in achieving optimal anticoagulation (assessed by INR measurements) and also in reducing deaths, hemorrhages, and thromboembolisms [40, 41].

Warfarin ranks among the top 10 drugs with the largest number of serious adverse event reports in the FDA's Adverse Event Reporting System and is also associated with about 29,000 emergency room visits per year for bleeding complications (50% major bleedings occurring within the first 90 days) [42]. If genotyping were known upon initiation of warfarin, 85,000 serious bleeding events and 17,000 strokes could be avoided annually,

saving over $ 1 billion in healthcare [43]. Besides, if genotyping is performed after therapy begins, lesser but still worthwhile cost savings would result, in part due to reduced risk of hospitalization for bleeding or thromboembolism in outpatients initiating warfarin [39, 44].

Prevalence of the most common variants in US Hispanics

Currently, most of the pharmacogenetic studies conducted in Hispanics living in the United States have included mostly Mexican-Americans. The 1000 Genomes Project includes a Puerto Rican sample of 55 individuals [45]. Common *CYP2C9* polymorphisms studied in the Puerto Rican population included in this project such as *CYP2C9**2, *3, *5, and *8 were present in 0.173, 0.036, 0.009, and 0.009 of the population, respectively [45] (Table 1). Studies by Duconge and coworkers investigated minor allele frequencies (MAFs) in Puerto Ricans for *CYP2C9**2, *CYP2C9**3, *CYP2C9**5, and *CYP2C9**6, which are presented in Table 1 [51–53]. The *CYP2C9**8 (*rs7900194*; 449G>A) variant has a frequency of 0.008 in a Puerto Rican population cohort of patients under warfarin therapy (unpublished data), not distant from the MAF reported for this population in the 1000 Genomes Project (0.009) [45].

We have also observed a relationship between population substructure and warfarin-related genotypes in Puerto Ricans. Our group used physiogenomic (PG) markers to infer the structure and ancestry of participants, finding an absence of the *2 allele in the cluster of Puerto Ricans genetically resembling Amerindians, consistent with the prevalence reported in Asians by the HapMap Project [57]. This finding was not surprising since it is hypothesized that Amerindians originated from Asians who migrated from the Bering Strait (Bering Migration Theory). *CYP2C9**2 was found in the cluster resembling Caucasians (7.7%), close to values reported for this ancestral population (10%) in the HapMap Project but different than expected in the West-African cluster (18.8% vs. 0% in Nigerians), showing significant admixture and the heterogeneity of the Puerto Rican population. *CYP2C9**3 frequencies found in clusters genetically resembling Caucasians (7.6%) and West-Africans (0%) are comparable to reported values for the referred populations in the HapMap Project (6% and 0%, respectively). These findings suggest that interindividual variations in ancestral contribution may influence the response to warfarin of each Puerto Rican [58, 59].

The MAFs of *2 and *3, among other variants of *CYP2C9*, in Mexican-Americans are shown in Table 1 [46–50]. Both *CYP2C9**2 and *CYP2C9**3 are at lower frequency in Mexicans living in Mexico (Mexican-Mestizos and Mexican-Tapehuana) than in Mexican-Americans [46, 50]. *CYP2C9* *4 (*rs56165452*; 1076T>C), *5, and *6 were not present in any of the individuals of Mexican-American descents examined [46, 47]. Reported literature in Cubans, classified as Cuban-whites (individuals descendants from four Caucasian grandparents) and Cuban-mestizos, showed that *CYP2C9**2 and*3 MAFs were 0.06–0.17 and 0.09–0.11, respectively. *CYP2C9**5 and *8 in Cubans were found in ranges of 0–0.004 and 0.004–0.02, respectively [54]. *CYP2C9**6 was not found in any Cuban individual, while *CYP2C9**4 was not found in any individual of Mexican-American, Puerto Rican, or Cuban origin [46–53].

Combined common allele variants in the *CYP2C9* gene (*2, *3, *4, *5, *6, *8, *11, and *13) can be found with a frequency of 0.178 in the Hispanic population [55]. MAFs for the

CYP2C9 *2 and *3 variants in Hispanics from unreported origin are available in Table 1 [55, 56]. The population of Hispanics in the study of Scott and colleagues are potentially mostly Caribbean Hispanics (Dominicans and Puerto Ricans), who constitute a large percentage of the Hispanic population in New York [60]. Frequencies of common variants for the *CYP2C9* may fluctuate even among Hispanics, implicating special considerations to each population when designing dosing algorithms for drugs metabolized by CYP2C9. *CYP2C9**4 was not found in Hispanics; this may implicate that this variant is too rare to be considered into genotyping panels for clinical decisions [55]. *CYP2C9**8 is found at higher frequencies in African descendants, which may explain its presence in Cubans and Puerto Ricans due to their high African contribution when compared to other non-Caribbean Hispanic ethnicities [11, 61, 62]. The MAFs in the global population for CYP2C9*2, *3, *5, and *8 are 0.068, 0.042, 0.005, and 0.012, respectively [45].

CYP2C19

CYP450, family 2, subfamily C, polypeptide 19 (*CYP2C19*) is another member of the *CYP2C* family [63]. *CYP2C19* has lower expression levels than *CYP2C9* does [15]. The gene has an approximate size of 90.2 Kb (ID:1557) that code for a protein precursor of 490 amino acids (GI:4503219). This enzyme binds neutral or weak bases, and endogenously, it metabolizes progesterone and melatonin. CYP2C19 enzyme is involved in the metabolism of approximately 6.8% of drugs such as omeprazole, amitriptyline, carbamazepine, and clopidogrel [15]. Carriers of polymorphisms in the *CYP2C19* gene that encodes for this enzyme may exhibit phenotypes classified as poor, intermediate, extensive, and ultrarapid metabolizers depending on the enzyme's activity.

CYP2C19 functional and clinical significance of the most common variant alleles

At least 16 genetic variants have been associated with changes in enzyme's activity, from which 7 result in an inactive enzyme [64]. As with other P450 genes, *CYP2C19**1 identifies the wild-type allele. *CYP2C19*2 (rs4244285;* 681G>A) and *CYP2C19*3 (rs4986893;* 636G>A) null alleles produce an inactive enzyme (http://www.cypalleles.ki.se/cyp2c19.htm) [20]. *CYP2C19**2 and *CYP2C19**3 are both SNPs in exon 5 and exon 4, respectively. *CYP2C19**2 leads to a splicing defect, while *CYP2C19**3 results in a premature stop codon and a truncated protein that lacks enzymatic activity (Trp212X). Homozygotes are poor metabolizers who may benefit when using proton pump inhibitors since the plasma drug concentration is higher, resulting in better control of gastro-esophageal acidity [15]. *CYP2C19**3 is associated with poor metabolism (PM) of proguanil (prophylactic antimalarial drug) [21].

