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Genetic Predictors for Cardiovascular Disease in Hispanics

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Abstract

A less favorable cardiovascular risk factor profile, but paradoxically lower cardiovascular morbidity and mortality have been observed in Hispanics, a pattern often referred to as the Hispanic Paradox. It was proposed the specific genetic susceptibility of this admixed population and gene-environment interactions may partly explain the paradox. The past few years have seen great advances in discovering genetic risk factors using genome-wide association studies (GWAS) for cardiovascular disease especially in Caucasians. However, there is no GWAS of cardiovascular disease that have been reported in Hispanics. In the Costa Rican Heart Study we reported both the consistency and disparity of genetic effects on risk of coronary heart disease (CHD) between Hispanics and other ethnic groups. We demonstrated the improvement in the identified genetic markers on discrimination of CHD in Hispanics was modest. Future genetic research in Hispanics would consider the diversities in genetic structure, lifestyle and socioeconomic among various sub-populations, and comprehensively evaluate potential gene-environment interactions in relation to cardiovascular risk.

INTRODUCTION

Hispanic or Latino Americans are people with origins in the Hispanic countries or those in the United States who are of Hispanic American origin. The Hispanic/Latino population became the largest minority in the United States in 2003 and will constitute 25% of the US population by 2050 (Rosamond et al., 2008). In general, Hispanics have higher prevalence of cardiovascular risk factors such as obesity, type 2 diabetes and metabolic syndrome than do non-Hispanic whites (Lindeman et al., 1998; Park et al., 2003). Paradoxically, some studies have reported lower cardiovascular morbidity or mortality among Hispanics especially compared with non-Hispanic Whites (Liao et al., 1997; Sorlie et al., 1993), a pattern often referred to as the Hispanic Paradox, though data from some epidemiology studies do not consistently support the existence of such a paradox (Hunt et al., 2003).

The potential mechanisms underlying the divergent prevalence of cardiovascular risk factors and mortality remain unclear. It has been proposed that the population-specific genetic susceptibility or gene-environment interactions might partly account for such divergence. Hispanics are a genetically admixed population, and represent a unique group in which the

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genetic effects may differ from other homogeneous populations. Owing to the diversity of their genomes, Hispanics offer both advantages and disadvantages for genetic studies of complex diseases (Seldin et al., 2011).

This review summarizes recent advances in genetic research of cardiovascular disease among Hispanic populations; data of genetic association and prediction in Costa Rican Heart Study from the Central Valley of Costa Rica are also presented. We argue that genetic research in Hispanics may provide evidence to explain the disparity of cardiovascular mortality among various ethnicities and offer a supplementary interpretation of the complexities in predicting cardiovascular disease using genetic markers.

1. Cardiovascular risk in Hispanics

Compelling evidence has shown that Hispanics are uniformly affected by excessive rate of cardiovascular risk factors such as type 2 diabetes, overweight and obesity, and poorly controlled hypertension (Lindeman et al., 1998; Park et al., 2003). Compared to non-Hispanic whites, Hispanics have higher circulating triglyceride (TG) and lower high-density lipoprotein (HDL) cholesterol levels (Haffner et al., 1993; Haffner et al., 1986). Hispanics also have the higher blood levels of inflammatory markers such as C-reactive protein (CRP) (Nazmi & Victora, 2007), and higher prevalence of metabolic syndrome than Caucasians (Ford et al., 2002; Park et al., 2003). Several previous studies suggest an unhealthy lifestyle, such as very low levels of physical activity and poor dietary habits, as well as limited access to both health protective foods and health care may partly account for the deleterious metabolic status in Hispanics (Bermudez et al., 2000; Tucker et al., 2000).

Despite the high prevalence of risk factors, cardiovascular morbidity or mortality is often observed to be lower in Hispanics/Latinos, sometimes referred as the Hispanic Paradox. In approximate 700,000 participants (aged >25 years), including 40,000 Hispanics in national surveys conducted by the United States Census Bureau, Sorlie et al. observed lower mortality from all causes and cardiovascular disease in Hispanics than in non-Hispanics (Sorlie et al., 1993). The results are consistent with the data from the National Health Interview Survey (1986 to 1994) including 246,239 non-Hispanic whites, 38,042 blacks and 14,965 Hispanics, in which it was found that all-cause, coronary heart disease (CHD) and cardiovascular mortality is approximately 20% lower among adult Hispanics than among whites in the United States (Liao et al., 1997). The reasons for the Hispanic Paradox are not clear, though it has been suggested that the relative survival advantage may be attributed to interactions between lifestyle, genetic factors, and greater family support in this population (Blue & Fenelon, 2011; Palloni & Arias, 2004).

