Prevalence of pharmacogenomic variants affecting the efficacy of clopidogrel therapy in the Hispanic Community Health Study/Study of Latinos cohort

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Purpose: Although clopidogrel is the most widely used oral P2Y12 receptor antagonist, up to 10% of acute coronary syndrome patients treated with clopidogrel will experience a recurrent myocardial infarction and 2–3% will experience stent thrombosis within 1 year. The purpose of this research is to describe the prevalence of pharmacogene variants associated with clopidogrel responsiveness (*CYP2C19, B4GALT2, ABCB1, PON1, CES1* and *P2RY12*) in Hispanic/Latino patients of diverse backgrounds. **Methods:** Minor allele frequencies of nine variants from participants of Hispanic Community Health Study/Study of Latinos were compared between subpopulations as well as to continental ancestry references using z-test for independent proportions. **Results:** MAFs for six out of nine variants differed between Caribbean and Mainland subpopulations ($p < 0.05$). Compared with European reference group, MAFs of *ABCB1*, *CES1* and *PON1* were higher in Hispanic Community Health Study/Study of Latinos, whereas *B4GALT2* and *CYP2C19*2* and ** 17* were lower. **Conclusion:** Significant differences in the prevalence of most pharmacogenomic variants related to clopidogrel response provide a foundation to better inform ongoing and future clinical studies of clopidogrel pharmacogenetics in the US Hispanic/Latino populations.

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Antiplatelet therapy is pivotal in the acute and long-term treatment of patients with acute coronary syndrome (ACS) following percutaneous coronary intervention [1–3]. The robust clinical trial data supporting the benefit of dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 receptor antagonist has made this regimen the cornerstone for the acute treatment and secondary prevention of atherothrombotic events. Clopidogrel is the most widely used oral P2Y12 receptor antagonist, largely attributed to its lower cost as a generic drug in the US [4,5]. However, although clinical trials have shown the benefit of DAPT, up to 10% of acute coronary syndrome patients on aspirin + clopidogrel will experience a recurrent myocardial infarction (MI) within 1 year, with 2–3% experiencing stent thrombosis [6].

Genes involved in drug metabolism and activity differ in frequency among ancestral populations [7,8]. When compared with non-Hispanic Whites, Hispanics have different responses to some cardiovascular (CV) drugs, a higher recurrence rate of thrombotic events and worse CV outcomes [9,10]. Further worsening CV risk, several

studies have shown that patients of minority racial groups with CV disease are less likely to be treated with evidence-based medications and were less compliant with secondary prevention medications [11–15]. Notably, there is limited data on antiplatelet drug response in Hispanics, who are often under-represented in clinical studies of antiplatelet agents.

The poor response to DAPT in some patients has been attributed to variability in clopidogrel responsiveness. In fact, evidence suggests up to 73% of the variability in clopidogrel response is heritable [16]. Among the genetic contributors to this variability, variants located within the *CYP2C19* locus have most consistently shown to affect clopidogrel activity and impact clinical outcomes [16,17]. In particular, the *CYP2C19*2* and **3* alleles confer loss of enzyme function which leads to attenuated bioactivation of clopidogrel and increased platelet reactivity. Numerous studies have confirmed a gene-dose effect of *CYP2C19* loss of function (LOF) alleles on ischemic outcomes, primarily in Caucasian populations. As a result, the clopidogrel label was revised twice by the US FDA to include 'diminished effect in poor metabolizers' [18]. Importantly, racial differences in the distribution of *CYP2C19* polymorphisms have been demonstrated [10,17,19], as has a tendency for higher levels of markers of platelet reactivity among African ancestry patients compared with non-Hispanic Whites [20].

Beyond the *CYP2C19* locus, several other gene variants may be predictors of poor outcomes for patients treated with clopidogrel. The *ABCB1* C3435 polymorphism has been associated with reduced bioavailability and increased the risk of CV death, MI or stroke for patients taking clopidogrel [21]. More recently, genetic variation in *B4GALT2* has been identified as contributing to reduced pharmacodynamic response to the drug, although the effect on clinical outcomes has not yet been documented [22]. Additional reports of polymorphisms in other genes (e.g., *P2RY12*, *CES1*, *PON1*) may also affect clopidogrel responsiveness, but further studies are warranted [23]. Again, such data from Hispanics are scarce.