Both *CYP2C19**2 and *3 haplotypes are associated with diminished response to clopidogrel. Clopidogrel is an oral antiplatelet that needs activation by CYP2C19 in order to prevent blood clotting [15]. Compared to wild-types, carriers of these variants are at risk of major adverse cardiovascular events and get fewer benefits from clopidogrel treatment. The FDA added a black-box warning to the clopidogrel label, to alert patients and healthcare professionals about its lower effectiveness in individuals who have *CYP2C19* variants associated with low enzymatic activity [65]. The gain-of-function *CYP2C19**17

(*rs12248560;*-806C>T) variant increases transcription of the gene, which may result in increased drug's metabolism.

Prevalence of the most common variants in US Hispanics

Polymorphisms in *CYP2C19* have not been well described in the Hispanic population. In previous studies, the *CYP2C19* *2 variant was present in 0.09–0.148 of the Puerto Rican population, while the *3 allele was found with a frequency of 0.035 in the studied group [66–68] (Table 2). Another study that used a PG array to interrogate 222 genes of cardiometabolic relevance in 71 genomic DNA specimens from Puerto Ricans found *CYP2C19* *3 allele frequencies of 0.05 among individuals of higher Amerindian heritage, 0.037 among subjects of greater European contribution, and 0.021 among those showing high African ancestry compared to the expected HapMap values of 0.056, 0.017, and 0.003 for each ancestral population, respectively [68]. The higher-than-expected frequencies observed in individuals of either European or African descent might be a direct consequence of significant admixture. Concerning the 1000 Genomes Phase I selection, MAFs in Puerto Ricans for the *CYP2C19 *2* and *3, among other variants, are shown in Table 2 [45].

In a study with Mexican-Americans, a prevalence of 0.902, 0.097, and 0.001 for *CYP2C19* *1, *2, and *3, respectively, was reported in 220 patients. This study did not observe *4 (*rs28399504*; 1A > G null), *5 (*rs56337013;* 1297 C>T null), *6 (*rs72552267*; 395G>A null), *7 (*rs72558186;* 19294T>A null), and *8 (*rs41291556*; 358T>C null) alleles in patients previously classified as poor metabolizers [64]. A single study conducted in 250 Hispanics living in New York of undetermined origin found that prevalence for *CYP2C19* *1 was 0.704. This study genotyped *2 through *17 (*rs12248560*; −806C>T) and *22 (*rs140278421;* 557G>A) variants. Allele frequencies found in this study are presented in Table 2. Linkage disequilibrium with members of the *CYP2C* cluster (*CYP2C9*, *CYP2C19*, and *CYP2C8)* was found among this group of Hispanics [69]. Worldwide prevalence for *CYP2C19* *2, *3, *4, *8, *9, *17, and *22 is 0.198, 0.014, 0.001, 0.002, 0.003, 0.152, and 0.000, respectively [45].

CYP2D6

CYP2D6 is the only member of the *CYP2D* subfamily that encodes for a functional protein [70]. This gene is approximately 4.4 Kb and is localized in chromosome 22q13.1 (ID:1565). The encoded protein is 497 amino acids long (GI:425706106) and is expressed in the endoplasmic reticulum of liver cells, gastrointestinal tract, and the brain. Interindividual variability in hepatic protein content might be explained, in part, by the presence of genetic polymorphisms. CYP2D6 in the brain is able to *O*-demethylate its substrate 5-methoxytriptamine, resulting in regeneration of serotonin [71]. CYP2D6 is also involved in progesterone hydroxylation [72]. Due to the role of CYP2D6 in the metabolism of endogenous compounds of the central nervous system, it was postulated that polymorphisms in the gene might have an effect on human behavior [73]. Furthermore, in Spanish and Cubans, one study found a significant association between CYP2D6 activity (measured by debrisoquine hydroxylation) and personality traits such as psychic anxiety and socialization [74]. CYP2D6 is the enzyme for metabolism of 15%–25% of drugs used in clinics [15]. Among drugs metabolized by CYP2D6 are tamoxifen, codeine, debrisoquine

(antihypertensive), paroxetine, aripiprazole, and risperidone. Like other CYP450s, the metabolic capacity of CYP2D6 is measured using phenotyping tests and is classified as poor, intermediate, extensive, and ultrarapid metabolizers. CYP2D6 activity is measured using debrisoquine, sparteine, and dextromethorphan, as substrates [7].

CYP2D6 functional and clinical significance of the most common variant alleles

More than 100 variant alleles have been identified, including SNPs and structural variants [20]. The *1 and *2 variants have normal activity and are considered wild-type. *CYP2D6**4 (*rs3892097*; 1846G > A) is a nonfunctional variant and results in a splicing defect. The *CYP2D6**10 (*rs1065852*; 100C > T), *17 (*rs16947*; 1023C>T), and *41 (*r s 28 3717 25*; 2988G>A) variants result in decreased enzymatic activity, with *10 and *17 through coding SNPs in the primary protein structure (Pro34Ser in *10 and Thr107Ile and Arg296Cys in *17), while *41 causes splicing defects. Structural variants identified in *CYP2D6* include deletions and amplifications of the gene. The *CYP2D6**5 variant has a 11.5 Kb gene deletion. All of the alleles mentioned above are associated with lower or absent enzymatic activity, and therefore, drugs that need inactivation through CYP2D6 can accumulate in the plasma, and carriers might be at higher risk of intoxication. On the other hand, drugs that need activation may not be effective, as what occurs with tamoxifen. The anticancer drug tamoxifen needs bioconversion by CYP2D6 into the active metabolites: 4-hydroxy-tamoxifen and 4-hydroxy-*N*-desmethyl-tamoxifen (endoxifen). Risk of breast cancer mortality and relapse has been associated with the presence of the nonfunctional variant *CYP2D6**4 [75].

Gene amplification commonly occurs in *CYP2D6*, resulting in higher-than-normal enzymatic activity if the amplified allele codes for a functional protein. Codeine is a prodrug that needs bioactivation to morphine by CYP2D6 in order to produce analgesia. Ultrarapid metabolizers are at greater risk of morphine-induced intoxication due to increased plasma concentration of morphine [76, 77]. In 2012, Kelly and colleagues [78] reported two fatal cases of children under codeine use: one had *CYP2D6**1/*2AxN gene duplication and the other one presented higher-than-normal codeine concentration relative to morphine but unknown genotyping.

