Admixture in Latin America

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Latin Americans arguably represent the largest recently admixed populations in the world. This reflects a history of massive settlement by immigrants (mostly Europeans and Africans) and their variable admixture with Natives, starting in 1492. This process resulted in the population of Latin America showing an extensive genetic and phenotypic diversity. Here we review how genetic analyses are being applied to examine the demographic history of this population, including patterns of mating, population structure and ancestry. The admixture history of Latin America, and the resulting extensive diversity of the region, represents a natural experiment offering an advantageous setting for genetic association studies. We review how recent analyses in Latin Americans are contributing to elucidating the genetic architecture of human complex traits.

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Introduction

The population of Latin America and the Caribbean currently accounts for about 9% of the world population[1]. The history of this region has been characterized by the extensive admixture of Native Americans and immigrants from around the world, a process set in motion by the Spanish colonial expansion to the Americas starting in 1492. Historical records provide an outline of the major demographic events accompanying this process, including the collapse of the Native American population and a mass immigration of Europeans and Africans[2-5]. However, historical accounts do not enable a precise assessment of the impact of these events on the ancestry of the current population of Latin America. Genetic studies are enabling a better delineation of the biological correlates of this history, including detailed descriptions of population structure and individual ancestry. In addition to representing a rich setting in which to explore a range of evolutionary questions, Latin America embodies a natural experiment involving the admixture of populations with a relatively large phenotypic differentiation. The resulting high diversity of Latin Americans can benefit the analysis of the genetic architecture of complex human traits, including disease, as illustrated by recent genome-wide association studies. In this short review we put into perspective some major findings from genetic analyses of the demographic history of Latin America, the bearing of

this history on phenotypic diversity in the region and how these are being exploited to dissect the genetic architecture complex human traits.

Genetic history of Latin America

A prominent finding emanating from early mtDNA and Y-chromosome studies is that Latin Americans commonly trace their paternal ancestry to Europeans and their maternal ancestry to Native Americans[6-11](Figure 1). This observation points to a strong sex bias during admixture, which must have involved mainly immigrant men and Native women. These results are consistent with historical records documenting that migration to the New World, particularly in the initial stages of the colonial expansion was overwhelmingly by men[12] and that admixture between these men and native women was extensive at the foundation of the early colonial settlements [13]. The uniparental marker studies have subsequently been extended by comparative analyses of X-chromosome and autosomal marker data (Figure 1). These studies have documented that estimates of European ancestry based on X-chromosome data are lower than the autosomal estimates, as expected under the scenario of sex-biased admixture inferred from mtDNA/Y-chromosome data (since women contribute two X-chromosomes to the next generation, while men only contribute one)[14-19]. This sex bias in admixture has been found to be a common phenomenon in many recently admixed populations[20-23].

Studies of autosomal markers have in the last decade increased dramatically in density, allowing population and individual ancestry analyses at increasing resolution. A salient observation emanating from these studies is that Latin Americans show great variation in African/European/Native ancestry between individuals and geographic regions (Figure 2)[24]. That is, Latin America far from being genetically homogeneous presents extensive population structure, individual admixture estimates often extending widely across the range of the three major continental ancestries [14-18,24-29]. A positive correlation exists between variation in individual ancestry and population census size, suggesting that recent demographic events (such as urbanization) have had a noticeable impact on the genetic makeup of Latin Americans[14,27]. Thus, although individuals from the parental populations admixed extensively at the foundation of the early colonial settlements, this admixture subsequently had a complex dynamic involving population subdivision and further input from the parental populations, in certain cases up to the present[30]. Interestingly, estimates for the time since the start of admixture obtained from genetic data (and representing a kind of historic average) have been found to be consistent with the dates recorded for major settlement events in the areas examined. For instance, estimates for Caribbean islands (~16 generations)[16], are in line with historical information (about 500 years, for a generation time of around 30 years) and older than those obtained for populations from the continental mainland (about 9-14 generations), which were settled by immigrants subsequently[16,18,31]. Other genetic analyses are consistent with a significant flow of immigrants over an extended time period[9] or with multiple major pulses of past admixture, both scenarios having some historical support for the areas examined[16-18]. These results illustrate the complex and variable dynamics of admixture across Latin America underlying the great variation in continental ancestry seen throughout the region.