The aim of this study is to determine the frequency of clinically relevant *CYP2C19, B4GALT2, ABCB1, PON1, CES1* and *P2RY12* allele/haplotype variants and genotypes in the Hispanic/Latino population in the USA. Individuals who identify as Hispanic/Latino possess a complex genetic structure reflecting a trihybrid admixture as a result of widespread geographic origins within the Americas and variation in patterns of immigration from other continents such as Europe and Africa [24–26]. There is a high and variable degree of admixture, and the percentage of contribution of each ancestry may vary substantially across Hispanic populations (i.e., ethno-geographic regions). We hypothesized that due to this significant genetic heterogeneity in the US Hispanic population, the prevalence of SNPs of clinically relevant pharmacogenes would vary significantly across Hispanic backgrounds as well as differ from that previously established in non-Hispanic, white populations. We stratified the Hispanic/Latino population by national background and region of origin, expecting to find genetic differences that might be attributed to admixtures of Amerindian, African and European backgrounds. Describing these genetic differences will help better understand the utility of genetic testing for personalized antiplatelet therapy in US Hispanics with the goal of preventing future adverse CV events in clopidogrel-resistant patients.

Methods

To measure the frequency of the genetic variants of interest (Table 1), we performed a cross-sectional study of the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) cohort. Genetic variants of interest were those with previously documented effects on individual response to clopidogrel based upon Clinical Annotations from PharmGKB database [23]. This study is the largest Hispanic/Latino cohort study to date with over 16,000 participants recruited from four US metropolitan areas: the Bronx, San Diego, Chicago and Miami [27]. The primary goals of HCHS/SOL are to identify risk factors for multiple diseases and determine the role of genes and environment, including acculturation, in the occurrence of diseases. The full details of the HCHS/SOL sample design and cohort selection have previously been described [27,28]. Adult Hispanic/Latino participants aged 18–74 from a random sample of households were recruited between 2008 and 2011. Participants have various self-reported backgrounds, with the primary groups being Central American, Cuban, Dominican, Mexican, Puerto Rican and South American. In order to resolve participants who reported multiple backgrounds or who declined to identify a national background, we used genetic ancestry markers to stratify the HCHS/SOL population into genetic analysis groups [26]. The six genetic analysis groups were further classified into two regional groups: Mainland (Mexican, Central American and South American) and Caribbean (Cuban, Dominican and Puerto Rican). Ethical oversight of HCHS/SOL activities was conducted by the Institutional Review Boards of each field center as well as the study coordinating center. All participants included in this analysis provided written informed consent for genetic studies at their baseline visit to a HCHS/SOL field site.

Table 1. Genetic variants affecting clopidogrel response.

Gene	SNP	Synonym	Sub	Potential clinical effect[†]
ABCB1	rs1045642	c.3435	A > G	↓bioavailability ↓drug response ↑MACE
B4GALT2	rs1061781	c909	C > T	↓drug response
CES1	rs8192950	CES1	T > G	↑ risk of TIA
CYP2C19	rs12248560	*CYP2C19*17*	C > T	↑ bioavailability
CYP2C19	rs4244285	*CYP2C19*2*	G > A	↓ bioavailability ↑MACE
CYP2C19	rs4986893	*CYP2C19*3*	G > A	↓ bioavailability ↑MACE
CYP2C19	rs28399504	*CYP2C19*4*	A > G	↓ bioavailability ↑MACE
P2RY12	rs2046934	Haplotype 2	G > A	↓drug response
PON1	rs662	Q192R	T > C	↑MACE

[†]Potential clinical effects based upon Clinical Annotations from PharmGKB database [23].
Sub: Nucleotide substitution.

Procedures

All genotypic information from HCHS/SOL was extracted from blood specimens collected at baseline and analyzed using a custom version of the Illumina HumanOmni2.5-8v1-1 array, consisting of ~150,000 custom variants added to the standard Omni2.5M array selected to include ancestry-informative markers, variants characteristic of Amerindian populations [26]. Genotype data cleaning (missing call rate, Mendelian errors, duplicate-sample discordance and deviation from Hardy–Weinberg equilibrium ($p < 10^{-5}$ in a meta-analysis of genetic backgrounds) and imputation analyses were previously performed at the HCHS/SOL Genetic Analysis Center at the University of Washington. In this study, frequency distributions of observed genotypes in genetically unrelated individuals consenting to genetic studies were compared within subgroups in the HCHS/SOL population as well as to the frequencies reported for various continental ancestry populations from Phase III of the 1000 Genomes project [29]. These reference populations were used to better compare the observed prevalence in HCHS/SOL with populations representative of the following continental ancestry groups: Africa, Americas, east Asia, Europe and south Asia. Of note, the reference population that might closely resemble the HCHS/SOL population is the Americas population: a composite of Puerto Ricans in Puerto Rico; Colombian in Medellin, Colombia; Peruvian in Lima, Peru; and Mexican Ancestry in Los Angeles, CA, USA.