Prevalence of the most common variants in US Hispanics

González-Tejera et al. [79] performed *CYP2D6* genotyping in a Puerto Rican cohort of psychiatric patients. The most prevalent allelic variants for this group of patients were normal activity alleles *1 and *2, the nonfunctional *4, and the reduced-function *41 (frequencies are shown in Table 3). Other variants such as *5, *9, *10, *17, *29, *31, *35, and *40 were also found at a range of 0.011–0.044. *CYP2D6* *3 and *6 and duplications (*1XN, *2XN, *4XN, *10XN, *17XN, *35XN, and *41XN) were not found [79]. The *CYP2D6* *10 variant was found with a frequency of 0.09 in 100 Puerto Rican newborn dried blood samples by Orengo-Mercado et al. [66], this frequency being higher than the one found in the patient cohort of 45 patients studied by González-Tejera (0.044) [79]. MAFs from 55 Puerto Ricans reported by the 1000 Genomes Project for *CYP2D6* *4 and *CYP2D6* *41, among others, are shown in Table 3. *CYP2D6* *10 was found in 0.20 of the population; therefore, the *10 variant frequency and possibly those other frequencies in this population

have not been consistent [45]. The study of González-Tejera and colleagues [79] mentioned previously included 45 psychiatric Puerto Ricans patients preselected based on suspected intolerance to drugs metabolized by the CYP2D6 Surprisingly, 2 out of 45 Puerto Rican patients were carriers of the rare *31 (4042G>A) variant with a MAF of 0.022 [79]. *CYP2D6* *31 was also found in a group of Spanish and Hispanics with a lower frequency (0.0057 and 0.0033, respectively). Gaedigk and colleagues [84] validated the lack of activity of the *31 variant using dextromethorphan as a probe for phenotyping analysis in a Spanish patient with *4/*31 genotype. Interestingly, *CYP2D6*31* was not found in Germans, Swiss, North-American Caucasians, African-Americans, Hispanics from South Florida, or Brazilians [84]. Therefore, it is suspected that the origin of *CYP2D6*31*, found in Spanish or Spanish descendants (Puerto Ricans and Hispanics), might be North African or Sephardic Jewish ancestry [84, 85].

An extensive study interrogating allelic variants of *CYP2D6* in Mexican-Americans found that similar to Puerto Ricans, the most prevalent variants were *1, *2, *4, and *41. Variants *5, *9, and *10 were found at lower frequencies (Table 3), while variants *3, *6, *17, and *29 were very rare among Mexican-Americans. Gene duplications (*41XN, *2XN, and *4XN) were found at a frequency of 0.008, while alleles *7, *8, *11, *14, *45, and *46 were not found in this population. The combined allelic frequency of decreased and null alleles is 0.261. In this study, Luo and colleagues [81] were interested in identifying the SNPs at positions −1584 and 2988 G>A used as markers of *41 due to previous findings that these changes may predict metabolic activity of the carriers. These findings highlight the fact that genotype-phenotype associations found in a certain population should not be extrapolated to other ethnic groups.

Another study by Casner [82] genotyped the variants *4, *5, *10, and *17 and gene duplications (*XN, *XN/*4, *XN/*17) in Mexican-Americans, finding a MAF of 0.17, 0.02, 0.01, 0.02, and 0.03, respectively, and showing that the nonfunctional *4 was the most frequent of the investigated alleles [82]. The *6 and *3 variants were not found by Casner, while the *7 and *8 variants are apparently absent in Mexican-Americans according to published studies [81, 82]. Mendoza et al. [83] also studied a Mexican-American population and found that the most common variants were *2 and *4, followed by *10 and *5 and *CYP2D6*XN (unidentified alleles) duplications (Table 3). This study also found that 63% of individuals with PM can be explained by the presence of *4. Mendoza et al. [83] explained that the detected allele frequencies for *4 and *10 in Mexican-Americans were more similar to the Spanish (0.12) than to the Asian (<0.001) population.

Currently, there is not much information available about genetic polymorphisms in the *CYP2D6* gene for the Cuban population. Llerena and colleagues [80] studied *CYP2D6* genetic variants in White-Cubans and Cuban mestizos and also included Nicaraguan-mestizos (Nicaraguans living in Nicaragua) for comparison purposes. In this study, the individuals were also phenotyped with debrisoquine to determine metabolic rate. The most frequent variants they found were *1 and *2, followed by *4 and *17 (Table 3). Among white Cubans, the MAFs for the *1 and *2 variants together were 0.754, for the *4 variant was 0.146, and for 17 variant was 0.027, while in Cuban-mestizos, the frequencies for the same *CYP2D6* variants were 0.663 (*1 and *2 together), 0.143, and 0.102, respectively.

CYP2D6 variants *5, *6, and *10 were also genotyped, and lower frequencies were found in both White-Cuban and Cuban-mestizos. Gene amplifications of normal alleles (*1XN or *2XN) were reported in frequencies within 0.038–0.047, while the −4XN variant was not present in Cuban-mestizos but was found with a frequency of 0.004 among White-Cubans. The *CYP2D6*3* variant was not found in any individual [80].

It is important to highlight the differences in *17 prevalence even within the Cuban population; Cuban-Mestizos showed higher prevalence (0.102) when compared to White-Cubans (0.027) [80]. The *CYP2D6**17 variant is found mostly in African populations, which might explain the higher allele frequency found among Cubans (0.027–0.102) and Puerto Ricans (0.033) when compared to Mexican-Americans (0.002–0.02) [79–83, 86]. This study suggested that differences in metabolism among extensive metabolizers could be explained by differential variations in defective or null alleles among populations and also to factors such as lifestyle and diet. Another study that evaluated the frequency of metabolic activities among Cubans (White-Cubans and Cuban-mestizos) and Spanish found similar frequencies of poor metabolizers between these ethnic groups (4.6% and 4.9%, respectively). But when comparisons were done among Cubans, the frequency of poor metabolizers was lower in Cuban-Mestizos (3.9%) when compared to White-Cubans (5.3%). In addition, the frequency of ultrarapid metabolizers in Spanish individuals (5.2%) was higher when compared to that in Cubans (3.8%) but almost identical when compared to that in White-Cubans (5.3%). The frequencies of the most common *CYP2D6* allelic variants found in the global population for *CYP2D6* *4, *9, *10, *17, and *41 are 0.106, 0.011, 0.256, 0.343, and 0.056, respectively [45].

CYP3A4/5

CYP3A4 and *3A5* belong to the CYP450s family 3 located in the 7q21.1 locus [15, 8 7, 88]. The *CYP3A4* and *CYP3A5* genes are about 27 Kb (ID:1576) and 32 Kb (1577) in size, respectively. The protein products of CYP3A4 (GI:13435386) and 3A5 (GI:4503231) are around 500 amino acids. Both are expressed in the endoplasmic reticulum of liver cells and intestines, but CYP3A5 is also expressed in lungs, prostate, and kidneys [89–91]. CYP3A4/5 interacts with large lipophilic substances and has overlapping substrate specificities. Endogenously, they are involved in the synthesis of sex hormones (progesterone and testosterone). CYP3A4/5 metabolizes a vast amount and wide spectrum of commonly used drugs in clinics, which include from antimicrobial and chemotherapeutic agents to psychoactive drugs (i.e., nevirapine, tamoxifen, and halo-peridol) [15].