In addition to examining the proportion of European, African and Native American ancestry in Latin Americans, genetic studies have allowed the exploration of sub-continental ancestry. Early efforts based on mtDNA data indicated that admixed Latin Americans carry haplotypes characteristic of Native American populations currently living in the vicinity[32]. This was interpreted as suggestive of a "genetic continuity" between local pre-Columbian populations and admixed Latin Americans currently living in those areas, the local Native populations effectively becoming incorporated into the post-Columbian admixed population[32,33]. Autosomal data have extended this inference at increasing resolution from genome-wide microsatellite surveys to high-density SNP scans [14,16,18 ,26,28,34-36]. For instance, these data have shown that the Native American component of Mexicans is most closely related to Native Meso-Americans, while that in Peruvians and Chileans relates most closely to Andean natives, and in Colombians this component is closest to the Chibchan-Paezan groups of North West South America (Figure 3). Analyses based on high-density SNP data have also revealed subcontinental-structure within Latin American countries. For instance in Mexico, the Native American component in individuals from the south east of the country is predominantly related to the Maya, while in individuals from central Mexico it relates most closely to the Nahua[37]. The detectable sub-continental ancestry seen in the Native American component of Latin Americans indicates that recent migration has not been extensive enough to erase the signal of Native American population structure across the region, particularly in rural settlements[14]. Similar analyses of the European component have confirmed that ancestry in Latin Americans traces mostly to the Iberian Peninsula, although some individuals have detectable Italian and Northern European ancestry (particularly in Southern South America)[18]. The African component in Latin Americans also shows substructure, it being mostly West African in the Caribbean but with some East African ancestry, particularly in Brazil[17]. The high-density SNP analyses have also allowed the detection of low levels of East Asian ancestry in individuals from Perú[18], consistent with historical information documenting a substantial immigration of Chinese workers to this country in the 19th century[3]. Altogether these results emphasize the high level of population structure present across Latin America. Other than its evolutionary interest it is essential to account for this structure in genetic association studies focused on Latin American samples (and US Latinos)[19].

Genetic admixture and phenotypic diversity in Latin America

The relatively high genetic and phenotypic differentiation of Africans, Europeans and Native Americans and their variable admixture in Latin America underlies not only an extensive genetic heterogeneity across the region but also its high phenotypic diversity. This is most apparent in the great variation in physical features seen in the general population of Latin America[27]. Of medical relevance, this diversity also impinges on patterns of disease susceptibility in the region. Genetic studies have shown that for a number of disorders the risk of disease in Latin Americans varies with continental ancestry [38,39]. For instance, Latin America has a very high prevalence of Type 2 diabetes[40] and risk for this disease has long been known to correlate positively with Native American ancestry[41,42]. Barring the possibility that the correlation of disease risk with ancestry relates to environmental

covariates[43,44], such a correlation suggests the existence of underlying susceptibility alleles with a variable frequency across Africans, Europeans and Native Americans [45,46]. Interest in identifying trait loci with differentiated allele frequencies between the populations that contributed to recently admixed populations prompted the development of "Admixture mapping" [47-49]. This approach seeks to exploit the variation in ancestry along the genome seen in admixed individuals and identify genomic regions in which variation in ancestry correlates with phenotypic variation [50-52]. A growing number of admixture mapping and standard genome-wide association studies (GWAS) in Latin American (and US Latino) samples have been conducted for disease phenotypes that correlate with Native ancestry, including Type 2 diabetes[53,54], breast cancer[55,56], asthma[57,58] and autoimmunity[59,60]. Other than disease traits, recent genome-wide analyses have also sought to identify loci for non-disease phenotypes, including platelet count [61], IgE levels[62] and physical appearance[63-65].