Statistical Analysis

The variants were tested for Hardy-Weinberg equilibrium (HWE) for each genetic analysis group by χ^2 goodness-of-fit test or alternatively Fisher's Exact test for frequencies lower than 5% as the departure from HWE indicates potential genotyping error. A threshold of $p < 10^{-5}$ was chosen because SNPs with p-value below this threshold were frequently artifacts in the genetic data of the HCHS/SOL while those above were not from the genotype cluster plots. For those variants satisfying the HWE, the allele frequency and its 95% CI of genetic variants were estimated for six genetic analysis groups and two regional groups in genetically unrelated individuals in HCHS/SOL population. Frequency distributions were compared between the two regional groups in HCHS/SOL and between these regional groups in HCHS/SOL and reference continental ancestry groups using z-test for independent proportions with statistical significance determined by p-value < 0.05.

Results

The demographic makeup of the HCHS/SOL cohort has been previously reported [30,31]. Genetic data were available for 12,633 participants who agreed to participate in genetic studies of HCHS/SOL and 10,496 unrelated individuals were included in our final analysis (after removing related individuals). All nine of the genetic variants of interest were found to be HWE for each self-identified background group. Table 2 reports the minor allele frequencies (MAFs) for the genetic variants of interest related to the activity of clopidogrel across each of the HCHS/SOL subgroups. MAFs for six out of nine pharmacogene variants differed significantly between the Caribbean Hispanic and Mainland Hispanic groups (Table 3). We observed a higher prevalence in Caribbean Hispanics of *ABCB1*

Table 2. Minor allele frequencies of genetic variants across Hispanic Community Health Study/Study of Latinos Region subgroups.

Genetic variant	*ABCB1* c.3435	*B4GALT2* c909	*CES1* rs8192950	*CYP2C19*2*	*CYP2C19*3*	*CYP2C19*4*	*CYP2C19*17*	*PON1*	*P2RY12* H2[†]
Caribbean Hispanics n = 4770[‡]	0.615	0.090	0.598	0.137	0.001	0.004	0.181	0.432	0.873
	(0.605–0.625)	(0.085–0.096)	(0.588–0.608)	(0.130–0.144)	(0.000–0.001)	(0.003–0.005)	(0.173–0.188)	(0.422–0.442)	(0.867–0.880)
Cuban n = 1965	0.597	0.110	0.645	0.196	0.135	0.001	0.004	0.371	0.865
	(0.582–0.613)	(0.100–0.119)	(0.630–0.659)	(0.184–0.209)	(0.124–0.146)	(0.000–0.002)	(0.002–0.005)	(0.356–0.386)	(0.854–0.875)
Dominican n = 942	0.660	0.081	0.501	0.156	0.001	0.005	0.179	0.516	0.876
	(0.638–0.681)	(0.069–0.094)	(0.478–0.523)	(0.139–0.172)	(–0.001–0.002)	(0.002–0.009)	(0.162–0.197)	(0.493–0.538)	(0.861–0.891)
Puerto Rican n = 1863	0.611	0.074	0.598	0.130	0.001	0.003	0.165	0.454	0.882
	(0.595–0.626)	(0.066–0.083)	(0.583–0.614)	(0.119–0.140)	(0.000–0.002)	(0.001–0.005)	(0.153–0.177)	(0.438–0.470)	(0.871–0.892)
Mainland Hispanics n = 5726[§]	0.545	0.087	0.667	0.111	0.000	0.002	0.107	0.484	0.892
	(0.535–0.554)	(0.082–0.093)	(0.659–0.676)	(0.105–0.117)	(0.000–0.001)	(0.002–0.003)	(0.102–0.113)	(0.475–0.493)	(0.886–0.897)
Central American n = 1182	0.529	0.080	0.672	0.090	0.000	0.001	0.110	0.483	0.896
	(0.509–0.549)	(0.069–0.091)	(0.653–0.691)	(0.078–0.101)	(0.000–0.001)	(0.000–0.002)	(0.098–0.123)	(0.463–0.503)	(0.884–0.908)
Mexican n = 4670	0.548	0.090	0.666	0.117	0.000	0.003	0.106	0.490	0.892
	(0.537–0.560)	(0.084–0.096)	(0.655–0.677)	(0.110–0.124)	(0.000–0.001)	(0.002–0.004)	(0.099–0.113)	(0.479–0.501)	(0.885–0.899)
South American n = 772	0.551	0.087	0.666	0.116	0.000	0.003	0.109	0.457	0.886
	(0.526–0.575)	(0.073–0.101)	(0.642–0.689)	(0.100–0.132)	(0.000–0.000)	(0.000–0.005)	(0.093–0.124)	(0.432–0.482)	(0.870–0.902)
Total HCHS/SOL n = 10,496	0.577	0.089	0.636	0.123	0.000	0.003	0.141	0.461	0.883
	(0.570–0.583)	(0.085–0.093)	(0.629–0.642)	(0.118–0.127)	(0.000–0.001)	(0.002–0.004)	(0.136–0.145)	(0.454–0.467)	(0.879–0.888)