CYP3A4/5 functional and clinical significance of the most common variant alleles

The most commonly studied variants in *CYP3A4/5* are *CYP3A4**1B (*rs2740574*; −392G>A) and *CYP3A5**3 (*rs776746*; 6986A>G). The *CYP3A4**1B variant is a base change in the promoter region of the gene that has been associated to prostate cancer, therapy-related acute myeloid leukemia, and higher antiviral exposure. The *CYP3A4**1B variant is most frequent in African populations [92–94]. On the other hand, *CYP3A* *3 (6986 A>G) produces an enzyme without function due to errors in splicing, most frequent among Europeans [95]. CYP3A4 is found in kidneys and has the ability to produce hydroxyl-cortisol, a molecule involved in sodium and water retention. The presence of the wild-type

allele (*CYP3A5**1) was thought to predispose to hypertension, which was not supported by previous studies [96].

Prevalence of the most common variants in US Hispanics

A case control study conducted by Blanco and colleagues [93] looked for an association between *CYP3A4**1B and the risk of developing therapy-induced myelodysplastic syndrome in children affected by acute lymphoblastic leukemia. Children classified as white, black, or Hispanic were genotyped for *CYP3A4**1B and *CYP3A5**3. Even though frequencies differed significantly among populations, the authors did not find an association between *CYP3A4* or *CYP3A5* polymorphisms and the risk of suffering therapy-induced myelodysplastic syndrome. *CYP3A5* was also interrogated due to the fact that previous studies have identified the wild-type allele of this gene to be in linkage disequilibrium with *CYP3A4**1B. Respective MAFs reported for *CYP3A4**1B and *CYP3A5**3 were 0.70 and 0.27 for blacks, 0.20 and 0.84 for Hispanics, and 0.036 and 0.91 for whites [93] (see Table 4). Another study that included Hispanics with HIV (Adult AIDS Clinical Trials Group) interrogated variants in *CYP2B6* and *CYP3A4/5* related to efavirenz (antiretroviral) exposure and central nervous system side effects, both potential causes of intolerance and eventual treatment failure. The *CYP2B6* gene product is the main metabolic enzyme for efavirenz, while *CYP3A* gene products are minor contributors. The patients were recruited in the United States and Puerto Rico. Reported allelic frequencies in Hispanics for *CYP3A4**1B (392 A>G) and *CYP3A5**3 (6986 A>G) were 0.40 and 0.867, respectively. The *CYP3A4*1B* and *C YP3A5**3 variants were weakly associated with higher exposure to efavirenz. Overall, *CYP2B6* variants were associated with greater efavirenz exposure and increased central nervous system side effects, but the authors refrained from making conclusions about Hispanics due to “ small sample size ” (n=15 Hispanics) [94]. Six years, later the Adult AIDs Clinical Trials Group performed genotyping in a larger study cohort (n=149 Hispanics) and reported a MAF of 0.76 for *CYP3A5**3 in Hispanics, but this time, they did not find an association between *CYP3A5**3 and efavirenz exposure in any population [98]. Not far from the MAF found for *CYP3A5*3* in Hispanics, Puerto Ricans present minor allele of 0.764 for this gene, while 0.20 was found for *CYP3A4*1B* according to data from the 1000 Genomes Project [45].

Establishing a potential association between *CYP3A5**3 and other antiviral drugs is a subject of research in other studies as well. Zhang and colleagues [95] found that *CYP3A5**3 did not affect the minimal concentration in plasma of the protease inhibitors lopinavir, amprenavir, and saquinavir. Global population MAF for *CYP3A5**3 is 0.312 [45]. MAFs reported for *CYP3A5**3 in Hispanics, blacks, and whites by Zhang et al. [95] were 0.755, 0.281, and 0.928, respectively. The mutant G allele is the most common in European descendants; therefore, the enzymatic activity of CYP3A5 is expected to be importantly reduced in this population [95]. As reported in previously mentioned studies, the G allele of *C YP3A5* is also highly prevalent among Hispanics (Table 4) [93–96, 98]. Black-American and Hispanic patients who have two *CYP3A5*1* functional alleles presented higher systolic blood pressure after verapamil antihypertensive therapy. Potential predisposition of *CYP3A5**1 homozygotes to have higher systolic blood pressure might explain these results but is not evidenced in the study. *CYP3A5**6 (14690G>A) frequency (0.04) was also investigated in

verapamil-treated Hispanics, and a weak association of this variant with systolic blood pressure response to verapamil was found in blacks and Hispanics [96].

Paris et al. [92] found that *CYP3A4*1B* was significantly associated with prostate cancer in African-American men, and indeed, this polymorphism is most frequent in this population. This fact should be of concern for Caribbean Hispanics since they have a relatively large African ancestral contribution when compared to other non-Caribbean Hispanics. In fact, prostate cancer is the most prevalent cancer in Puerto Rican men [99]. *CYP3A4**1B presents with wide variation among different populations: almost not found in Asians, prevalent among Hispanics, and more common in African-Americans than the wild-type (A) allele. The MAF of the *CYP3A4**1B variant in the global population is 0.201 [45]. Paris [92] and colleagues selected a group of Hispanics from southern California and found that the frequency of the *CYP3A4**1B variant in this population was 0.20, while Zhang et al. reported a frequency of 0.164 in Hispanics [92, 95]. Questions about whether the *CYP3A4**1B variant is the causal polymorphism associated with prostate cancer and therapy-induced myelodysplastic syndrome merit further research. A large study conducted with about 800 individuals that included a broad range of racial groups aimed to genotype for the *CYP3A4**1B variant and determine the related enzyme's activity. Hispanic volunteers were recruited from Southern California and presented a frequency of 0.093 of *CYP3A4**1B. Similarly to previously mentioned studies, this polymorphism was also highly prevalent in Black-Americans than in other racial groups but was not associated to lower metabolism of erythromycin [97].

Phase II metabolizing enzymes: *N*-acetyl transferases

N-acetyl transferase (NAT) 1 and 2, known as *NAT1* (ID:9) and *NAT2* (ID:10) genes, respectively, are located in chromosome 8p22 and comprehend a region of 180 Kb [100, 101]. NAT1 is present in all human tissues, whereas NAT2 is expressed mainly in liver and gastrointestinal tract [14]. NATs are responsible of the addition of an acetyl group derived from acetyl-coenzyme A to molecules containing an aromatic amine or hydrazine group, resulting in either activation or detoxification of these compounds [14, 102]. NAT enzymes metabolize isoniazid (used as treatment for tuberculosis), hydralazine (antihypertensive drug), and benzocaine (local anesthetic) [14]. Polymorphisms in *NAT* s are annotated in an online database (http://nat.mbg.duth.gr). Polymorphisms associated to slow acetylation may lead to accumulation of adducts, raising the question of a possible involvement in birth defects (clubfoot) and cancer (breast and bladder) [14, 100, 102]. A study conducted on Hispanics from New Mexico interrogated polymorphisms associated to NAT2 rapid acetylation: *4 (reference), *12 (*rs1208* ; 803 A>G), and *13 (*rs1041983* ; 282 C>T), whose frequencies are shown in Table 5. Polymorphisms associated with slow acetylation phenotype are *6 (*rs1799930*; 590G>A) and *7 (*rs1799931* ; 857 G>A), and their prevalence, as well as for *5 alleles (*rs1801280* ; 803 A>G; *5A, *5B, and 5C), is found in Table 5. In the same study, alleles associated with slow acetylation were more prevalent among non-Hispanic whites than among Hispanics [102]. Another study by Hecht and colleagues [100] found MAFs for *NAT2*5, *6, *7, *11* (*rs1799929* ; 481 C>T), and **13* (*rs1041983*; 282 C>T) equal to 0.3274, 0.1956, 0.1204, 0.3227, and 0.2996, respectively. In a different study, Lin et al. [103] genotyped only alleles *6, *7, and *11, finding minor allele