However, data from some other studies question whether the Hispanic Paradox exists. Hunt et al. examined the relation between ethnicity and mortality in 1,438 Mexican-Americans and 921 non-Hispanic Whites in the prospective San Antonio Heart Study (Hunt et al., 2003). Different from the previous findings, the authors found that age- and gender-adjusted hazard ratios for all-cause, cardiovascular, and coronary heart disease mortality were 1.50 (95% confidence interval [CI]: 1.23–1.81), 1.70 (1.30–2.24), and 1.60 (1.09–2.36), respectively, comparing Mexican Americans with non-Hispanic Whites. Lerman-Garber et al. performed systemic review of 140 publications to assess data reliability and potential bias in the analysis related to the Hispanic Paradox. The results suggest that the observed lower mortality in Hispanics might be due to migratory factors and selection bias that may produce the appearance of a paradox when there is none at all (Lerman-Garber et al., 2004). More recent data from the Study of Women's Health Across the Nation (SWAN) showed significant differences in the risk profiles of Hispanic subgroups (Derby et al. 2010), suggesting differential relationship between risk factors and cardiovascular risk may exist in

Hispanic subgroups. There is evidence showing that the Hispanic mortality advantage may be a feature of some but not other sub-populations (Palloni & Arias, 2004).

2. Genetic structure in Hispanics and impact on cardiovascular risk

Hispanics represent a genetically admixed population, which means a population formed from the mixing of two or more groups whose ancestors had long been separated in the past several hundred years as a consequence of historical events such as colonization of Central and South America or the slave trade. Contemporary Hispanics result from the encounter of Europeans with the indigenous peoples of the Americas in 1490s, followed by waves of migration from Europe, Africa and Asia (Velez et al. 2011). This creates mosaic chromosomes containing segments of distinct ancestry in Hispanics, which often have high variation across individuals in the proportions of ancestry from the source populations (Rosenberg et al. 2010). Of note, the ancestry proportions in various Hispanic sub-populations may differ significantly. For example, in an analysis of Puerto Ricans living in Boston, it was found that ancestral composition of this Hispanic population was 57.2% European, 27.4% African, and 15.4% Native American (Lai et al., 2009). In a population of Costa Rica descended from Central Valley ancestors (Segura-Wang et al., 2010), estimated mean ancestry proportions were 54%, 32%, and 13% for European, Amerindian, and African components, respectively, with some regional variation. By comparison, an analysis of the sample from Mexico City showed substantial American Indian and European contributions, and very limited West African influence. For example, average ancestry proportions were 63% for American Indian and 34% for European, with only a 3% contribution from West Africa.

It has been noted for a long time that the genetic susceptibility to chronic diseases such as cardiovascular disease may vary across different ancestral populations of Hispanics. For example, familial aggregation of CHD risk has been found to be stronger in blacks than whites in a family study (Katzmarzyk et al., 2000). Lai et al. examined the genetic ancestry of 1,129 subjects from the Boston Puerto Rican Health Study based on genotypes of 100 ancestry informative markers (AIMs), and the effects of ancestry on major disease outcomes including type 2 diabetes, obesity, cardiovascular disease, and depression. It was found that African ancestry was negatively associated with type 2 diabetes and cardiovascular disease, and positively correlated with hypertension (Lai et al., 2009). Genetic association studies have also shown interesting trend of differences in genetic effects across populations. For example, it was found that the risk of myocardial infarction (MI) associated with variants in the *LTA4H* gene was over three-fold higher in African Americans than European Americans (Torres & Kittles, 2007). The disparity in genetic susceptibility for common diseases may be partly shaped by natural selection (DiRienzo & Richard, 2005). Many genetic variants have been positively selected over the past several thousand years and are unique to particular continental groups (Grossman et al., 2010). Therefore, Hispanics are likely to harbor a larger number of genetic variants with functional effects that originate from various ancestral populations. These observations may form the basis that genetic effects in Hispanics may be consistent to a certain degree with, but not identical, to the genetically homogeneous ancestral populations.

