

Analysis of genomic diversity in Mexican Mestizo populations to develop genomic medicine in Mexico

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Mexico is developing the basis for genomic medicine to improve healthcare of its population. The extensive study of genetic diversity and linkage disequilibrium structure of different populations has made it possible to develop tagging and imputation strategies to comprehensively analyze common genetic variation in association studies of complex diseases. We assessed the benefit of a Mexican haplotype map to improve identification of genes related to common diseases in the Mexican population. We evaluated genetic diversity, linkage disequilibrium patterns, and extent of haplotype sharing using genomewide data from Mexican Mestizos from regions with different histories of admixture and particular population dynamics. Ancestry was evaluated by including 1 Mexican Amerindian group and data from the HapMap. Our results provide evidence of genetic differences between Mexican subpopulations that should be considered in the design and analysis of association studies of complex diseases. In addition, these results support the notion that a haplotype map of the Mexican Mestizo population can reduce the number of tag SNPs required to characterize common genetic variation in this population. This is one of the first genomewide genotyping efforts of a recently admixed population in Latin America.

admixture | genetic variation | population genetics | SNP tagging

More than 560 million people live in Latin American countries, and according to U.S. Census Bureau estimates the Latino population reached ≈ 45.5 million in 2007, representing the largest and fastest-growing minority group in the United States. Mexican Mestizos, as other Latino populations, are a recently admixed population composed of Amerindian, European, and, to a lesser extent, African ancestries. Although the diversity of Latino populations poses several challenges for genetic studies (1), it makes them a powerful resource for analyzing the genetic bases of complex diseases (2). In the past 5 years, Mexico has been committed to develop a human and technological infrastructure for genomics with special emphasis on the development of a national platform of genomic medicine to improve healthcare of Mexicans (3–6). This effort, together with a population of ≈ 105 million inhabitants including 60 Amerindian groups and a complex history of admixture, makes Mexico an ideal country in which to perform genomic analysis of common complex diseases.

Two current approaches to identify genes influencing complex diseases are genomewide association studies (GWAS) and admixture mapping (AM). GWAS depend on efficient SNP tagging (7, 8), and AM on the availability of panels of genomewide markers with frequency differences between parental populations (9, 10). For populations not comprehensively represented in the HapMap (11), such as Latinos, limitations exist for an efficient tagging and imputation, because of the need of a higher number of markers to achieve the same relative power compared to that for Asians and Europeans (12) and the lack of knowledge about population-specific linkage disequilibrium (LD) patterns (13). In addition, false positives because of population structure are minimized in GWAS by excluding individuals with ancestry differences (7). This is not practical in studies including Latinos such as Mexicans, where $>80\%$ of the population consists of Mestizos with known differ-

ences in ancestral proportions (2). As for AM, there are a few SNP panels developed for Latino populations (14–16); however, detailed genomewide information from Mestizo and Amerindian populations remains limited (17, 18). Recent studies of Latin American populations have shown differential ancestral contribution patterns between and within groups that correlate with pre-Columbian native population density and with patterns of recent demographic growth (2). These differences should be considered to improve AM panels for Latin American populations.

Historically, admixture patterns throughout Mexico have been influenced by differences in parental population densities and demographic growth (19–21). Genetic heterogeneity between and within Mestizos from different regions has been documented (22–29). However, no genomewide comparison of different Mestizo and Amerindian populations in Mexico is currently available in the public domain. To analyze genomic diversity and LD patterns in Mexicans, we developed the Mexican Genome Diversity Project (MGDP). This resource will be useful to develop strategies for the genetic analysis of Mexican and related admixed populations, such as marker selection for optimal coverage of common genetic variation in GWA and targeted association studies, and also for the adequate application of tagging and imputation approaches (30, 31) and for AM (10) in Mexicans and other Latino populations. Our study is one of the first extensive genomewide genotyping efforts performed in Latin America. The MGDP will contribute to the development of genomic medicine in Mexico and the rest of Latin America.