frequencies corresponding to 0.23–0.32, 0.17–0.19, and 0.10–0.17, respectively, among two Hispanic populations living in California and Harbor. *NAT1* variant alleles were found at frequencies of 0.4886 for *NAT1*3* and 0.4972 for *NAT1*10* [100]. Concerning Puerto Ricans, *NAT1*3*, *NAT2*5*, *6*, *7*, *11*, *12*, and *13* have MAFs as presented in Table 5. The worldwide frequencies for *NAT1* and *NAT2* alleles are 0.424, 0.296, 0.245, 0.072, 0.278, 0.315, and 0.356, respectively [45].

Uridine diphosphate-glucuronosyl-transferases

Uridine diphosphate (UDP)-glucuronosyl-transferases (UGTs) are encoded by 19 genes, from which 9 located in chromosome 2 produce the enzymes known as UGT1 and 10 located in chromosome 4 produce UGT2. UGT enzymes transfer glucuronic acid from UDP-glucuronic acid to compounds in order to be excreted out of the body. The expression of these enzymes occurs mainly in the liver and gastrointestinal tract. UGT1A is an enzyme of great physiological relevance since it catalyzes the glucuronidation of bilirubin, a conversion needed for the excretion of this endogenous substance derived from breakdown of hemoglobin and proteins that contain heme-group [105]. Drugs metabolized by UGTs are irinotecan, acetaminophen, morphine, and oxazepam [14]. Pharmacogenetic studies of *UGT s* in Hispanics are not abundant. Li and colleagues reported MAFs for seven SNPs in *UGT2B7* in Hispanics. The database for UGT allelic variants is available at http://www.pharmacogenomics.pha.ulaval.ca/cms/ugt_alleles/ [106]. Frequencies reported by Li et al. [107] were retrieved from the 1000 Genomes Project until 2012, which included 17 Mexican-Americans and 5 Puerto Ricans. In order to provide updated information, the same SNPs reported by Li et al. [107] were accessed from the 1000 Genomes Project for this review (Table 6). The −327 G>A (*rs7662029)*, −138 G>A (*rs73823859)*, −125 T>C (*rs7668282)*, 211 G>T (*rs12233719)*, IV1S +985 A>G (*rs62298861)*, 802 T>C (*rs7439366)*, and 1191 C>T (*rs57913007)* mutated alleles are present in Puerto Ricans with a frequency of 0.600, 0.055, 0.973, 0.009, 0.236, 0.409, and 0.055, respectively, and for Mexicans-Americans, these SNP frequencies were 0.265, 0.038, 0.008, 0.008, 0.432, 0.311, and 0.038, respectively. In the global population, these allelic variants are present with a frequency of 0.356, 0.030, 0.032, 0.039, 0.185, 0.397 and 0.031, respectively [45].

Glutathione S-transferases

Glutathione S-transferases (GSTs) are classified as cytosolic and microsomal. The cytosolic type is divided in classes termed as alpha (GSTA), mu (GSTM), omega, pi, sigma, theta (GSTT), and zeta. The genes for the different classes are dispersed among different human chromosomes. The main function of GSTs is to transfer glutathione to reactive electrophilic molecules, preventing the interaction of the latter with macromolecules (proteins, lipids, DNA, and carbohydrates). Endogenous ligands of GSTs are hydrophobic molecules such as prostaglandins, leukotriene, heme, bilirubin, and bile acids [14, 108]. GSTs are involved in the inactivation of anticancer drugs. *GSTs* are also polymorphic, where *GSTM1* and *GSTT1* are common among all populations [109, 110]. Both *GSTM1*0* and *GSTT1*0* present a gene deletion that produces a null phenotype, which may result in drug-induced toxicity of chemotherapeutic agents [14]. *GSTM1**0 frequency has a prevalence of 0.40 among Mexican-Americans, quite close to that of Mexican-Mestizos (0.426) (Table 5) [104, 111]. A study by Woo and colleagues [109] aimed to determine the association of *GST* null alleles

with the predisposition to present treatment-related myeloid malignancies in children with acute lymphoblastic leukemia (ALL). Among Hispanics, 36% of study controls (patients with ALL but not myeloid malignancies) and 50% of study cases (patients with ALL and myeloid malignancies) had *GSTM1* null allele, while 11% of controls and 17% of cases had the *GSTT1* null allele. The percentage of controls and cases presenting both null alleles (*GSTM1* and *GSTT1)* was 7% and 17% of Hispanics, respectively. Woo et al. [109] found that carriers of *GSTM1* and *GSTT1* null alleles are not predisposed to develop treatment-induced myeloid malignancies.

Clinical implementations in US Hispanics

Currently, multiple sites in the US mainland have been operationally implementing a prospective (often preemptive) genotyping program by interrogating many of the pharmacogenes herein discussed. Such comprehensive programs (e.g., Vanderbilt PREDICT project, Mayo Clinic) are linked to advanced, computer-aided, clinical (point-of-care) decision-support systems and algorithms and have been deployed at medical and academic health institutions to guide individualized healthcare (i.e., the choice of prescription medicines and dosages for each patient) in clinical settings. Although these initiatives are also available for people of Hispanic heritage residing in the United States, cultural, socioeconomic, and legal barriers limit their access to these programs. Clinical Pharmacogenetics Implementation Consortium guidelines for drugs metabolized through *CYP2C9*, *CYP2C19*, *CYP2D6*, and *TPMT* are currently available, but their validity and clinical utility have not yet been fully investigated in US Hispanics [112 115]. To the best of our knowledge, only a limited number of studies have been conducted in US Hispanics to validate and ascertain the benefits of genotyping warfarin pharmacogenes (*CYP2C9* and *VKORC1)* in this population, but not for the other genetic markers.

The corresponding derivation or replication cohorts for some of the available multiethnic pharmacogenetic algorithms (e.g., International Warfarin Pharmacogenetics Consortium [IWPC] derived, Gage et al. algorithm, and Wu et al. algorithm) have included a few individuals of Hispanic descent; however, there are reports of pharmacogenetic-guided algorithms developed to predict effective warfarin dosing in US Hispanic populations (i.e., Mexican-Americans and Puerto Ricans). These algorithms include the clinically actionable *CYP2C9* and *VKORC1* polymorphisms commonly interrogated in other populations (e.g., *CYP2C9**2, *3 and *VKORC1*-1639G>A) [48, 52, 116].