3. Genetic studies in the Costa Rican Heart Study

The history of the Costa Rican population, similar to other populations in Latin America, involves a complex process of admixture. The population of the Central Valley of Costa Rica offers a unique opportunity to assess the role of genetic ancestry on the risk of disease because this population is derived from the admixture of a relatively small number of founders of Spanish, Amerindian, and West African origin. In addition, the expansion of the Central Valley population has occurred mostly by reproduction rather than immigration, and

therefore the vast majority of the present population would be descendants of the intermarriage between the ancestral groups (Ruiz-Narvaez et al., 2010). The Costa Rican Heart Study is a population-based case-control study designed to examine the genetic risk factors, gene-diet interactions and risk of coronary heart disease. Data collection on incident cases of a first non fatal acute MI and matched controls for age, sex and area of residence took place between 1994 and 2004 in thirty-six counties in the Central Valley of Costa Rica. In total more than 2,000 pairs of MI cases and matched healthy controls were enrolled. Mean individual ancestry proportions in controls are 57.8% European, 38.3% Amerindian, and 3.8 West African (Ruiz-Narvaez et al. 2010) (Figure 1). This study has generated numerous publications particularly on diet and lifestyle risk factors, as well as genetic markers for cardiovascular risk (Baylin et al., 2010; Baylin et al., 2007; Campos et al., 2008; Martinez-Ortiz et al., 2006). Admixture mapping has been used to find genes that underlie ethnic differences in disease risk among admixed populations (Mao et al., 2007). In Costa Rican Heart Study, we have demonstrated that ancestry of the source populations may differentially affect cardiovascular risk. Ruiz-Narváez et al. (Ruiz-Narvaez et al. 2010) genotyped 39 AIMs to determine the ancestry proportions and their association with disease risk in our study population. Compared with Southern European ancestry, each 10% increase in West African ancestry was associated with a 29% increase in MI (OR=1.29; 1.07–1.56), and with a 30% increase on the risk of hypertension (OR=1.30; 1.00–1.70). Each 10% increase in Amerindian ancestry was associated with a 14% (OR=1.14; 1.00–1.30) increase on the risk of metabolic syndrome, and 20% (OR=1.20; 1.01–1.42) increase on the risk of impaired fasting glucose. Of note, African ancestry was related to an increased CVD risk in another study in Puerto Rican Hispanics, though its relation to increased hypertension was consistent with our findings (Lai et al., 2009).

We have also analyzed a group of candidate genes for their associations with CHD. In a study, Baylin et al. (Baylin et al. 2010) examined the association between the –514 C/T polymorphism of the hepatic lipase gene (*LIPC*) and nonfatal MI in total of 1940 pairs of cases and controls. The –514T variant was not associated with MI in the whole population. However, it was found that history of hypercholesterolemia might modify the genetic associations. The disease-increasing effect of the risk allele was only observed in those with history of hypercholesterolemia. Ruiz-Narváez et al. (Ruiz-Narvaez et al., 2008) examined the APOC3 promoter variations for their effects on plasma apo C-III concentrations and MI. The APOC3*222 haplotype, defined by the minor alleles of the SNPs 3238C>G, –455T>C, and –482C>T, was found to be associated with higher apo C-III concentrations, but only in those with the lowest waist circumference or fasting glucose concentration. The association between the APOC3*222 haplotype and nonfatal MI was strongly influenced by fasting hyperglycemia and abdominal obesity. The 719Arg allele of SNP rs20455 in the gene for the KIF6 protein—a member of the kinesin 9 family—has been reported to be associated with coronary heart disease in Caucasians in several prospective studies (Bare et al., 2007; Shiffman et al., 2008). Bare et al. examined this SNP in 1,987 MI cases had survived a first MI and 2,147 matched controls, but did not replicated the association in Hispanics (Bare et al. 2010). These data suggest that the genetic associations in Hispanics may differ from those observed in other ethnics such as Caucasians, and are likely modulated by the metabolic status of the population.