Results

We analyzed data from 300 nonrelated self-identified Mestizo individuals from 6 states located in geographically distant regions in Mexico: Sonora (SON) and Zacatecas (ZAC) in the north, Guanajuato (GUA) in the center, Guerrero (GUE) in the center–Pacific, Veracruz (VER) in the center–Gulf, and Yucatan (YUC) in the southeast. Considering that Zapotecos have been shown as a good ancestral population for predicting Amerindian (AMI) ancestry in Mexican Mestizos (16), we included 30 Zapotecos (ZAP) from the southwestern state of Oaxaca (Fig. 1). For comparative purposes, we included similar data sets from HapMap populations: northern Europeans (CEU), Africans (YRI), and East Asians (EA), including Chinese (CHB) and Japanese (JPT). A HapMap-like database with SNP frequencies in Mexicans and HapMap populations was generated (<http://diversity.inmegen.gob.mx>).

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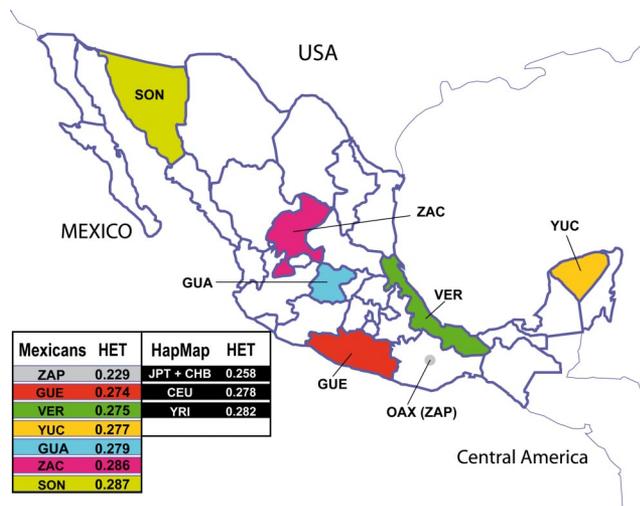


Fig. 1. Genetic diversity measured by heterozygosity (HET) in Mexican and HapMap populations. Northern, central, central-Gulf, central-Pacific, and southern regions in Mexico were included. Average HET values are shown for Amerindian Zapotecos (ZAP), 6 Mexican Mestizo subpopulations (GUA, GUE, SON, VER, YUC, and ZAC), and HapMap populations (YRI, CEU, and JPT + CHB).

Analysis of Genetic Diversity in Mexicans. We measured heterozygosity (HET), performed principal components analysis (PCA) (32), and calculated F_{ST} statistics using data sets obtained for Mexican and HapMap populations. Mexican Mestizo subpopulations had HET values between 0.274 in GUE and 0.287 in SON. Among HapMap populations, YRI displayed the highest genetic diversity (HET = 0.282) and JPT + CHB the lowest (HET = 0.258), as previously reported (33). Among Mexicans, northern subpopulations (SON and ZAC) had the highest HET values, suggesting more genetic diversity, and the ZAP Amerindian samples had the lowest (HET = 0.229), as expected for an isolated population. For PCA analysis, we used different combinations of data sets and conditions. In all scenarios the 2 most informative eigenvectors for each data set are displayed (Fig. 2 A–D). When included, the HapMap and ZAP populations formed defined clusters, while the Mexican Mestizo subpopulations were widely distributed between the CEU and ZAP samples (Fig. 2 A and B). The ZAP population clustering in the PCA plot suggests the absence of recent admixture in this Amerindian group. As expected, when all groups were analyzed (Fig. 2 A), the largest genetic distance exists between the YRI population and the rest of the groups. In the second axis, the ZAP cluster is located between CEU and EA and, in both the first and the second axes, all Mexican Mestizos are spread between CEU and ZAP (Fig. 2 A and B). To better display the distribution of Mexican Mestizos, we generated 2 additional data sets, one leaving out YRI samples (Fig. 2 B) and another including only CEU and ZAP. These analyses gave evidence of genetic diversity between and within Mexican Mestizo populations. In addition, a PCA including only CEU, ZAP, and the 2 Mestizo groups with the largest HET difference (SON and GUE) showed that samples from SON were closer to the CEU, and those from GUE were closer to the ZAP (Fig. 2 C and D). In both plots, some individuals were displaced along eigenvector 2, reflecting additional ancestral contributions in Mestizos. To evaluate whether this effect is related to African (AFR) ancestry, we analyzed an additional data set including YRI [supporting information (SI) Fig. S1 A and B]. The distribution of Mestizos in eigenvector 3 (Fig. S1 B) indicates that the spread observed in eigenvector 2 (Fig. 2 C and D) reflects AFR ancestral contribution. Interestingly, Mestizos did not organize in a straight line between CEU and ZAP (Fig. 2 C and D). This is most probably because those 2 groups of samples do not fully

represent the genetic variability of European and Amerindian ancestral origin present in these Mestizos (2).