The analyses carried out on physical appearance traits illustrate well some of the advantages of conducting genetic association studies in Latin Americans. Many of these traits are highly heritable and show a considerable differentiation between continental populations[66,67]. Variation in Latin Americans for these traits can span the range seen in the parental populations involved in the admixture and there is a significant correlation between ancestry and phenotypic variation[27]. In addition to replicating associations previously reported in the GWASs carried out in Europeans, studies in Latin Americans have identified a number of novel trait loci and, as anticipated, these new loci often show marked differences in allele frequencies between Europeans and Native Americans[63-65]. Figure 4 presents the example of nose protrusion. This trait has ~84% heritability, shows considerable differentiation between Native Americans and Europeans (with greater protrusion correlating with European ancestry)[65]. About 5.5% of variation in this trait is explained by basic covariates such as age and sex, 12.2% being explained by the genetic Principal Components (i.e. continental and sub-continental ancestry)[65]. About 1% of the phenotypic variance is explained by a SNP (rs2045323) showing genome-wide significant association in the DCHS2 (Dachsous Cadherin-Related 2) gene region in 4q31[65]. This SNP shows a 57% difference in allele frequencies between Europeans and Native Americans.

Thus far, GWASs have been carried out mostly in Europeans, thus representing a relatively narrow sampling of human diversity[68,69]. By comparison, studies in Latin Americans allow analyses of much wider genetic and phenotypic scope. Trans-ethnic genome-wide association studies have been advocated as a tool for fine-mapping trait loci shared by continental populations[70]. As illustrated by the recent studies mentioned above, the mixed ancestry of Latin Americans can in addition lead to the identification of novel trait loci characterized by differentiated allele frequencies between the continental groups that admixed in Latin America. Noticeably, in the extreme case of trait loci with different alleles fixed across continents, such trait loci would be detectable by association tests in admixed samples but not in the un-admixed parental groups. In sum, the high genetic and phenotypic diversity of Latin Americans can empower genetic association analyses and are contributing significantly to draw a fuller picture of the genetic architecture of complex traits in humans.

Conclusions and future work

Studies performed in Latin American samples have established that genetic analyses provide an enriching perspective on the demographic history of the region and results from these studies are of general relevance for the characterization of the genetic architecture of human phenotypes, including disease. High marker-density analyses are likely to continue to increase in geographic coverage, providing more refined evolutionary analyses across the region. In areas where there are few extant ethnically defined native populations (eg Caribbean islands), the study of admixed Latin-Americans can contribute to our understanding of the pre-Columbian patterns of settlement. It will be interesting to evaluate further the role that selection could have played in shaping patterns of diversity at the trait loci identified by the recent GWAS. Other than investigating pre-Columbian evolutionary events, an interesting area of work is the analysis of post-Columbian factors, other than admixture, potentially impacting on the genetic make-up of Latin American populations, including patterns of mating[71,72] and recent selection. It has long been realized that the colonization of the Americas resulted in the exposure of natives and immigrants to novel environmental challenges, including many infectious diseases[73], which could have impacted on the genetic makeup of admixed Latin Americans. Thus, admixture mapping has been used to explore the possibility that selection could have shaped variation in regional ancestry along the genome[74,75]. Results obtained so far include a marked variation in ancestry around the HLA region, which could relate to selection of HLA haplotypes by infectious agents[76]. These observations are contentious[77,78] and require further validation, including relating specific genetic variants with particular environmental factors and detailing the mechanism of this interaction.

An important topic of research, particularly for the future development of precision medicine initiatives targeting Latin Americans, is the extent to which continental sub-structure could impact on disease-related phenotypes (beyond the effects of continental ancestry)[79,80]. This is particularly relevant for the Native American component of Latin-Americans as the high genetic differentiation of many Native populations potentially involved in historic admixture could result in alleles impacting on trait phenotypes being geographically localized [28]. In view of these developments it is important to bear in mind that the history of Latin America has impacted not only on its present genetic diversity but has also had major socioeconomic effects. The area has historically been highly structured both genetically and socially, Latin America being the region with the most unequal wealth distribution in the world[81]. Ancestry and wealth correlate with each other and with phenotypic diversity, including major disease patterns[27,82-84]. Latin Americans thus present a number of research challenges on how the interaction of genetic and socioeconomic factors impinge on biological diversity and disease susceptibility [85-89]. Further research on these topics should be of general significance for the development of effective genomic applications in biomedicine.