In addition to the main genetic effects, we also observed interesting interactions between genetic factors and dietary factors in relation to CHD risk. Some potentially important gene by diet interactions include coffee and the cytochrome P4501A2 gene (*CYP1A2*) (Cornelis et al., 2006), cruciferous vegetable and the glutathione S-transferase gene (*GSTT1*) (Cornelis et al., 2007), as well as arachidonic acid and the 5-Lipoxygenase gene (*ALOX5*) (Allayee et al., 2008). These data suggest that the different prevalence rate of cardiovascular risk factor

in Hispanics may be due to the combined effects of genetic variation interacting with environmental factors.

4. Genetic prediction of cardiovascular risk

In the past few years, GWAS have contributed to a major leap forward in unraveling of the genetic basis of complex disorders, including cardiovascular disease. The panel of the identified susceptibility genes for cardiovascular disease has been recently expanded to approximately thirty (Ho et al., 2011; Schunkert et al., 2011). These findings have been considered as a first step to identify the causal variants and provide novel insights into disease biology. In addition, as the heritability of CHD is substantial, it had been expected that these disease-predisposing genetic markers could be also useful to create genetic predictors of disease risk beyond traditional risk factors (Wray et al., 2007). In epidemiological analyses, the area under the receiver operating characteristic curve (AUC) or C-statistic is the most commonly used instrument for modeling whether genetic markers can help improve the accuracy of prediction. An AUC of 0.5 can be interpreted as a prediction that is equivalent to chance, and an AUC of 1.0 represents perfect prediction.

Several studies have compared the accuracy of risk prediction of models including traditional risk factors with and without genetic markers in Caucasians. Paynter et al. (Paynter et al., 2010) examined the prognostic capability of 101 SNPs identified from previous GWAS. An integrated “genetic risk score” for coronary artery disease (CAD) was calculated by summing the number of risk alleles. The carrier status of these SNPs did predict a heightened risk for CAD, but failed to add considerable value to prediction models beyond traditional risk factors. However, the majority of the genetic variants included in Paynter’s study were selected based on their relation with risk factors but not disease outcome. Ripatti et al. (Ripatti et al. 2010) tested SNPs at 13 genomic regions associated with CHD or MI in previous GWAS in a case-control design including 3,829 prevalent CHD cases and 48,897 controls; and a prospective cohort design including 30,725 participants (Median follow-up of 10.7 years; 1,264 incident cases of CHD). The AUC estimates for CHD and MI models with traditional risk factors and genetic risk score were 0.872 and 0.881, respectively, and they were not significantly higher than the estimates from the models with only traditional risk factors (0.871, $p=0.19$ and 0.880, $p=0.35$, for CHD and MI, respectively). However, the results also suggested that the addition of a genetic risk score might improve risk reclassification in participants who were at intermediate risk on the basis of traditional risk factors. The clinical net reclassification improvement (NRI) was 9.7% ($P=3\times 10^{-6}$).

We recently tested fourteen SNPs identified from GWAS in Caucasians among 1,898 cases with MI and 2,096 population-based controls from the Costa Rican Heart Study (Qi et al., 2011). The allele frequency of some SNPs shows significant differences between this Costa Rican population and the white population. We found that seven SNPs at 3 loci, including *CELSR2-PSRC1-SORT1*, *CXCL12*, and *CDKN2A/2B*, showed significant associations with MI risk, with ORs (95% CI) ranging from 1.12 (1.02–1.24) to 1.22 (1.08–1.38), and that the direction of associations was consistent with those observed in Caucasians. We evaluated the joint effects of the best-associated SNPs by calculating a genetic risk score representing the sum of the risk alleles and observed that increasing genetic risk score was significantly associated with higher risk of MI, with an OR of 1.18 (95% CI, 1.11–1.25) for each increase of 1 risk allele ($P=4.83\times 10^{-8}$). We further examined whether addition of the genetic markers improved the discrimination of MI status. The AUC was 0.67 (95% CI, 0.65–0.69) for the model incorporating conventional risk factors (age, waist-to-hip ratio, smoking, alcohol consumption, physical activity, total calories, and family history of CHD), which slightly, but significantly, increased to 0.68 (95% CI, 0.66–0.70) when the genetic risk score was added ($P=0.02$; Figure 2).