To measure genetic distances between Mexican subpopulations, and between these populations and those from the HapMap, we performed a pairwise F_{ST} statistical analysis (Table 1). Of all Mexican groups, the Amerindian ZAP population showed the highest F_{ST} values when compared to all HapMap populations. As expected, the highest value was observed when compared to YRI (23.9), followed by CEU (15.4), JPT (11.9), and CHB (12.0). F_{ST} values between ZAP and each Mestizo subpopulation (Table 1) were consistent with their distribution in the PCA plot (Fig. 2 C), with GUE and VER closest to the ZAP cluster (F_{ST} values 3.2 and 3.8, respectively) and SON at the other end of the distribution (F_{ST} of 8.2). Pairwise comparisons between Mexican groups showed that SON when compared to all other Mestizo subpopulations had higher F_{ST} values than that observed between CHB and JPT. Moreover, the F_{ST} value between SON and ZAP (8.2) was higher than that of any other comparison between any Mestizo subpopulation and non-African HapMap group (Table 1). These results support the presence of considerable genetic heterogeneity between Mexican Mestizo subpopulations and suggest that this diversity is mainly related to a differential distribution of AMI and EUR ancestral components.

To assess genetic ancestry in Mexicans, we determined individual and population average ancestral proportions using STRUCTURE (34, 35). For this, we used 1,814 ancestry informative markers (AIMs) selected using different criteria to ensure genome-wide distribution and minimize LD between SNPs (see *Materials and Methods*). We used HapMap data and the ZAP population as EUR, AFR, EA, and AMI ancestral sources in the analyses. Our results were most consistent with 4 population groups ($K = 4$), explaining the major substructure in this set of Mexican Mestizos (Fig. 3 A and B). In this model, their mean ancestries (\pm SD) were 0.552 ± 0.154 for AMI, 0.418 ± 0.155 for EUR, 0.018 ± 0.035 for AFR, and 0.012 ± 0.018 for EA (Table S1). We observed differences within and between Mestizo subpopulations, mainly in EUR and AMI ancestries (Fig. 3 A and B). The highest and lowest estimates of mean EUR ancestry were 0.616 ± 0.085 for SON and 0.285 ± 0.120 for GUE. Most Mestizo subpopulations displayed statistically significant differences in mean EUR ancestral contribution, and both SON and GUE showed differences when compared to any other Mestizo subpopulation (Table S2). Mestizo groups with similar mean EUR ancestry were those from central and central-coastal regions (VER, YUC, and GUA). In contrast, most Mestizo subpopulations had a similar average AMI ancestral contribution—GUE the highest (0.660 ± 0.138) and SON the lowest (0.362 ± 0.089) (Fig. 3 B)—and only subpopulations in the northern states (SON and ZAC) showed statistically significant differences compared with all other Mestizo groups (Table S2). The other 2 ancestries analyzed, AFR and EA, were smaller and almost homogenous among all Mestizo subpopulations. Significant differences in AFR ancestry were observed for SON and ZAC against VER and YUC (Table S2). To evaluate the contribution of ancestry differences to the overall regional genetic diversity between Mestizo subpopulations, we calculated Pearson correlation coefficients between pairwise F_{ST} values and differences in AMI, EUR, and AFR ancestral proportions. This analysis revealed a high correlation between overall genetic diversity (F_{ST}) and EUR ($r = 0.937$) and AMI ($r = 0.944$) ancestry differences. To estimate the size of this effect, we calculated genetic distance between Mexican subpopulations, specifically attributable to differences in the 2 main continental ancestry proportions (Table S3). This analysis revealed that for most pairwise comparisons between Mestizo subpopulations (10 of 15), 50% of the genetic distance between them is attributable to differences in continental ancestry. Interestingly, most comparisons with low contribution of continental ancestry differences to overall genetic distance included the subpopulation of YUC. These

Table 2. Percentages of common haplotypes shared between Mexican and HapMap populations

Population	JPT +		CEU + JPT +		CEU + JPT +
	CEU	CHB	YRI	CHB	CHB + YRI
GUA	81	75	64	93	96
GUE	79	76	65	93	96
SON	82	71	63	94	97
VER	80	75	64	93	96
YUC	81	74	64	93	96
ZAC	81	73	64	93	97
MEX average	81	74	64	93	96

HS was assessed by comparing the frequencies of 5 SNP haplotypes spanning ≈ 100 kb. The percentages of shared common haplotypes ($>5\%$ frequency) between Mexican and HapMap populations are shown.

proportion of shared haplotypes increases to an average of 96% (95–97%) when each subpopulation is compared to any pair of subpopulations (Table S6). These results support the idea that a haplotype map of the Mexican Mestizo population may help reduce the number of tag SNPs required to characterize common genetic variation in this population.