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FIGURE LEGENDS

Figure 1. Proportion of African, European and Native American ancestry estimated with mtDNA, Y-chromosome, X-chromosome and autosomal markers in thirteen Latin American population samples. The proportion of European ancestry estimated from the Y-chromosome is consistently larger than estimated from mtDNA markers. Conversely, Native American (and African ancestry is larger on the mtDNA than the Y-chromosome). This pattern points to a sex-bias during admixture (mainly European men and Native/African women). Consistent with this pattern, European ancestry in the autosomes is larger than estimated with X-chromosome markers (since men and women contribute equal number of autosomes but men only one X-chromosome and women two). This pattern is seen in the different sites sampled across countries (the geographic location of the sites sampled is indicated in the map of Figure 3). This figure is modified from Wang et al. (2008) [14] and Ruiz-Linares (2015)[10]

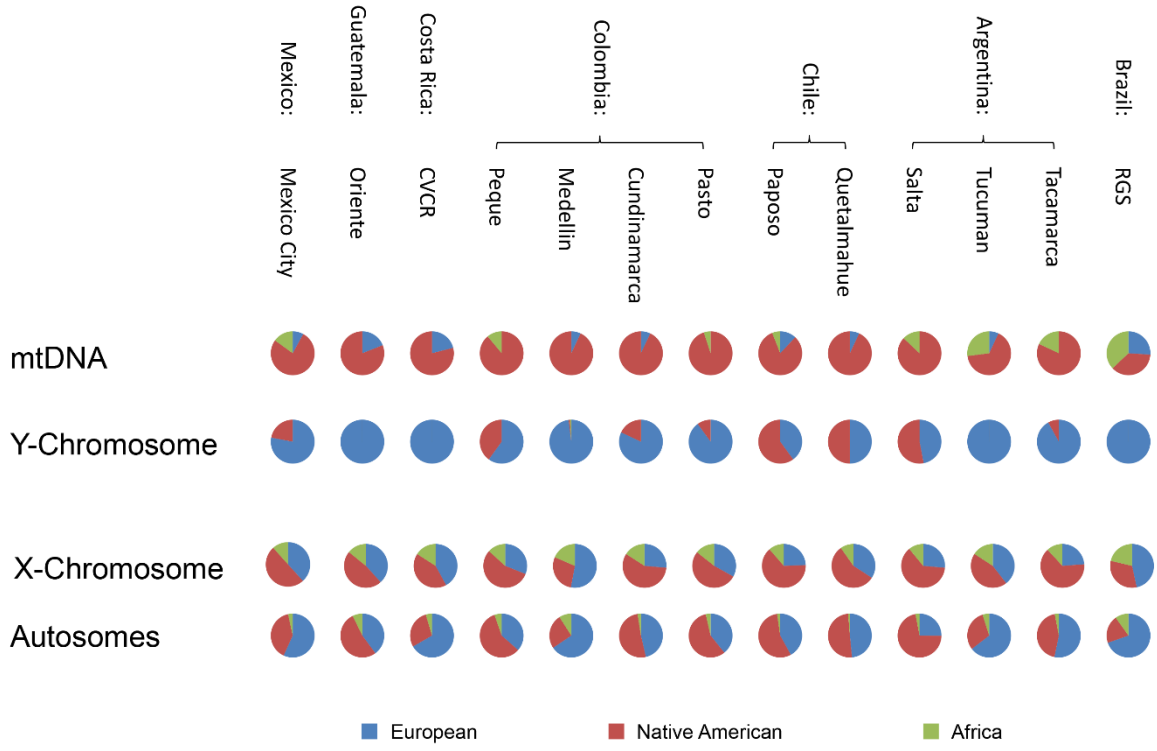

Figure 2. Proportion of individual African, European and Native American ancestry estimated from 93,328 SNPs typed in 6,357 Latin Americans from five countries (Brazil, Chile, Colombia, México and Perú). The mean admixture estimates are given at the edges of the triangle plots. The location of the countries sampled is indicated on the map of Figure 3. This figure is modified from Adhikari et al. 2016[64].