The algorithm for warfarin dose prediction in Puerto Ricans explained two-thirds ($R^2=0.68$) of variability in dose requirements and provided better dose estimations than the clinical algorithms did [52]. In addition, a pharmacogenetic algorithm for 3-day initial dosing that includes genotypes, admixture, and clinical covariates explained 48% of the dose variability in Puerto Ricans. A pharmacogenetic dose-refinement algorithm after the third day accounted for 76% of observed variability, after incorporating natural logarithm-transformed INR at day 4 and initial doses for days 1–3 [116]. The algorithms provided consistently better dose predictions in Puerto Ricans than the IWPC algorithm did, particularly for patients who required low or intermediate doses (≤ 7 mg/day).

Another study by Cavallari et al. [48] investigated the performance of pharmacogenetic-driven dosing algorithms in 50 US Hispanics from Chicago, most of whom were of Mexican descent. The authors developed a pharmacogenetic regression model to predict warfarin dosing in the study population and found that patients with *CYP2C9*2* or *3 required 42% less of the warfarin dose than noncarriers did. Polymorphisms in *CYP2C9* and *VKORC1* explained 55% of the interpatient variability in warfarin dose among Hispanics. Their Hispanic cohort had a similar prevalence of *CYP2C9* and *VKORC1* alleles when compared to European Caucasians, which explains the effectiveness of previously published dosing algorithms [48]. On the other hand, the Clarification of Optimal Anticoagulation Through Genetics trial selected a group of 65 Hispanics among the studied cohort to compare the pharmacogenetic vs. clinical algorithms, but the data analysis of this subgroup was not performed separately from other studied populations [5].

Conclusions

This review article discussed the prevalence of some clinically relevant polymorphisms in pharmacogenes encoding for drug-metabolizing enzymes (phase I and II), addressing a need for compiling available pharmacogenetic data in the admixed Hispanic populations living within the Unites States. Reviewed data for this publication consider mainly allele frequencies reported for the biggest Hispanic populations in the United States: Mexican-Americans, Puerto Ricans, and Cubans (Supplemental Material, Table 1, that accompanies the article, http://www.degruyter.com/view/j/dmdi.2015.30.issue-2/dmdi-2015-0023/dmdi-2015-0023.xml?format=INT) but also considers data from the 1000 Genomes Project, further including data of Colombians. From the alleles reviewed, the most prevalent alleles found in Hispanics were *CYP2C9**3 (rs *1057910*; 1075A>C at exon 7) that results in decreased CYP2C9 activity and the loss-of-function *CYP2C19**4 (rs *28399504*; 1A>G null) identified in mephenytoin poor-metabolizers (Supplemental Material, Table 2) [117]. *CYP2C9**3 frequency in Hispanics is close to the allele frequency reported in Europeans genotyped in the 1000 Genomes Project. *CYP2C19**4 is a rare variant not found in Africans or Europeans (as reported by the 1000 Genomes Project) but was reported in 0.002 of Asians, which is a lower prevalence when compared to Hispanics (ranges from 0.000 to 0.006). *UGT2B7* IVS1+985 A>G (rs*62298861*) is a change in intron 1 associated with an increase in morphine glucuronidation and mRNA levels, with higher frequency in Hispanics than in other populations [118]. *CYP2C9**13; *CYP2C19* *5, *6, *7, *10, *12, *16, and *22; and *CYP2D6* *7, *8, *11, *14, and *45 were not found in Hispanics. There are no reports about novel polymorphisms found in Hispanics as far as we know.

Currently, a few ongoing international efforts in this field (e.g., the 1,000 Genomes Project) are recruiting individuals of Hispanic heritage (i.e., Colombians, Mexican-Americans, and Puerto Ricans), becoming an invaluable resource for gaining knowledge about the frequency and distribution of common genetic variants in these often marginally represented minority populations, thus bridging the gap of information between white Caucasians and these ethnically diverse groups. In addition, some independent studies of relatively small sample sizes have been conducted by a limited number of researchers. However, there are still quite a few issues that need to be addressed before making significant progress in the field with

regard to the inclusion of Hispanics for a proper pharmacogenetic ascertainment. Some of these concerns are highlighted below.

The first and most important point to consider is the pharmacogenetic variability and the wide range of genetic diversity (i.e., mosaic of ancestries) observed within the Hispanic population. We investigated the population structure of 35 Puerto Ricans using the Hap1M Duo Bead-Chip™ on Illumina iScan™ by a high-resolution total genome-driven pairwise allelic dissimilarity analysis and compared the result to a randomly selected subset of a US reference population from Kentucky (30 Caucasians and 10 African-Americans). It can be seen clearly that the reference population is segregated into two distinct groups (Figure 2). As suspected, all the dark stripes (no. 31–40) in the upper panel belong to individuals who self-identified as African-Americans. It is remarkable how clearly the whole genome array is able to distinguish ethnic origin here. The gradation in the black bands indicates the range of Caucasian admixture in the African-American group. There appears to be little corresponding admixture in the Caucasians (stripes, no. 1–30). The same procedure on Puerto Ricans yields a much different image (bottom). The population is much more admixed and there is no clear distinction between separate groups. However, the average distance between individuals is clearly larger than within the same ethnic group in the reference population, as indicated by the darker background (gray) color. It is easy to use ancestry as a covariate in the United States and Europe because the grouping is so distinctive and categorical. For Hispanics, the admixture is continuous and is best quantified by a vector.

In this review article, we reported results from several published studies on Hispanics without a clear definition of their ethnic or geographic origin, which makes it difficult to draw valid conclusions on the relevance of the findings to a certain ethnic group (e.g., Caribbean Hispanics). However, cultural barriers to recruit and retain individuals of Hispanic origin in clinical studies also need further consideration. The label “ Hispanic or Latino ” comprises multiple countries of origin that share the same language and culture and similar habits and history, but they should not be considered as a single monolithic population for pharmacogenetic purposes. Intergroup differences, cryptic population structures, and stratification within the Hispanic population are expected due in part to a differential pattern of ancestral contributions and admixture, but intraethnic differences have also been observed. For example, *CYP2C9*3* prevalence is higher in Mexican-Americans than in Mexican-Mestizos and Mexican indigenous Tapehuana [46, 47, 50]. *CYP2C9* polymorphisms also showed intraethnic variations among Cuban-Mestizos and Cuban-Whites [54]. Therefore, given the great genetic diversity within Hispanics, we should treat the person as an individual rather than a member of an ethnic group while applying the DNA-guided personalized medicine paradigm in this population [8, 80].

Considering the high level of admixture and heterogeneity of Hispanics, new methodological approaches should be considered as part of the experimental designs to gain more insight into the clinical relevance of genetic polymorphisms involved in drug responses among these groups. Some of these methods are admixture mapping, pathway analyses, and population-based sequencing. Changes in linkage disequilibrium need to be considered given a distinct population structure that characterizes Hispanics as a

consequence of a differential contribution from multiple ancestries; new putative markers or association signals may arise from a unique combination of haplotype blocks.

