Pharmacogenomic assessment of Mexican and Peruvian populations

Sharon Marsh*,1,2, Cristi R King3, Derek J Van Booven2,4, Jane Y Revollo5, Robert H Gilman6, and Howard L McLeod2,7
1Faculty of Pharmacy & Pharmaceutical Sciences, 3142F Katz Centre for Pharmacy & Health Research, University of Alberta, Edmonton, AB T6G2E1, Canada
2Pharmacogenetics for Every Nation Initiative, Tampa, FL, USA
3Department of Biomedical Engineering, Washington University in St Louis, St Louis, MO, USA
4John P Hussman Institute for Human Genomics, University of Miami Miller School of Medicine, Miami, FL, USA
5Department of Pharmacy, Jackson Memorial Hospital, Miami, FL, USA
6Johns Hopkins University, Bloomberg School of Public Health, Department of International Health, Baltimore, MD, USA
7Moffitt Cancer Center, Tampa, FL, USA

Abstract

Background—Clinically relevant polymorphisms often demonstrate population-specific allele frequencies. Central and South America remain largely uncategorized in the context of pharmacogenomics.

Materials & methods—We assessed 15 polymorphisms from 12 genes (ABCB1 3435C>T, ABCG2 141K, CYP1B1*3, CYP2C19*2, CYP3A4*1B, CYP3A5*3C, ERCC1 N118N, ERCC2 K751Q, GSTP1 1105V, TPMT 238G>C, TPMT 460G>A, TPMT 719A>G, TYMS TSER, UGT1A1*28 and UGT1A1 −3156G>A) in 81 Peruvian and 95 Mexican individuals.

Results—Six polymorphism frequencies differed significantly between the two populations: ABCB1 3435C>T, CYP1B1*3, GSTP1 1105V, TPMT 460G>A, UGT1A1*28 and UGT1A1 −3156G>A. The pattern of observed allele frequencies for all polymorphisms could not be accurately estimated from any single previously studied population.

Conclusion—This highlights the need to expand the scope of geographic data for use in pharmacogenomics studies.

*Author for correspondence: Tel.:+1 780 492 2266, Fax:+1 780 492 3175, smarsh1@ualberta.ca.

Financial & competing interests disclosure
This work was supported in part by the NIH Pharmacogenetics Research Network (GM63340), the Pharmacogenetics for Every Nation Initiative and the Global Research Training Fund of the Fogarty International Center of the NIH. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.
Clinically relevant DNA polymorphisms have significantly variable allele frequencies among different world populations [1–7]. However, many areas of the world are under-represented in current pharmacogenomics research [8,9]. Organizations such as the Pharmacogenetics for Every Nation Initiative are attempting to redress this balance by collecting country and region-specific data on pharmacogenomically relevant polymorphisms to ensure rational medication selection not based on Western European data [2,8–13].

Hispanic populations represent an important challenge for pharmacogenomics. Mexico is the 11th most populous nation in the world, and Mexican–Americans comprised 10.9% of the US population as of 2010 [14]. With over 30 million people of Mexican descent living in North America, this population is too large to be ignored by researchers. Approximately 60% of Mexicans classify themselves as Mestizo, with an ancestry that includes both Amerindians and Europeans. Another 30% are of Amerindian descent and 9% self-classify as white [15]. A study of Texas Hispanics (90% Mexican–Americans) calculated the degree of admixture to be approximately 36% Amerindian and 64% European [16]. Such a significant non-European genetic contribution to the Mexican population makes inferences based on European–American pharmacogenomic data problematic [17].

Peru has a population of approximately 30.15 million people. The major ethnic groups are 45% Amerindian, 37% Mestizo (mixed Amerindian and white) and 15% white, with the remaining 3% made up from Japanese, Chinese and African ethnicities [18]. A study of 25 regions of Peru found different levels of European ancestry depending on location [19]. As with the Mexican population this admixture provides a distinct population [20–22] that does not allow for assumptions from existing data for any one ethnic group.

