Ancestral Effect on HOMA-IR Levels Quantitated in an American Population of Mexican Origin

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OBJECTIVE—An elevated insulin resistance index (homeostasis model assessment of insulin resistance [HOMA-IR]) is more commonly seen in the Mexican American population than in European populations. We report quantitative ancestral effects within a Mexican American population, and we correlate ancestral components with HOMA-IR.

RESEARCH DESIGN AND METHODS—We performed ancestral analysis in 1,551 participants of the Cameron County Hispanic Cohort by genotyping 103 ancestry-informative markers (AIMs). These AIMs allow determination of the percentage (0–100%) ancestry from three major continental populations, i.e., European, African, and Amerindian.

RESULTS—We observed that predominantly Amerindian ancestral components were associated with increased HOMA-IR ($\beta = 0.124$, $P = 1.64 \times 10^{-7}$). The correlation was more significant in males (Amerindian $\beta = 0.165$, $P = 5.08 \times 10^{-7}$) than in females (Amerindian $\beta = 0.079$, $P = 0.019$).

CONCLUSIONS—This unique study design demonstrates how genomic markers for quantitative ancestral information can be used in admixed populations to predict phenotypic traits such as insulin resistance.

Diabetes Care 35:1–3, 2012

Ethnicity has been suggested as a factor affecting the susceptibility to insulin resistance and related chronic diseases (1,2). However, genetic admixture and major confounding by environmental heterogeneity among human populations complicates the assessment of the role of ethnicity. The opportunity to address these issues was presented to us by our community-recruited Cameron County Hispanic Cohort (CCHC). In this cohort, participants are randomly selected from the adult Mexican American population of a small city: Brownsville, Cameron County in South Texas (3). Cultural and lifestyle homogeneity avoids compounding factors in a way that would be problematic in a major city or across a large geographic area. All the CCHC participants are self-identified Mexican Americans, a rapidly growing minority population known to be genetically admixed with European, African, and Native Amerindian ancestries (1). Elevated homeostasis model assessment of insulin resistance (HOMA-IR) index is commonly seen in this population (4). In the current study, our objective was to assess the ancestral effect on insulin sensitivity by measuring the correlation between quantitative ancestral status of our population and fasting HOMA-IR levels using genomic information from ancestral component analysis.

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Received 3 April 2012 and accepted 12 June 2012.
DOI: 10.2337/dc12-0636
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc12-0636/-/DC1.

RESEARCH DESIGN AND METHODS

Subjects

This study investigated 1,551 randomly recruited individuals in the CCHC (3). Sampling bias was corrected based on Census 2000 data to account for age, sex, tract/block, and household clustering.

Genotyping

We genotyped 103 continental ancestry-informative markers (AIMs) for Mexican Americans identified by Kosoy et al. (5), using the Sequenom iPLEX assay (Sequenom, Cambridge, MA). The genotyping call rates of the 103 AIM single-nucleotide polymorphisms were between 95.4 and ~100%, with a median of 99.9%. For the purpose of quality control, 93 DNA samples were genotyped in duplicate. The concordance of duplicate genotypes was 100%.

Data analysis

We used the Eigensoft Software (version 2) for principal component analysis (PCA) (6) and conducted the ancestral analysis using Admixture 1.1 algorithm (7,8). Ancestral components of each CCHC participant were expressed as percentage units (%) referring to each of three major continental populations, i.e., European, African, and Amerindian. The African and European genotyping data were obtained from the HapMap project (http://hapmap.ncbi.nlm.nih.gov), and genotyping data of 105 Amerindians were obtained from the study by Kosoy et al. (5)

RESULTS—By PCA of the 103 AIMs, the CCHC participants showed a predominant admixture of European and Amerindian ancestries (Fig. 1). The genetic ancestry components of this population are superimposable with a population sample of Mexican Americans in Los Angeles, California that were studied in the HapMap project (Fig. 1). There was considerable variation in the proportions of ancestral components between individuals: the median European