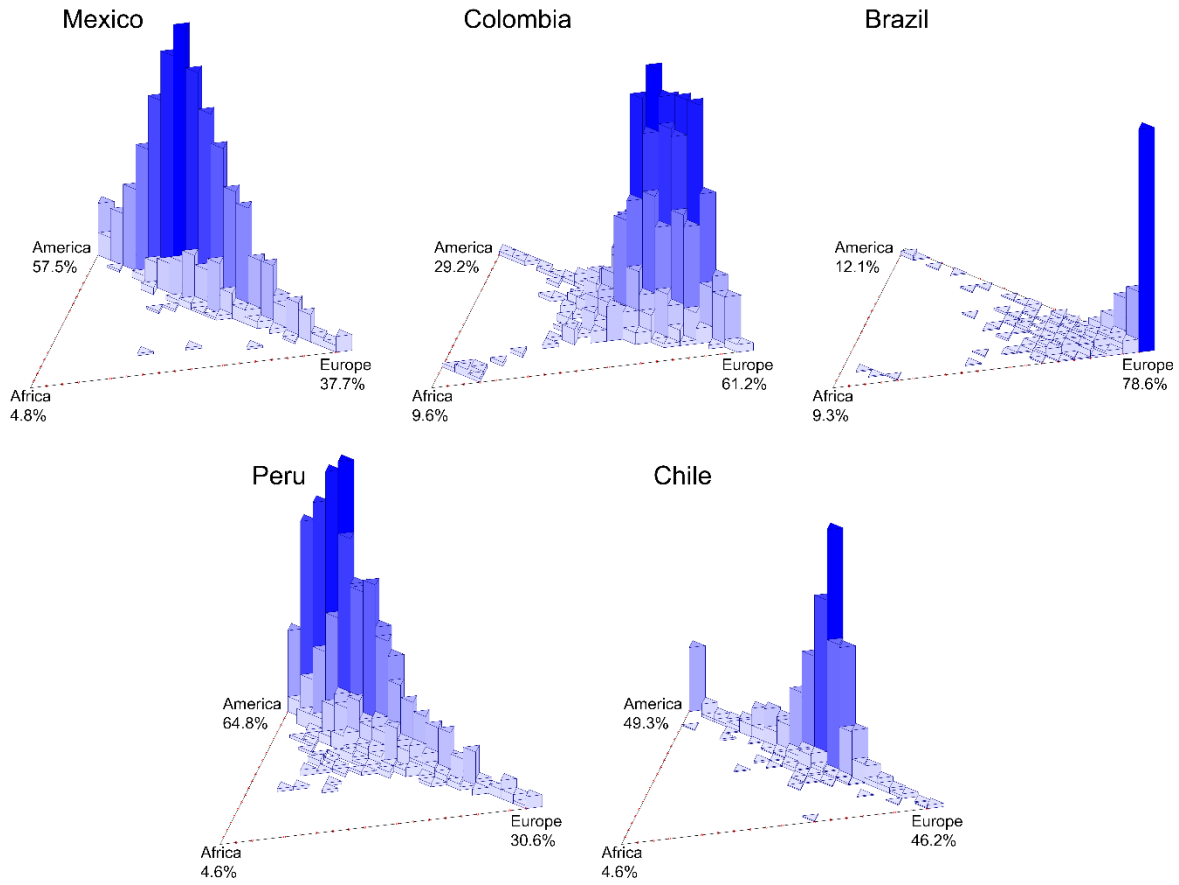

Figure 3. Population structure and sub-continental ancestry in Latin America. A Principal Components (PC) analysis was carried out on the data of Figure 2 (this analysis was conducted to account for population structure in genome-wide association studies performed in this sample[63-65]). On the right we show the plot for PC4 and PC5. To simplify, the spread of individuals on this plot is presented as a coloured range. Data for Native American populations[90] were also included in the analysis (with population names colour-coded based on the linguistic classification of Ruhlen[91], as listed in the middle of the figure). The map on the left shows the geographic location of countries and populations sampled. This map also displays the location of the sampling sites examined in Figure 1 (shown as black triangles). This figure is modified from Wang et al 2008[14], Reich et al 2012[90] and Adhikari et al. 2016[64].