Even generalizations across Hispanic groups are not viable. Both admixture levels and disease prevalence vary across Central and South America. For example, in New Jersey, where the majority of the Hispanic population is of Puerto Rican descent, the relative genetic contributions of Europeans, Amerindians and Africans are approximately 85%, 9% and 6%, respectively [16]. This variation in admixture correlates with real clinical problems. Puerto Ricans have the highest asthma rates in the US while Mexican–Americans have the lowest, and a meta-analysis has shown that Hispanics with African ancestry are at risk for more severe asthma in both Mexican–American and Puerto Rican American populations [23].

There is a paucity of pharmacogenomics data for Hispanic populations. Indeed, the majority of Central and South America are largely uncharacterized in the pharmacogenomics literature [24]. Previous studies have shown that Mexican–Americans have lower frequencies of the CYP2D6*4 alleles than European populations, but similar CYP2E1 and CYP3A4 enzyme activity [24–26]. Significant differences between Mexican–American and Spanish populations have also been observed for the CYP2C9*2 polymorphism, with the
Spanish population carrying at least double the amount of \textit{CYP2C9}*2 alleles (16\% vs 8\% for Mexican–Americans, 7\% for Mexican-Mestizos and 1\% for Mexican-Tepehuanos) [27].

Even within genes assumptions cannot be made about allele frequencies based on previously studied populations. In the \textit{MTHFR} gene, two commonly studied polymorphisms (677 C>T and 1298A>C) showed inconsistent frequencies within the Mexican population. \textit{MTHFR} 677C>T had the highest reported frequency in Mexicans (58\%), significantly different from European (36.1–47.3\%) and West African (9\%) populations and was also high in Peruvians (46\%) [28]. In contrast, the \textit{MTHFR} 1298 A>C polymorphism had one of the lowest recorded frequencies in Mexico (14.7\%), similar to West African populations (13.9\%) and significantly differing from Europeans (28–36\%) [29]. In Amerindian Peruvians the \textit{MTHFR} 1298A>C frequency was rare (1.5\%) [30]. The \textit{ITPA} polymorphism, P32T, putatively responsible for toxicity from azathioprine therapy [31] is present at a similar frequency in Peruvians (1\%) and Mexicans (2\%) [32], which is significantly lower than other world populations studied for this polymorphism (5–19\%) [32].

Additionally, frequencies of polymorphisms and haplotypes for the warfarin pathway genes \textit{CYP2C9} and \textit{VKORC1} highlight that differences also occur between Peruvian and Mexican populations. The warfarin high-dose predictive allele \textit{VKORC1} Asp36Tyr was not found at all in Peruvians [33]. For warfarin low dose prediction, 45\% of Mexicans carried the \textit{CYP2C9}/\textit{VKORC1} genotype combination compared with only 28\% of Peruvians [6]. For this combination the Peruvians were most similar to the African populations (22–23\%) despite the low incidence of African admixture [20–22], and the Mexicans were closer to the Caucasian population (55\%) [6].

To further elucidate the pharmacogenomic similarities and/or differences within and between Hispanic and other world populations, we have assessed the allele frequencies of key polymorphisms in \textit{ABCB1}, \textit{ABCG2}, \textit{CYP1B1}, \textit{CYP2C19}, \textit{CYP3A4}, \textit{CYP3A5}, \textit{ERCC1}, \textit{ERCC2}, \textit{GSTP1}, \textit{TPMT}, \textit{TYMS} and \textit{UGT1A1} in Mexican and Peruvian individuals. These genes were selected because they are involved in the transport, metabolism, or are the target for at least 76 systemic drugs from the WHO Essential Medicines List [34], and the specific alleles have previously been identified as clinically relevant in more than one population. Whilst studies on polymorphisms in these genes in many populations have previously been reported (Supplementary Tables 1–3; see online at: www.futuremedicine.com/doi/supp/10.2217/pgs.15.10), this represents the first comparison of multiple pharmacogenomically relevant polymorphisms in Mexicans and Peruvians.