95% CIs for each MAF are provided in parenthesis.
[†] tagSNP for calling (defining) the P2RY12 haplotype 2.
[‡] Caribbean Hispanics is a composite group of Cuban, Dominican, and Puerto Rican.
[§] Mainland Hispanicsis a composite group of Central American, Mexican, and South American; Total HCHS/SOL is a composite of all previous subgroups.
MAF: Minor allele frequency.

Table 3. Minor allele frequencies of genetic variants of Hispanic Community Health Study/Study of Latinos Region Groups versus Reference Populations.

Genetic variant and MAF in HCHS/SOL (p-value for comparison)		1000 G African (n = 661)	1000 G American (n = 347)	1000 G east Asian (n = 504)	1000 G European (n = 503)	1000 G south Asian (n = 489)
ABCB1	MAF	0.850	0.572	0.602	0.482	0.425
MAF_{CH}: 0.615	p-val CH	**<0.001**	**0.028**	0.451	**<0.001**	**<0.001**
MAF_{MH}: 0.545 ($p < 0.001$)	p-val MH	**<0.001**	0.171	**<0.001**	**<0.001**	**<0.001**
B4GALT2	MAF	0.048	0.078	0.153	0.100	0.098
MAF_{CH}: 0.090	p-val CH	**<0.001**	0.298	**<0.001**	0.316	0.448
MAF_{MH}: 0.087 ($p = 0.497$)	p-val MH	**<0.001**	0.418	**<0.001**	0.186	0.285
CES1	MAF	0.769	0.467	0.812	0.362	0.649
MAF_{CH}: 0.598	p-val CH	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.002**
MAF_{MH}: 0.667 ($p < 0.001$)	p-val MH	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.269
*CYP2C19*2*	MAF	0.170	0.105	0.313	0.145	0.358
MAF_{CH}: 0.137	p-val CH	**0.001**	**0.021**	**<0.001**	0.501	**<0.001**
MAF_{MH}: 0.111 ($p < 0.001$)	p-val MH	**<0.001**	0.666	**<0.001**	**0.001**	**<0.001**
*CYP2C19*3*	MAF	0.002	0.000	0.056	0.000	0.012
MAF_{CH}: 0.001	p-val CH	0.215	0.999	**<0.001**	0.829	**<0.001**
MAF_{MH}: 0.000 ($p = 0.214$)	p-val MH	**0.012**	0.999	**<0.001**	0.999	**<0.001**
*CYP2C19*4*	MAF	0.000	0.003	0.001	0.001	0.000
MAF_{CH}: 0.004	p-val CH	**0.048**	0.960	0.254	0.255	0.102
MAF_{MH}: 0.002 ($p = 0.107$)	p-val MH	0.136	0.999	0.564	0.566	0.231
*CYP2C19*17*	MAF	0.235	0.120	0.015	0.224	0.136
MAF_{CH}: 0.181	p-val CH	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.001**
MAF_{MH}: 0.107($p < 0.001$)	p-val MH	**<0.001**	0.343	**<0.001**	**<0.001**	**0.007**
PON1	MAF	0.753	0.499	0.666	0.290	0.424
MAF_{CH}: 0.432	p-val CH	**<0.001**	**<0.001**	**<0.001**	**<0.001**	0.662
MAF_{MH}: 0.484 ($p < 0.001$)	p-val MH	**<0.001**	0.486	**<0.001**	**<0.001**	**<0.001**
P2RY12 H2†	MAF	0.873	0.899	0.848	0.827	0.900