At present, the majority of the commercially available genotyping platforms include only the most common variants, failing to detect those “rare” polymorphisms showing higher prevalence in admixed minority populations [79]. González-Tejera and coworkers [79] interrogate the *CYP2D6* gene for polymorphisms on this locus in Puerto Rican patients who are intolerant to drugs metabolized by this enzyme. Strikingly, two patients carried the rare variant *CYP2D6**31, and one has the *CYP2D6**40 variant, both of them not included in commercial platforms. The authors also found uncommon combinations of alleles and suggested that the Puerto Rican population is unique and may harbor other alleles less common to other populations [79].

Pharmacogenetic studies in the admixed Hispanic population should not be limited to ascertain commonly occurring allelic variants. Instead, they should also encompass other less frequent variants that might be either part of multiple causative loci or in extended linkage disequilibrium with functional alleles relevant for drug responses in a certain population. Further studies are warranted to accomplish this major goal. The success of the Personalized Medicine paradigm will depend on our capabilities to recognize the genetic diversity existing between and within different ethnic groups, as well as the uniqueness of their genetic backgrounds [8, 80].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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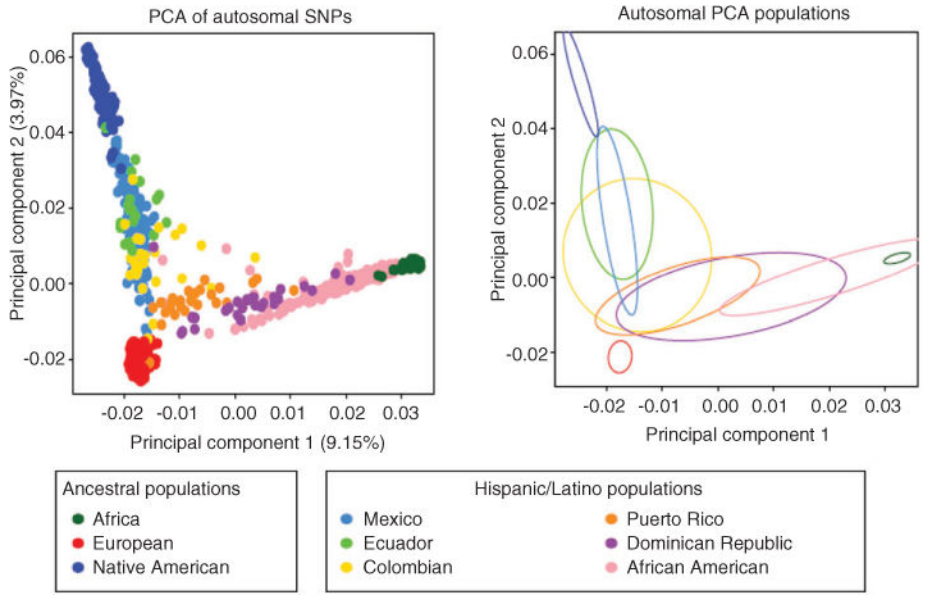

Figure 1.

Principal component analysis (PCA) results of the Hispanic individuals with Europeans, Africans and Native Americans. PC 1 vs. PC2 scatter plots based on autosomal markers (left plot). Ellipses are fitted to the PCA results on the autosomes (right plot). Reprinted from Bryc et al. [11] with permission.

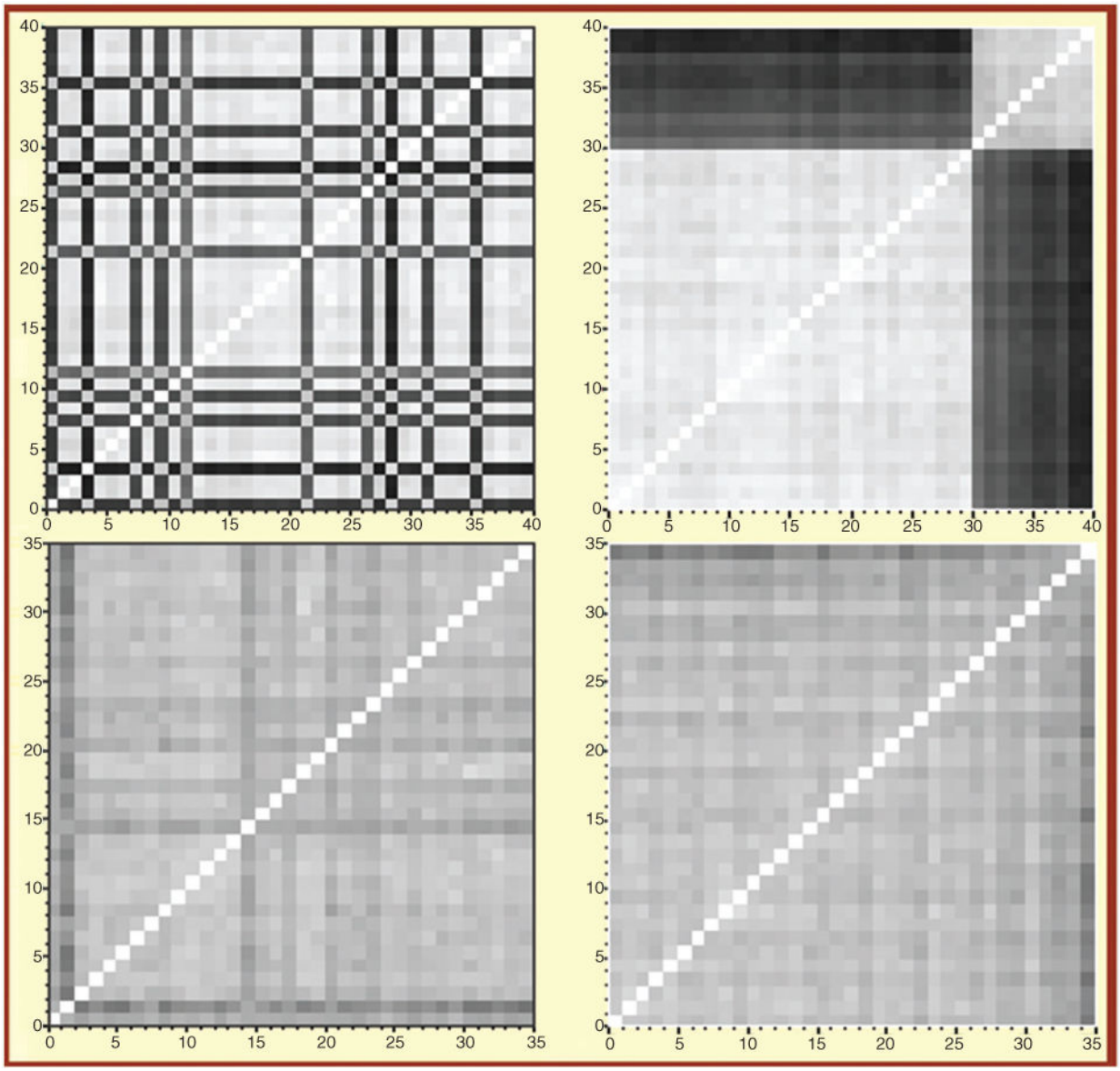

Figure 2.