**Materials & methods**

**Population samples**

Genotyping was performed on genomic DNA from 81 healthy unrelated Peruvian volunteers (35 female, 44 male, 2 unknown) recruited as controls in a TB Vitamin D study [35], and 95 healthy unrelated Mexican individuals (50 female, 45 male) from the Coriell Institute [36]. The Mexican individuals were from Los Angeles, CA and defined as individuals with at least three Mexico-born grandparents [37]. This study was approved by the Washington University Human Studies Committee.
Genotyping

Genotypes for ABCB1 3435C>T, ABCG2 Q141K, CYP1B1*3, CYP2C19*2, CYP3A4*1B, CYP3A5*3C, ERCC1 N118N, ERCC2 K751Q, GSTP1 1105V, TPMT 238G>C, TPMT 460G>A, TPMT 719A>G, UGT1A1 −3156G>A and UGT1A1*28 were determined using PCR and Pyrosequencing® methodology as previously described [38–41]. The TYMS TSER polymorphism was assayed using PCR and agarose gel electrophoresis with primers and conditions as previously described [42].

Analysis

Hardy–Weinberg equilibrium was assessed using HWSIM [43]. TPMT variant allele frequencies were combined to determine the overall frequency of high-risk variants in the populations. Pairwise linkage (D') analysis for UGT1A1 was performed using the Polymorphism and Haplotype Analysis Suite [44]. Significant differences between Mexican and Peruvian genotype frequencies were assessed with χ² analysis using Statistica (StatSoft Inc. Tulsa, OK).

Results

All genotype frequencies were in Hardy–Weinberg equilibrium. Variant allele frequencies for all 15 polymorphisms in the Peruvian and Mexican populations were not universally similar to each other (Table 1) or any one population previously studied (Supplementary Tables 1–3). Six polymorphisms differed significantly between the Peruvian and Mexican populations in this study: ABCB1 3435C>T, CYP1B1*3, GSTP1 1105V, TPMT 460G>A, UGT1A1*28 and UGT1A1 −3156G>A (Table 1). Combined frequency of TPMT variant alleles was 0.1 in the Peruvian population and 0.06 in the Mexican population (predominantly TPMT*3A, an allele containing a combination of 719G>A and 460G>A for both populations). TPMT*2A (238G>C) was not observed in either population. Pairwise linkage analysis for UGT1A1*28 and −3156G>A indicated that the two alleles were in tighter linkage in the Mexican population (D' = 0.97; p < 0.001) than the Peruvian population (D' = 0.86; p < 0.001).

Discussion

The Peruvian and Mexican populations are both highly admixed and this is reflected in the lack of similarity to any one commonly genotyped population for the polymorphisms assessed in this study (Supplementary Tables 1–3). Even in this small-scale study, we found that the Mexican and Peruvian populations did not consistently demonstrate similar allele frequencies to each other or to other South American countries. This is understandable taking into account the differences in admixture between the two populations [15,18]. Of particular note is that previous studies in these populations also yielded differences in allele frequencies [6]. We postulate that the admixture in these populations makes basing assumptions on allele frequencies, even within countries, from existing pharmacogenomics data inaccurate. Even resources such as the 1000 Genomes Project [45,46], which uses family trios of LA Mexican samples and Peruvian family trios from Lima, do not accurately reflect the same allele frequencies found here. Consequently, any one source is not a viable
surrogate for an estimate of the likelihood of a clinically relevant polymorphism occurring in an individual in Peruvian or Mexican populations. It is important to not make assumptions based on previously published allele frequencies without further assessment of admixture and population comparisons within different regions of each country.

