COMMENTARY

Bringing DNA-Guided Medicine to the Hispanic Population

DNA-guided medicine poses great advantages for the highly heterogeneous Hispanic population. Similar to others in Latin America, the Puerto Rican population originated as a result of admixture between Amerindians, whose ancestors had migrated from the Amazon Basin and arrived in Puerto Rico 2200 years before present, and Spaniard and West-African individuals. The island of Puerto Rico thus is endowed with a distinctive population in terms of its gene flow. There are growing numbers of Puerto Ricans in the USA. Currently, Puerto Ricans represent 1.2% of the USA population and 9.6% of the Hispanic population in the USA. Admixture studies in Puerto Ricans, either in the island or the continental USA, have been scarce. The history of migration and admixture can be reconstructed and interpreted using genetic markers. Our results demonstrated that population analysis can be performed with functionally important genes instead of conventional ancestry informational markers to increase the relevance of population genetic studies for clinical epidemiology and personalized medicine. In this commentary, we examine the various implications of these findings and suggest an interpretation of the data utilizing a collage technique.

Physiogenomic Profile of the Puerto Rican Population

We performed physiological genomic analysis on 196 important cardiovascular, neuroendocrine and metabolic genes (including key pharmaceutical targets) in 100 anonymous, geographically representative DNA samples from the Newborn Screening Program at the University of Puerto Rico Pediatric Hospital (1). Population structure was examined using gene polymorphisms for clustering. The Puerto Rican sample is found to be broadly heterogeneous. We observed 3 main clusters in the population, which we hypothesize to reflect the historical origin of the Puerto Rican population as Amerindian with relatively recent European and African admixture. We present evidence for this interpretation by comparing inferred allele frequencies for the 3 clusters with the allele frequencies found for the same gene polymorphisms by the Human Genome Project in European, African and Asian populations. Each individual in the cohort was a 'genetic mosaic', with contributions from each of the clusters, but in widely different proportions. The maximal contribution from a single cluster observed in this sample is ~85% for African, ~85% for European and ~70% for Amerindian ancestries. The range of possible genetic combinations in the Puerto Rican populations is considerable, and certain to exceed that in populations without admixture.

Implications for healthcare and clinical research

In highly heterogenous populations, existing "one-size-fits-all" medications and prescription recommendations are likely to be ineffective, or worse, cause harm through side effects. With history and ancestry spanning African, Amerindian, and European origins, the typical Puerto Rican person defies conventional ethno-geographic definitions. Clinical research should be undertaken in diseases demonstrating higher prevalence in the Hispanic population to improve the existing treatments and re-adjust dosing regimens in targeted recipients from such a highly heterogeneous population. Heterogeneity in how people respond to medications has confounded the prescription of modern medicines, with detrimental consequences for the safety, efficacy and patient compliance of potent drugs. A major advance in healthcare would be a transition from the current empirical approaches and trial employed in drug therapy to a genetically predictive framework for determining the individual patient's response to medicines.

What are the barriers to getting these technologies used by healthcare system? How could we overcome these barriers? The first step in developing the genetic rules for personalized medicine is clinical research to "train the algorithms" supporting medical decision making. For example, a range of responses to a drug (efficacy, side effects, therapeutic ratios) in a target populations can be modeled by additive effects of DNA polymorphisms when a drug is given and the recipients have agreed to have their DNA and clinical response analyzed. This research can be fundamentally observational, and not pose any risk to subjects beyond that of standard medical therapy.

Implications for economic development

Genome diversity provides an opportunity to leapfrog health standards in heterogeneous Hispanic populations to areas of medical need with potential disparities of care including diabetes, heart disease, mental health, and cancer. Genomic heterogeneity also poses a great resource for translational clinical science in Latin America and innovation in healthcare. The paradigm of drug development in homogeneous populations for questionable extrapolation to real world heterogeneous populations can thus be supplanted with one of intentional diversity for broader export applicability. The determination of

individualized treatment most suitable to each patient, using the personal genome for clinical decision support, and the implementation of drug prescription safeguards, are integral to personalized health. Such DNA-guided personalization provides a new venue to assure advances in medical technology improve the health of the Hispanic population.

Within the broad personalization paradigm, we have an enormous opportunity to turn our genetic variability into a clinical asset rather than a complication. Similar to the Global Positioning Systems used in vehicles today to help us reach our intended destinations, a 'genetic prescription system' could be configured from correlations of gene variation and clinical outcomes. This other GPS will help lead physicians and patients to their desired treatment goal, resulting in more effective healthcare.

Implications for education

Often new concepts require unconventional ways of depicting them in order to enhance understanding. The fusion of art and science is relevant to this quest, and we had utilized a digital montage technique in a previous illustration, *DNA Collage I*, published in 2008 (2). In order to construct an image relevant to the Puerto Rican physiogenomic data, we turned to the illustrious painter Francisco Oller, who in his iconic *El Velorio* (1893) had encompassed a mosaic of Puerto Rican society where the characters in effect demonstrate the range of diversity in the population. He was one of the first painters to bring the techniques of the French impressionists to interpret the tropical landscape. In *Hacienda Aurora* (1898) he captured the essence of this landscape with generous blue space for the sky, lush greenery and strokes of yellow for the countryside brightly illuminated by the tropical sun. These works provided inspiration to the *Mosaico Genético Boricua* (DNA Collage PR), which is shown in the cover of this issue of the *Puerto Rico Health Sciences Journal*.

For this collage, we utilized the genotype data for single nucleotide polymorphisms (SNPs) in cardiometabolic and neuroendocrine genes, shown vertically, one per column, and Puerto Rican people aligned horizontally, one person per row. Each SNP is a variable site in the DNA with either of two sequences. In total, the cover represents an array of 25,489 DNA markers for 359 variable gene sequences (columns) from each of 71 individuals (rows). The colors represent the genotype a person has inherited from both parents at every SNP site: two copies of either sequence (homozygous) or one of each (heterozygous). Each genotype was colorized as green if heterozygous, and randomly as blue or yellow if homozygous. The genotypes ensembles, while unique for each person, blend harmoniously in colorful patterns with the pointillist touches of variability preventing any column or row from being homogeneous. This image reflects the admixture in the Puerto Rican population, and subtly suggests the unique societal aspects that led to the fusion of people in Puerto Rico, "la isla del encanto" (the island of enchantment).

In explaining the genetic characteristics of the Puerto Rican people, the image in the *Mosaico Genético Boricua* contextualizes the diversity and admixture as an innate asset. It would have been the case that such characteristics pose a drawback in a world where one medication is supposed to fit all. But in the era of DNA-guided medicine and personalized health, such diversity is precisely the enabling platform of opportunity. The delivery of DNA-guided healthcare for each person is good medicine for all people.

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Reference

1. Ruaño G, Duconge J, Windemuth A, Cadilla CL, Kocherla M, Villagra D, Renta J, Holford T, Santiago-Borrero PJ. Physiogenomic analysis of the Puerto Rican population. Pharmacogenomics 2009;10:565-77.
2. Ruaño G. DNA Collage and Personalized Medicine. Connecticut Medicine 2008;72:322-cover

About the Cover

Mosaico Genético Boricua, Digital Montage on vinyl board of 25,489 pixels colorized algorithmically from DNA variability by Gualberto Ruaño, MD, Ph D and Mohan Kocherla.