The data from our study and other prediction analyses suggest that although the accuracy of risk models based on various combinations of traditional clinical risk factors could be improved by addition of genetic markers, the improvement in accuracy was small. Thus, the currently identified genetic markers provide statistically significant, but not clinically relevant, contributions to risk prediction for CHD. However, it should be noted that C-statistics alone are not sufficient for assessing the improvement of risk factors in disease prediction, particularly with regard to risk models with already high levels of accuracy. The clinical utility of risk models can also be estimated by measures of reclassification. The net reclassification index (NRI) and the integrated discrimination improvement (IDI) assess whether a novel marker can improve the risk classification for individuals, as compared with models without the marker of interest (Cook & Paynter, 2011; Steyerberg et al. 2010). Studies incorporating such analyses will also be needed to determine whether a genetic risk score provides any additional clinical utility

5. Future challenges and conclusion

As discussed above, the established genetic variants for cardiovascular disease explain only a small proportion (10%) of the observed variance of the disease and these markers contribute modest improvement in predicting disease risk. Therefore, the utility of these genetic determinants in prediction of risk at later stages of life currently has limited immediate clinical impact. This raises the question of whether the identification of additional loci can be expected to improve prediction models with clinical relevance? Recent data suggest that most of the 'missing' heritability may be hidden in a large number of fairly common SNPs with small effect sizes or rare variants, and these additional risk alleles could be identified in even larger GWAS and sequencing projects, respectively, to improve prediction models (Yang et al. 2010). Strong argument has also been proposed to emphasize the importance of expanding GWAS to more ethnically diverse populations. True genetic effects can vary greatly among various ethnic populations due to differences in linkage disequilibrium between the tested and functional variants. Therefore, GWAS in different ethnic groups, such as Hispanics, would facilitate detection of novel cardiovascular-associated variation but are lacking and need to be performed.

In addition to the genetic heterogeneity, substantial variation in socioeconomic status and culture, and other risk factors have been also noted among the various subgroups of Hispanics. For example, Derby et al. found that there is significant heterogeneity in cardiovascular risk status among middle-aged Puerto Rican, Cuban, Dominican, Central American and South American women (Derby et al. 2010). In addition, the subgroups of Hispanics who live at different geographic locations are exposed to various environments that are mostly determined by the places they live. Genetic ancestry is highly correlated with both disease risk and exposure to lifestyle and environmental factors. Therefore, in genetic association studies in which the participants are recruited from multiple geographic locations, it will be imperative to assess this heterogeneity and control for it to avoid potential confounding. In addition, a comprehensive evaluation of gene by environment interactions would be of particular importance to shed light on the observed heterogeneity in cardiovascular risk among Hispanic subgroups.

Genetic research increasingly has projected population comparisons to detect causal variants and explain the population disparity in health. Hispanics represent a population harboring the genetic information of multiple ethnicities; this underscores the particular importance of genetic research in Hispanics to explore the origin of ethnic disparities in cardiovascular disease. Our analysis and several other studies indicate that the inclusion of currently established genetic markers is unlikely to lead to substantial gains in our ability to predict cardiovascular onset beyond that of the traditional risk factors and the translation of research findings into practice is not a straightforward process. Further genome-wide scans and

analysis of the complex interactions with environmental heterogeneity especially among various sub-populations of different geographic origins are needed to comprehensively understand the roles of genetic factors in predicting for cardiovascular disease among Hispanics.

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Abbreviations

CHD	coronary heart disease
CAD	coronary artery disease
MI	myocardial infarction
SNP	single nucleotide polymorphism
TG	triglyceride
HDL	high-density lipoprotein
LDL	low-density lipoprotein
CRP	C-reactive protein
GWAS	genome-wide association study
AIM	ancestry informative marker
PCA	principal component analysis
AUC	area under the receiver operating characteristic curve

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Figure 1. Distribution of individual admixture proportions in 1998 case-control pairs in the Costa Rican Central Valley. Ancestry proportions were estimated using the Admixmap software and 39 ancestral informative markers (AIMs). Individual admixture proportions were also estimated in HapMap YRI and CEU samples to assess the validity of the selected set of AIMs. Reprinted with permission from Hum Genet. (Ruiz-Narváez. et al. 2010)

Figure 2. Receiver-operating characteristic curves for MI

The curves are based on logistic regression models incorporating conventional risk factors (age, sex, area of residence, waist-to-hip ratio, family history of myocardial infarction, smoking, alcohol intake, total calories, and physical activity) with and without the genetic risk score (GRS). AUC = area under the curve; GRS = genetic risk score. (Qi et al. 2010)