Mexicans born in Los Angeles demonstrated allele frequencies with the most similarities to previously studied European populations, specifically for ABCB1, CYP1B1, CYP2C19, CYP3A4 and TYMS (Supplementary Tables 1–3). However, both Mexicans and Peruvians were closer in allele frequencies to Asian populations for ERCCI N118N. UGT1A1 polymorphisms in Mexicans were similar to African population allele frequencies. The frequency of GSTP1 I105V in Mexicans was one of the highest reported globally. Peru tracked with Asian populations for ERCCI, African populations for ABCB1 and UGT1A1, Central/South American for CYP2C19, and European for CYP3A4 and CYP3A5 polymorphisms. GSTP1 I105V in Peruvians was similar to both European and Asian reported frequencies (Supplementary Table 3). For ABCG2 Q141K and ERCC2 K751Q Mexico and Peru had similar allele frequencies (Table 1); however, these were unrelated to previously reported populations apart from Pacific Islanders for ABCG2 (Supplementary Tables 1 & 3), highlighting that using existing population frequencies to represent different world populations would be erroneous.

Peru had one of the lowest reported frequencies of CYP2C19*2, a polymorphism important for predicting adverse events from clopidogrel [47], whereas the TPMT combined *2, *3A, *3B and *3C alleles demonstrated one of the highest frequencies (10%) in Peru of all the populations previously studied (1–11%; Supplementary Table 1). In this instance the Peruvian population was most similar to the Ghanaian and Bulgarian populations (11 and 8%, respectively) [48,49] and least similar to Asian populations (1–2%) [50,51]. This polymorphism has been assessed in several South American populations (Figure 1) [52–59]. The allele frequency in Mexicans (6%; Supplementary Table 1) was closest to Bolivians (6%) [52] and almost half of the frequency in Peruvians. The Peruvian TPMT data suggests caution when using azathioprine in Peruvian populations. Taking into account the low frequency of the clinically relevant ITPA polymorphism [32], the TPMT alleles are a likely cause of toxicity from azathioprine in up to one tenth of Peruvians. Genotyping should be considered prior to therapy selection in this population.

Likewise, UGT1A1 polymorphisms in Peru were among the highest previously reported (48% for both UGT1A1*28 and –3156G>A; Table 1), suggesting the Peruvian population would be at increased risk from drugs such as irinotecan, where these polymorphisms have shown significant associations with life-threatening toxicities [60]. As genotyping is suggested in the US prior to irinotecan dose selection, this should also be considered in Peruvian populations where available. A dose reduction in UGT1A1*28 patients could significantly reduce the impact and incidence of severe irinotecan-related toxicity.

The UGT1A1 −3156G>A polymorphism is in tight linkage with the UGT1A1*28 polymorphism in multiple populations [61,62]. However, in populations where the linkage between the two is diminished, as seen in the Peruvian population (D’ = 0.86), it may be important to genotype both variants to get an accurate profile of UGT1A1 activity. This

Pharmacogenomics. Author manuscript; available in PMC 2016 February 01.
difference in linkage highlights the need to comprehensively screen target populations before selecting haplotype tagSNPs to use as markers for association studies. Using public resources such as the International HapMap Project [63], which identified haplotypes in four populations (European Caucasian, Chinese, Japanese and Yoruba) to pre-select tagSNPs would likely miss-represent haplotypes in populations where the linkage disequilibrium blocks, and population-specific polymorphisms and mutations across genes/chromosomes are uncharacterized. Indeed, screening for causative mutations in open-angle glaucoma identified mutations in MYOC exon 3 in Peruvians that had previously been missed by sequencing other populations [64], supporting the need for caution when making assumptions based on previously published data.

**Conclusion**

This pilot study supports previous studies [17] that it is not possible to estimate the frequency of pharmacogenomic variants in Hispanic populations based on existing information from other populations. Nor can data from one Hispanic country be used to inform medical decision-making in another Hispanic country. The population admixture in Mexico [15] and Peru [18] has likely played an evolutionary role in diversifying allele frequencies and linkage disequilibrium, and caution should be exercised when making assumptions even within populations from different regions of the country [19]. Obviously, there are limitations with such a small sample set lacking in family cohorts and without a detailed population structure analysis on each sample. However, the lack of trend toward other commonly studied populations is clear even from a small-scale study. As the Hispanic population is a significant component of the World’s population [14], it should not be omitted from future large-scale genomics projects. The data presented here suggest that prior genotype testing of individuals should be considered before prescribing common therapeutics, such as azathioprine and irinotecan, in Mexican and Peruvian individuals.