Genome-wide allelic dissimilarity and genomic admixture of a Puerto Rican population (n=35), as compared to a reference population from Kentucky (n=40, including European- and African-Americans).

Plot depicts allelic dissimilarities as a distance matrix for reference (top) and Puerto Ricans (bottom). Each square represents a pair of individuals. Data are shown with samples reordered according to nearest neighbor clustering (right panels) and random order (left panels). The darker the spot, the more genetically distant the individuals are.

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Table 1

Distribution of *CYP2C9* allelic variants among Hispanics.

Population	N[a]	*1	*2	*3	*4	*5	*6	*8	*11	*13	Reference
Mexican-Americans	98	0.86	0.08	0.06							[46]
Mexican-Americans	193		0.070	0.044	0.00	0.00	0.00				[47]
Hispanics (mostly Mexican-Americans)	50		0.09	0.06							[48]
Mexican-Americans	38	0.86	0.08	0.06							[49]
Mexican-Tapehuana	99		0.01	0.015							[50]
Mexican-Mestizos	102		0.07	0.015							[50]
Puerto Ricans	100	0.701	0.0652	0.0543	0.000	0.000	0.0054				[51]
Puerto Ricans	163	0.840	0.107	0.043		0.01					[52]
Puerto Ricans	103	0.748	0.189	0.053		0.01					[53]
Puerto Ricans	55		0.173	0.036		0.009		0.009			[45]
Cuban-whites	132	0.720	0.170	0.110	0.000	0.000	0.000	0.004			[54]
Cuban-mestizos	128	0.830	0.060	0.090	0.000	0.004	0.000	0.020			[54]
Hispanics	202	0.822	0.069	0.064	0.000	0.015	0.005	0.015	0.010	0.000	[55]
Hispanics	22	0.93	0.000	0.070							[56]

[a]Number of individuals.

Table 2

Distribution of *CYP2C19* allelic variants among Hispanics.

Population	N[a]	*1	*2	*3	*4	*5	*6	*7	*8	*9	*17	Reference
Puerto Ricans	100		0.09	0.000								[66]
Puerto Ricans	122		0.139	0.000								[67]
Puerto Ricans	55		0.127	0.000	0.009					0.009	0.145	[45]
Mexican-Americans	346	0.902	0.097	0.001	0.000	0.000	0.000	0.000	0.000			[64]
Hispanics	250	0.704	0.128	0.000	0.000–0.002	0.000	0.000	0.000	0.004	0.002	0.152	[69]

[a]Number of individuals.

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Table 3

Distribution of *CYP2D6* allelic variants among Hispanics.

Population	N[a]	*1	*2	*3	*4	*5	*6	*7	*8	*9	*10	*11	*14	*17	*29	*31	*35	*40	*41	*45	*46	Multi-plications[b]	Reference
Puerto Ricans	45	0.378	0.189	0.000	0.122	0.033	0.000			0.033	0.044			0.033	0.011	0.022	0.011	0.022	0.10			0.00	[79]
Puerto Ricans	100										0.09												[66]
Puerto Ricans	55				0.173						0.200			0.409					0.155	0.000			[45]
Cubans[c]	256	0.663–0.754	0.663–0.754	0.000	0.143–0.146	0.016–0.019	0.008–0.012				0.004–0.008			0.027–0.102								0.038–0.047 (wt) 0.00–0.004 (*4)	[80]
Mexican-Americans	264	0.550	0.180	0.002	0.100	0.017	0.004	0.000	0.000	0.011	0.028	0.000	0.000	0.002	0.002				0.05	0.000	0.000	0.008	[81]
Mexican-Americans	50			0.000	0.170	0.020	0.000	0.000	0.000		0.010			0.020								0.030	[82]
Mexican-Americans	349		0.228	0.003	0.103	0.023	0.000				0.074			0.007								0.010	[83]

[a] Number of individuals.

[b] Multiplications may refer to two copies or more. In Cubans, the frequency of multiplications studied by Llerena and Dorado was reported in conjunction with the presence of wild-type or *4. Frequency for multiplications with the wild-type allele was 0.038 to 0.047 and with *4 was 0 to 0.004. Gene duplications studied by Gonzâlez-Tejera et al. were *1XN, *2XN, *4XN, *10XN, *17XN, *35XN, and*41XN.

[c] MAFs for the Cuban population were reported as Cuban-whites and Cuban-mestizos; therefore, values in the table are expressed in ranges that comprise values among all Cuban population.

Table 4

Distribution of *CYP3A4/5* allelic variants among Hispanics of undetermined ethnicities and Puerto Ricans.

Population	N[a]	*CYP3A4*1B*	*CYP3A5*3*	*CYP3A5*6*	Reference
Hispanics	27	0.20	0.84		[93]
Hispanics	15	0.40	0.867		[94]
Hispanics	~149		0.760		[95]
Hispanics	55	0.164	0.245		[96]
Hispanics	188	0.093			[97]
Hispanics	334		0.700	0.040	[96]
Puerto Ricans	55	0.20	0.764		[45]

[a]Number of individuals.

Table 5

Distribution *of NATI, NAT2,* and GST allelic variants among Hispanics of undetermined ethnicities and Puerto Ricans.

Population	N[a]	*NAT1*3*	*NAT1*4*	*NAT*10*	*NAT2*5*	*NAT2*5A*	*NAT2*5B*	*NAT2*5C*	*NAT2*6*	*NAT2*7*	*NAT2*7B*	*NAT2*11*	*NAT2*12A*	*NAT2*13*	*GSTM1*0*	Reference
Hispanics	157	0.489		0.497	0.327				0.196	0.120		0.323		0.300		[100]
Hispanics	496		0.289–0.314			0.004–0.006	0.355–0.359	0.002–0.012			0.076–0.092		0.014–0.024	0.002–0.010		[102]
Hispanics	296								0.170–0.190	0.100–0.170		0.230–0.320				[103]
Puerto Ricans	55	0.309			0.400				0.200	0.091		0.373		0.300		[45]
Hispanics	146														0.400	[104]

[a]Number of individuals.

Table 6

Distribution of *UGT2B7* allelic variants among Puerto Ricans and Mexican-Americans.

Population	N[a]	UGT2B7 (*rs7662029*)	UGT2B7 (*rs73823859*)	UGT2B7 (*rs7668282*)	UGT2B7 (*rs12233719*)	UGT2B7 (*rs62298861*)	UGT2B7 (*rs7439366*)	UGT2B7 (*rs57913007*)	Reference
Puerto Ricans	55	0.400	0.055	0.027	0.009	0.236	0.409	0.055	[45]
Mexican-Americans	66	0.265	0.038	0.008	0.008	0.432	0.311	0.038	[45]

[a]Number of individuals.