



Genetic diversity in populations across Latin America: implications for population and medical genetic studies

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Hispanic/Latino (H/L) populations, although linked by culture and aspects of shared history, reflect the complexity of history and migration influencing the Americas. The original settlement by indigenous Americans, followed by postcolonial admixture from multiple continents, has yielded localized genetic patterns. In addition, numerous H/L populations appear to have signatures of pre-colonization and post-colonization bottlenecks, indicating that tens of millions of H/Ls may harbor signatures of founder effects today. Based on both population and medical genetic findings we highlight the extreme differentiation across the Americas, providing evidence for why H/Ls should not be considered a single population in modern human genetics. We highlight the need for additional sampling of understudied H/L groups, and ramifications of these findings for genomic medicine in one-tenth of the world's population.

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Introduction

The intercontinental migrations of our recent evolutionary history have drastically changed the genetic makeup of human populations across the globe. Due to the confluence of highly diverged ancestry components, the admixture process in Latin America is considered one of the most pervasive forces having shaped diversity across two continents. Hispanic/Latino (H/L) populations are a heterogeneous group whose genetic roots trace their origin back to multiple continental and subcontinental lineages, with a modern population size over 700 million. Large-scale sampling efforts coupled with advancing genomic technologies have shed light on the admixture composition of H/L populations both at a continental scale [1–3], and regionally [4,5,6*].

A common finding across these studies and others is the strong evidence of a correlation between genetic patterns and geography, where the Native American fraction of admixed genomes shows greater affinities with local ethnic groups across the Americas. This is in part due to isolation of the ancestral groups soon after divergence and limited gene flow between them [7], but also because such ancestral groups were characterized by extremely small effective population sizes, creating a serial founder effect during the colonization of the Americas. Overall, this evolutionary pattern increased genetic differentiation and population diversification, resulting in a strongly substructured Native American population. Interestingly, such substructure is mirrored in the ancestry composition of admixed Latin Americans, supporting the importance of characterizing H/L populations at a finer scale beyond their continental ancestry proportions and questioning the simplified view of encompassing a continent-wide diversity in a single population group.

Population genetic history of Hispanic/Latinos

During Colonial times, not all Native American components contributed equally into the mixture of the emerging admixed population. In fact, some of the most isolated components may have not contributed at all, like some populations from desert or rainforest regions. Whereas others, like the descendants of big civilizations such as the Aztecs and the Mayans in Mesoamerica, or the Inca in Peru, have had a major impact in the composition of large present day populations across Latin America [8]. Likewise, only a fraction of all the possible sources from

Europe or Africa contributed to the mixture of H/L populations and, more importantly, they have played a differential role in shaping H/L genomes, with smaller contributing components having a potential stronger founder effect in the admixed population.

This mechanism is particularly relevant for disease mapping and medical genomic studies in H/L populations as the allele frequency of deleterious variants and missense mutations may have drastically changed from the patterns observed within its source population compared to that in H/L populations. Colonialism, through admixture and history record assimilation, has also favored the erasing of admixed individuals' origins, so much of the specific sources within the Americas, Europe, Africa and other contributing regions like Asia and the Middle East, remain largely uncharacterized. However, with the increasing availability of global genomic data and more sophisticated computational approaches to infer subcontinental ancestry components, these hidden ancestries are being brought to light by recent and ongoing studies aimed at filling the gaps in our understanding of H/L population genetic architecture, including detailed sampling of indigenous communities [9^{*}]. Ongoing studies in other parts of the world therefore are likely to improve H/L genetic studies as well.

Deep structure in Hispanic/Latino groups enriches for founder populations

In population genetics, the 'founder effect' is the loss of genetic variation that occurs when a new population is established by a relatively small number of individuals. This process results in a randomly sampled genetic drift of variants relative to the parent population. In this scenario, potentially deleterious alleles can segregate at appreciable frequencies and these alleles can contribute substantially to the population specific disease burden of founder populations. Consequently, in genetic research much attention has been paid to populations that, due to geographical or cultural isolation, or patterns of endogamy, migration and diaspora, share signatures of a founder effect. In concert with the majority of genomic research, much of the focus has been on founder populations of European descent. Populations like the Icelandic, Sardinian, Finnish, and U.S. population isolates like the Amish and Hutterites, have been extraordinarily important for advancing Mendelian and complex trait genetics in European populations.

To date discovery efforts in non-European populations remain limited. This is especially true of the Hispanic/Latino (H/L) populations of the Americas. The term H/L encompasses a broad and highly heterogeneous group of populations. As mentioned, many of the contemporary H/L populations are the result of complex, recent demographic events including admixture, bottlenecking, and subsequent recent, rapid post-Colonial population

growth. These demographic processes can result in founder effects that can create the conditions necessary for disease variants to drift to detectable frequencies. This suggests that, similar to European founder populations, researching H/L could be instrumental in driving discovery in both Mendelian and complex human disease. However, identifying these founder effects can be challenging due to the relative under representation of these population in genomic research databases, and that the underlying processes of gene flow do not necessarily correlate perfectly with the cultural, ethnic and regional labels that are typically used in research to categorize populations into discrete groups.

Some H/L groups have been studied via a classic founder population framework. For example the population of the Central Valley of Costa Rica (CVCR) has been studied as a genetic isolate population using haplotype based approaches to explore the genetic etiology of various complex disorders such as bipolar disorder, schizophrenia and asthma over the past two decades [10,11]. Recent population genetic surveys, however, have made discoveries in ostensibly cosmopolitan H/L populations that suggest founder effects may be more broadly ubiquitous across Latin America. For example in two studies [12,13], there was clear evidence of ancestry-specific bottlenecks, measured both in the indigenous and European components of ancestry in populations throughout the Caribbean and in the populations from the Americas in the 1000 Genomes Project. A recent study improved on these by systematically quantifying the relative magnitude of founder effects on different ancestral backgrounds in admixed H/L populations by estimating effective population size over time from the distribution of lengths of identical-by-descent (IBD) haplotypes stratified by different continental ancestral origin [14^{*}]. Analyses of Colombian, Puerto Rican, Dominican, Ecuadorian, Guatemalan, Cuban, Honduran, Mexican and Nicaraguan populations derived from the Hispanic Community Health Study/Study of Latinos (HCHS/SOL) revealed variance in pre-admixture N_e , as well as a marked reduction in N_e around 12 generations ago, coincident with European contact with the Americas.

Another prominent H/L founder population are the Honduran Garifuna. Thought to be descendants of West African survivors of a shipwreck that crashed off the coast of St. Vincent in 1635, who subsequently admixed with the Island's Native Carib population before eventually being displaced to Central America [15], growing to over 1 million individuals today. Patterns of strong founder effect in Garifuna have been detected in multiple large independent population-scale studies inclusive of H/L groups. Genetic inference of the historical effective population size (N_e) of the Garifuna estimated using IBD supports this account; indicating that the population underwent a profound bottleneck ~12 generations ago,

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