Discussion

This work is an initial assessment of the potential benefit of generating a haplotype map to optimize the design and analysis of genetic association studies in Mexicans. During the pre-Hispanic period, ethnic groups living in Central and Southern Mexico were more numerous and had stronger political, religious, and social cohesion than ethnic groups from northern regions. African slaves were brought into the region after a notable reduction of the Amerindian population, due to epidemics, between 1545 and 1548 (19). Since then, admixture processes in geographically distant regions have been affected by different demographic and historical conditions, shaping the genomic structure of Mexicans. These factors have generated genetic heterogeneity between and within subpopulations from different regions throughout Mexico (2, 26, 29, 38). Even though participants in our study came from regions corresponding to modern political divisions, they represent different demographic dynamics, human settlement patterns, and Amerindian population densities. Because of known bias of admixture estimates due to socioeconomic stratification in Mexicans (28), Mestizo participants were recruited at state universities, in which most attendees come equally from urban and rural areas and belong to a wide range of socioeconomic strata.

Our results show that genetic differences among Mexican Mestizos from different regions in Mexico are mainly because of differences in AMI and EUR contributions. In most analyses, samples from central regions were closer to ZAP, while samples from northern regions were located closer to CEU, correlating with Amerindian population density in those regions, both in modern days and in the pre-Hispanic period (19). Although our analysis

Table 3. Percentages of common haplotypes shared between Mexican subpopulations

Population	GUA	GUE	SON	VER	YUC	ZAC
GUA		86	87	87	87	88
GUE	88		87	88	87	88
SON	83	82		82	83	84
VER	87	86	87		87	88
YUC	87	85	87	86		87
ZAC	85	83	87	85	85	
MEX Av	86	84	87	86	86	87

Haplotype sharing was assessed by comparing the frequencies of 5 consecutive SNP haplotypes spanning ≈ 100 kb. The percentages of shared common haplotypes ($>5\%$ frequency) between Mexican subpopulations are shown.

showed that mean AFR ancestry was low ($<10\%$) and mostly homogenous among subpopulations, we observed the presence of individuals with high AFR ancestry in GUE and VER. This is in agreement with historical records indicating these states as the main entry points of Africans during the Colonial period and as residence of African-Mexicans since then (39). Interestingly, samples from the southeastern region (YUC) had the lowest contribution of continental ancestry to genetic distance. Mestizos from Yucatan are the only group in our sample with a distinctive Maya AMI contribution. Mayas are a distinct ethnic group, geographically distant from other AMI groups, with strong cultural, social, and historical differences compared to them (20); thus this result suggests that some of the genetic diversity observed in our Mestizos is related to differential AMI contribution.

Alleles private to Mexican Mestizos have an AMI origin and conservatively represent the genetic variation absent in other continental groups, considering that most SNPs analyzed were identified in populations with genetic backgrounds lacking an AMI contribution (40). Positive detection of SNPs private to AMI is related to the use of a genotyping assay with SNP information from a multiethnic group that included Hispanics/Latinos: <http://www.genome.gov/10001552> (40). These SNPs represent variants not covered by the HapMap that may not be captured when tag SNPs are selected using only HapMap information. To better describe SNPs and haplotypes private to Mexicans it is necessary to perform extensive resequencing projects in both Mestizos and Amerindians.