CH = Caribbean Hispanics (n = 5661); MAF_{CH} stands for MAF in Caribbean Hispanics; p-val CH stand for p-value for comparison between Caribbean Hispanics and reference population; MH = Mainland Hispanics (n = 6,972); MAF_{MH} stands for MAF in Mainland Hispanics; p-val MH stand for p-value for comparison between Mainland Hispanics and reference population; 1000 G = 1000 Genomes Phase III Superpopulation;
†tagSNP for calling (defining) the P2RY12haplotype 2.
MAF: Minor allele frequency.
Note: Statistically significant differences between groups (p-value < 0.05) are indicated with bold.

c.3435 and *CYP2C19*2*(previously associated with poorer treatment outcomes) and *CYP2C19*17* (associated with increased clopidogrel bioavailability) [16,17,21]. Mainland Hispanics, however, had a higher prevalence of *CES1* (rs8192950), *PON1* Q192R and *P2RY12* haplotype 2 (all associated with decreased platelet inhibition and/or poorer treatment outcomes) [23].

Table 3. Minor allele frequencies of genetic variants of Hispanic Community Health Study/Study of Latinos Region Groups versus Reference Populations (cont.).

Genetic variant and MAF in HCHS/SOL (p-value for comparison)		1000 G African (n = 661)	1000 G American (n = 347)	1000 G east Asian (n = 504)	1000 G European (n = 503)	1000 G south Asian (n = 489)
MAF_{CH}: 0.873	p-val CH	0.989	0.056	**0.026**	**<0.001**	**0.020**
MAF_{MH}: 0.892 ($p < 0.001$)	p-val MH	**0.042**	0.588	**<0.001**	**<0.001**	0.472

CH = Caribbean Hispanics (n = 5661); MAF_{CH} stands for MAF in Caribbean Hispanics; p-val CH stand for p-value for comparison between Caribbean Hispanics and reference population; MH = Mainland Hispanics (n = 6,972); MAF_{MH} stands for MAF in Mainland Hispanics; p-val MH stand for p-value for comparison between Mainland Hispanics and reference population; 1000 G = 1000 Genomes Phase III Superpopulation;
†tagSNP for calling (defining) the P2RY12haplotype 2.
MAF: Minor allele frequency.
Note: Statistically significant differences between groups (p-value < 0.05) are indicated with bold.

For the purposes of comparison with the continental reference populations, data were available for 2504 unrelated individuals from the 1000 Genomes project. Significant differences were observed for all genetic variants between both regional groups from HCHS/SOL and other continental groups (Table 3), apart from *CYP2C19*4*. Both Mainland and Caribbean HCHS/SOL regional groups had lower MAFs for *CYP2C19* genetic variants associated with poorer treatment outcomes but higher MAFs for *ABCB1* c.3435 when compared with the European continental group.

Discussion

Our cross-sectional study describes the frequency distribution of nine relevant pharmacogenetic markers in six candidate pharmacogenes associated with clopidogrel effectiveness. To our knowledge, this is the largest such descriptive study of these variants in the US Hispanic/Latino population. As can be observed in Table 2, MAFs varied significantly within the HCHS/SOL subpopulations. For many of the variants, important differences between the regional groups of Caribbean Hispanics/Latinos and Mainland Hispanics/Latinos emerged. As such, we chose to compare the MAFs for each of these regional groups independently to the continental reference populations from 1000 Genomes.

For these comparisons, the American continental superpopulation of Phase III of 1000 Genomes might have been expected to be the closest estimate of the HCHS/SOL. Nonetheless, we observed statistically significant differences in MAFs in five of the nine variants of interest when comparing the Caribbean Hispanic/Latino population of HCHS/SOL to this American continental group. When comparing the Mainland Hispanic/Latino population, only one variant (*CES1*) differed significantly from this reference population. This suggests that data from the American continental group of Phase III of 1000 Genomes may not be the best proxy for prevalence of pharmacogenes in Caribbean Hispanics/Latinos living in the US.