**Future perspective**

Currently, drug development is mainly based on data from European-derived reference populations. The frequencies of key polymorphisms in the Peruvian and Mexican populations could not be predicted from knowledge of any one commonly studied ethnic group. This study demonstrates that it is essential to take into account a range of world populations when deriving global strategies for optimizing therapy regimens. For example, in the Peruvian population the high frequency of TPMT variant alleles (Figure 1) suggest an elevated toxicity risk from thiopurines. Genotyping every patient for panels of polymorphisms before any drug therapy will not be on the horizon in the majority of countries for some time [8,9,11]. However, polymorphism frequency cannot be extrapolated from similar countries or ethnic groups. Even within countries, population admixture can present with widely different genotype frequencies [27,65–67]. Knowledge of the frequency of functional polymorphisms in the patient’s representative population or subpopulation, compared with the frequencies observed in the reference populations used in drug development, is vital for enhancing the ability to make appropriate therapeutic decisions at a national level.
Acknowledgments

The efforts of D Berg and F Arenas, and the technical support of JB Phu, D Sara, RM Engen, HD Kannall, TJ Scott-Horton and MR Minton are greatly appreciated.

References

Papers of special note have been highlighted as:

•• of considerable interest


34. WHO Essential Medicines List. www.who.int/selection_medicines/list/en/


45. 100 Genomes Project: Peru. https://catalog.coriell.org

46. 1000 Genomes Project: Mexico. https://catalog.coriell.org


Executive summary

Background

- Differences in allele frequencies and linkage disequilibrium are common between populations.
- The majority of the pharmacogenomic literature centers around Caucasian, Asian and African populations.
- Pharmacogenomic data for Hispanic countries are severely lacking in published literature.

Methods

- Genotyping of 15 pharmacogenomically relevant polymorphisms was performed on unrelated individuals of Peruvian and Mexican descent.

Results

- Peruvians and Mexicans showed significantly different allele frequencies for \( ABCB1 \ 3435C>T \), \( CYP1B1*3 \), \( GSTP1 \ I105V \), \( TPMT \ 460G>A \), \( UGT1A1*28 \) and \( UGT1A1 \ −3156G>A \).
- \( UGT1A1 \) linkage disequilibrium was lower in Peruvians (\( D' = 0.86 \)) than Mexicans (\( D' = 0.97 \)).

Discussion

- No consistent pattern could be identified that could predict either Peruvian or Mexican allele frequency distribution for any one polymorphism.

Conclusion

- The admixture of the populations is likely a causative factor in the divergent allele frequencies and linkage disequilibrium.
- Caution when dispensing medication with known pharmacogenomic influence on drug efficacy and toxicity should be exerted for Hispanic populations in the absence of individual genotype testing.

Future perspective

- Ultimately frequencies of all clinically relevant polymorphisms will be archived and medical decisions will be informed by, at the least, population-based risk. However, this is still a long way from current practice.
Figure 1. *TPMT* allele frequency (combined *2, *3A, *3B and *3C) distribution in North and South America [52–59]

USA Caucasian (blue) represents the reference frequency (0.04) [56]. Green = between 0.5 and 2× the reference frequency, yellow = allele frequencies greater than 2× the reference frequency, gray = unknown frequency. Allele frequencies are listed in Supplementary Table 1.
Table 1

Genotype and variant allele frequencies for polymorphisms in the Peruvian and Mexican populations.

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<th>rs number</th>
<th>Population</th>
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<th>Heterozygous</th>
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† Genotype frequencies significantly differ at p<0.001.
‡ Genotype frequencies significantly differ at p<0.05.
§ TYMS TSER*4 allele frequency = 0 in Peruvians and 0.005 in Mexicans.
¶ Frequency of TYMS TSER*3 allele.
# (TA)₈TAA repeat allele frequency = 0.01 for both populations.