Considering that LD decay patterns of all Mexican groups behaved similarly to those of non-African HapMap populations, average haplotype block size in Mexicans is expected to be similar to that of non-African HapMap populations. The reduced LRHD observed in Mexicans correlates with the AMI contribution, being consistent with the fact that Amerindian populations have significantly reduced haplotype diversity and long-range LD (35) and thus in possible relationship to the progressive decrease in haplotype diversity in human populations migrating out of Africa (41). Shared haplotype analysis was used as an approach to indirectly estimate tag SNP transferability from HapMap to Mexican populations and between Mexican subpopulations. This analysis was performed using different combinations of Mexican and HapMap populations to evaluate the potential benefits of a Mexican haplotype map. Common genetic variation in Mexicans is efficiently covered (96%) only when combined data from all HapMap populations are used, in accordance with previous findings for Latino populations (12), which suggests that selection of tag SNPs exclusively from the HapMap, for studies in Mexicans, will result in a significant increase in costs due to overgenotyping. An indication that a haplotype map for Mexicans could be useful for tag SNP selection is that the use of any combination of two Mexican subpopulations as a reference provided better coverage than using the combination of all HapMap populations. These results support the fact that a haplotype map describing common genetic variability and LD patterns in Mexicans is feasible and useful.

Public availability of data from the MGDGP will be important for a more effective design of association studies and resequencing projects in Latino populations. Our study suggests that either genome-wide or targeted approaches that use tag SNPs selected with HapMap data may adequately capture 96% of the common genetic diversity in Mexicans. However, it seems possible to generate optimized sets of tag SNPs to improve the efficiency of targeted association studies and help reduce costs without compromising coverage. This is critical for Mexico and other Latin American countries where funding for research is limited. Also, a Mexican haplotype map would help in haplotype tagging and subsequent SNP discovery in Latino populations, improving the search for rare variants associated with common complex diseases.

Imputation is used to improve power and combine data from GWAS that employ different SNP sets (30, 31). However, this

approach assumes similar genomewide LD patterns between the analyzed samples and the reference panel (30). Tagging or imputation using HapMap information is not as efficient in Mexicans and other Latinos as it is in other populations because of the presence of a genetic component not captured by HapMap data (13). The MGDGP data set will be of great value to test the accuracy of the imputation paradigm in Mexicans and to improve imputation approaches by the inclusion of adequate estimates of individual and local ancestry. The MGDGP data will also be useful to optimize existing sets of AIMs (14–16, 29) to perform AM studies in traits and diseases showing ethnicity-based differences in prevalence in Mexicans, such as HDL cholesterol levels (42), gall bladder disease (43), and type 2 diabetes (44).

We are currently increasing the SNP density to ≈ 1.5 million SNPs per genome using a combination of microarray platforms. Here we present one of the first public genomewide data sets for Mexican Mestizo and Amerindian populations. This effort will contribute to the design of better strategies aimed at characterizing the genetic factors underlying common complex diseases in Mexicans. In addition, this information will increase our knowledge of genomic variability in Latino populations. The scientific and technological infrastructure derived from this project will significantly contribute to the development of genomic medicine in Mexico and Latin America (3, 6).

Materials and Methods

Anonymous blood samples from 300 nonrelated and self-defined Mestizos and 30 Amerindian Zapotecos were collected in 7 states in Mexico: Guanajuato, Guerrero, Sonora, Veracruz, Yucatan, Zacatecas, and Oaxaca (ZAP). The Scientific,

Ethics, and Bio-Security Review Boards from the National Institute of Genomic Medicine (INMEGEN) approved this study. An ad hoc process for community consultation and engagement was implemented. Genomic DNA was extracted from blood (QIAGEN). Genotyping was performed according to the Affymetrix 100K SNP array protocol and 99,953 SNPs passed quality control in all populations. Phasing was performed with fastPhase v1.1.4 (45). All genotypes and raw signal intensity files are available (<ftp://ftp.inmegen.gob.mx>). Average HET was calculated with PLINK (<http://pngu.mgh.harvard.edu/purcell/plink/>) (46). The PCA was done with EIGENSTRAT (32), and F_{ST} with EIGENSOFT (39). Ancestral contributions were assessed with Mann–Whitney U tests, Pearson correlations, box-plot distributions, and their coefficients of variation. For ancestry analysis 1,814 AIMs were used to run STRUCTURE v.2.1 (34, 35). Scripts for informativeness for assignment were kindly provided by N. Rosenberg (37). Alleles private to the Mexican population had a MAF > 0.05 in any of the Mexican subpopulations, but were absent in all HapMap populations. Alleles private to any particular Mexican subpopulation had a MAF > 0.05 in 1 Mexican group and were absent in the other 6. LD calculations, long-range haplotype diversity, and H5 analysis were done with Haploview and special-purpose code, as previously described (47, 48). All data analyses were performed at INMEGEN in Mexico City. (see *SI Materials and Methods*).

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