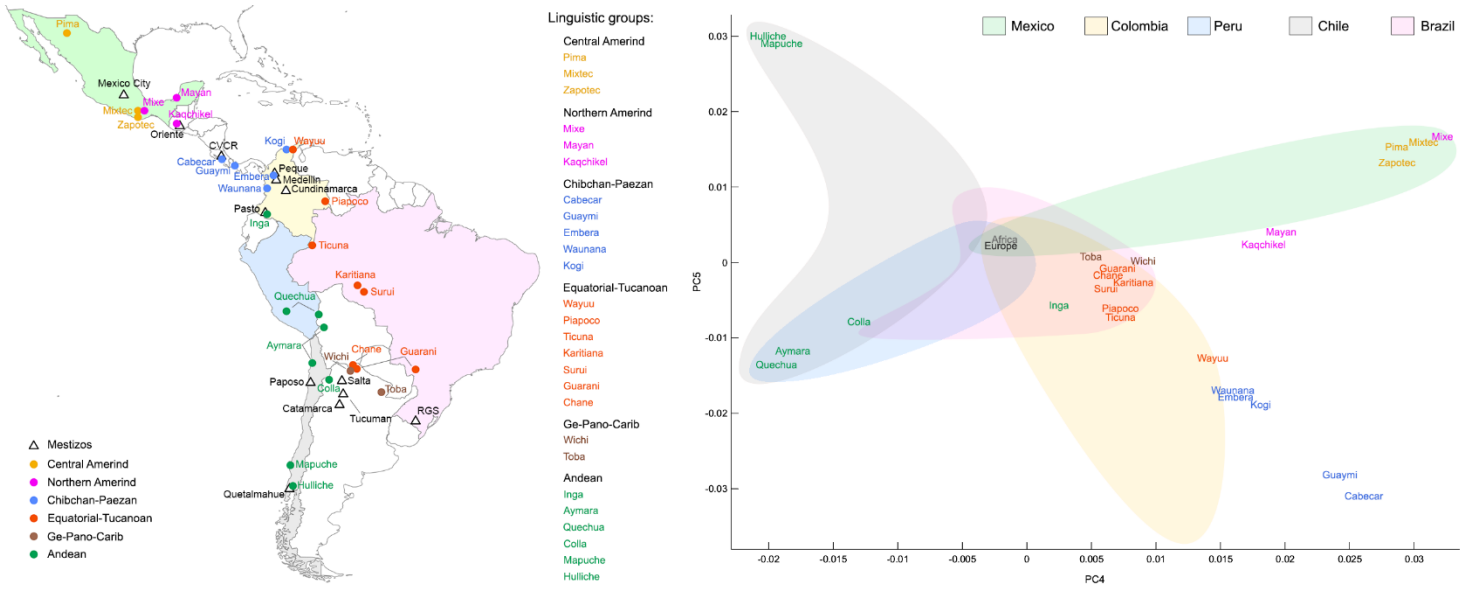

Figure 4. Phenotypic variation in Latin Americans and a locus for nose protrusion. (A) Density plots for nose protrusion for individuals included in the analyses of Figures 2 and 3. To illustrate the phenotypic differentiation between populations contributing to Latin American admixture separate plots are shown for individuals with >95% Native ancestry (in red) or >95% European ancestry (in blue). Variation in the rest of the sample is shown in the yellow plot. Nose protrusion was measured as a Procrustes Distance (PD) (calculated as detailed in Adhikari et al. (2016)[65]). (B) Scatterplot comparing individual nose protrusion with European ancestry and evidencing a significant correlation (r =0.36; *P*-value=2 x 10^{-16}). As a corollary, panel (C) shows that geographic variation in nose protrusion in Chileans matches variation in European ancestry in this country (as reported in Ruiz-Linares et al. [27]). (D) Manhattan plot identifying 4q31 as a region including SNPs significantly associated with nose protrusion in Latin Americans. (E) Allele frequencies in the CEPH-HGDP population panel for the index SNP (rs2045323) in the 4q31 region associated with nose protrusion (obtained from http://genome.ucsc.edu/). Plots A-D are modified from Ruiz-Linares et al. (2014) [27] and Adhikari et al. 2016[65].