CYP2C19 locus

As has been previously reported, loss of function (LOF) alleles of the *CYP2C19* pharmacogene are most strongly associated with decreased efficacy and poorer CV outcomes [17,21] In the HCHS/SOL cohort, we observed a 3% absolute increase in the MAFs of these LOF alleles in the Caribbean Hispanic population compared with Mainland Hispanics. However, we also observed a 7% absolute increase in the *CYP2C19*17* gain of function allele in this population as well. Although data on the mixed **2–*8/*17* is limited, current evidence suggests the **17* increased function allele is unable to completely compensate for the **2* LOF allele, thus suggesting the Caribbean Hispanic population may be at an increased risk of treatment failure compared with Mainland Hispanics due to genetic variation in the *CYP2C19* pharmacogene. The *CYP2C19*3* LOF allele was rare across all subgroups of the HCHS/SOL population, consistent with the 1000 Genome data that this allele is not usually found outside the East Asian population. The *CYP2C19*4* LOF allele, although rare, was observed at rates consistent with the American continental group from 1000 Genomes. Interestingly, the highest observed MAF for this LOF allele was in the Dominican subgroup of HCHS/SOL (a group not included in the American superpopulation of 1000 Genomes).

ABCB1 locus

Although there is less data on the *ABCB1* c.3435 allele (rs1045642) than that which exists for the *CYP2C19* locus, it too may contribute to poor clopidogrel responsiveness and CV outcomes [21,32]. In fact, one of the few pharmacogenomic outcome studies conducted in a Hispanic/Latino population (Mexican) demonstrated an association with rs1045642 and poor platelet response to clopidogrel [32]. Interestingly, this previous study presented a lower frequency of the allele (44%) compared with our observed 55% in the Mexican subgroup of HCHS/SOL. Furthermore, we observed a 7% absolute increase in the MAF of this allele in Caribbean Hispanics when compared with Mainland Hispanics. Compared with the 1000 Genome continental groups, Caribbean Hispanics had the second highest prevalence of this allele behind only Africans as Caribbean Hispanics have higher proportion of African genetic ancestry than Mainland Hispanics.

B4GALT2, CES1, PON1 & *P2RY12* Loci

Although several studies have examined the association between polymorphisms in *B4GALT2, CES1, PON1* and *P2RY12*, data is inconsistent regarding their significance in clinical outcomes. Nonetheless, we observed a great amount of variability in the MAFs for these variants between Caribbean and Mainland Hispanics as well as when compared with other continental groups. In particular, the 24–31% absolute increase in prevalence of *CES1* (rs81929500) compared with the European continental group is noteworthy. Similarly, an 14–19% absolute increase was also observed for the T allele of *PON1* (rs662). Ongoing clinical studies of clopidogrel effectiveness in Hispanic/Latino populations will help further elucidate the significance of these variants in this population [33].

Study limitations

Our study has several limitations. First, because HCHS/SOL recruits from four major urban areas in the continental US, the cohort may not necessarily be representative of the overall US Hispanic/Latino population. However, as the largest US Hispanic/Latino cohort to date, we believe the prevalence data reported are robust. Additionally, the pharmacogene variants of interest described in this study are based on clinical trial and genetic association studies comprising primarily white, North American and European patient populations. Therefore, it is possible that these variants may not confer the same magnitude of clinical effect in other continental ancestry groups, including Hispanic/Latinos. Ongoing clinical studies in this patient population should further define the effect of these pharmacogene variants on clopidogrel effectiveness.

Conclusion

In summary, we describe the prevalence of nine allelic variants and resulting genotypes in six pharmacogenes (*ABCB1, B4GALT2, CES1, CYP2C19, PON1* and *P2RY12*) in the HCHS/SOL cohort and compare them to continental reference populations to reveal genetic differentiation with regard to clopidogrel response among these groups. Our comparison between Mainland and Caribbean regional groups highlights the genetic differences even within the US Hispanic/Latino population, often considered and labeled as a monolithic group.

Future perspective

Poor response to clopidogrel in some patients is due to the highly heritable variability in clopidogrel responsiveness. In this report, we describe the diversity in prevalence of genotypes in six relevant pharmacogenes to clopidogrel responisveness in HCHS/SOL. These data provide a foundation to better inform ongoing and future clinical studies of clopidogrel pharmacogenetics in the US Hispanic/Latino populations.

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Ethical disclosure

The authors state that they have obtained appropriate institutional review board approval. Ethical oversight of all HCHS/SOL activities was conducted by the Institutional Review Boards of each field center as well as the study coordinating center. All participants included in this analysis provided written informed consent for genetic studies at their baseline visit to a HCHS/SOL field site

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