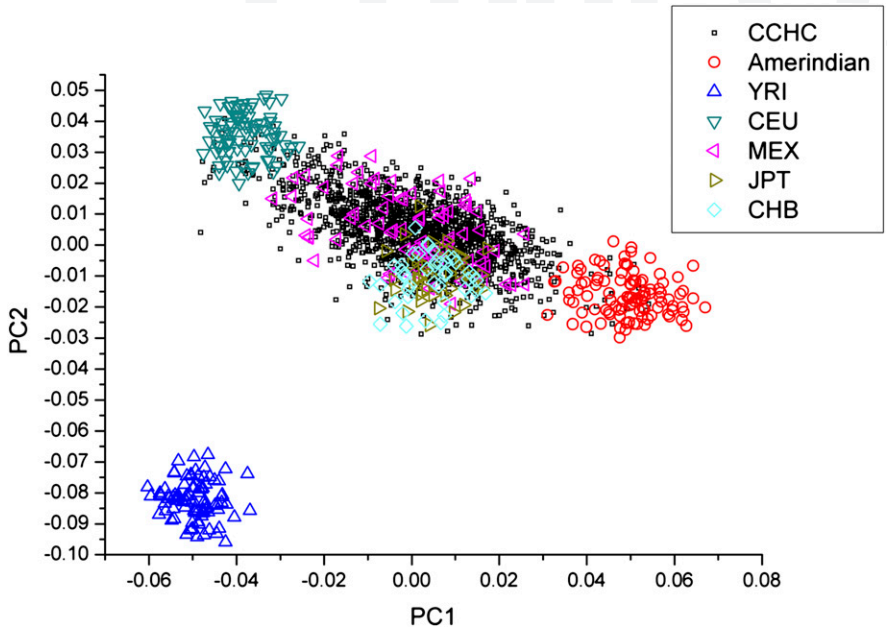

Figure 1—*PCA of the population structure of the CCHC participants. CCHC participants show a predominant admixture of European and Amerindian ancestries. Amerindian, Mayan from Chimaltenango Guatemala, Nahua Amerindians from central Mexico, and Quechuan Amerindians from Peru (5); CEU, Utah residents with Northern and Western European ancestry from the CEPH collection; CHB, Han Chinese in Beijing, China; JPT, Japanese in Tokyo, Japan; MEX, Mexican ancestry in Los Angeles, California; YRI, Yoruba in Ibadan, Nigeria.*

ancestry was 45.8%, with 25% percentile of 35.7% and 75% percentile of 55.1%; the median African ancestry was 11.0%, with 5% percentile of 6.6% and 95% percentile of 15.3%; and the median Amerindian ancestry was 42.9%, with 5% percentile of 33.1% and 95% percentile of 53.0%. The coefficient of variation (CV) of European ancestries was 32.5%, the CV of African ancestries was 59.5%, and the CV of Amerindian ancestries was 37.0%.

To explain high levels of HOMA-IR in this population, we tested the correlation between ancestral components and HOMA-IR levels (Supplementary Table 1). Aging and obesity are known risk factors for insulin resistance (9). Socioeconomic status has also been highlighted as an important factor for the development of insulin resistance (10). After adjusting for age, BMI, household annual income, educational levels, and ancestral components, we found that the Amerindian ancestral component is positively associated with elevated HOMA-IR levels ($\beta = 0.124$, $P = 1.64 \times 10^{-7}$), and the European ancestral component (also expressed as a percentage) is negatively associated with HOMA-IR levels ($\beta = -0.111$, $P = 3.18 \times 10^{-6}$). The correlation is more significant in males (Amerindian $\beta = 0.165$, $P = 5.08 \times 10^{-7}$) than in females (Amerindian $\beta = 0.079$, $P = 0.019$). The adjusted sex effect on HOMA-IR levels has $\beta = 0.062$ and $P = 5.26 \times 10^{-3}$.

CONCLUSIONS—In this study, we demonstrated that higher HOMA-IR levels are correlated with Amerindian ancestry in a Mexican American population. Amerindian and European populations have different susceptibilities to many metabolic diseases (2). The considerable variability of European and Amerindian ancestries between Mexican American individuals that we show in this study suggests that individuals may have different genetic susceptibility to diseases. The incomplete understanding of the genetic susceptibility to complex diseases increases the importance of examining ethnicity information to identify people at high risk of a disease.

We estimated the proportion of ancestry from each contributing population (European, African, and Amerindian) using AIMs developed specifically for the Mexican American population by Kosoy et al. (5). Kosoy et al. have shown that a subset of as few as 24 AIMs is sufficient for ancestral analysis in Mexican Americans (5). Considerable variation of ancestral components found in CCHC participants allows us to more precisely assess ancestral effects within one single population with limited environmental confounding factors. The decreased insulin sensitivity that we have shown to be associated with Amerindian ancestry may thus contribute substantially to high rates of insulin resistance syndrome in Mexican Americans (4). We also observed an interesting sex effect from ancestry in the degree of insulin sensitivity, possibly related to the protective effect of estrogen in females (11). Compared with the Mexican American reference population in the HapMap project, the CCHC participants of our study have similar distributions of ancestral components. Therefore, the results of this study are representative of the broader population of Mexican origin.

A number of genetic variants with key roles in insulin sensitivity have been identified (12,13), including the glucokinase regulatory protein gene (*GCKR*) variant rs780094, which tags the strongest genetic effect among identified genetic loci of insulin sensitivity (13,14). The *GCKR* gene variant partially explains lower insulin sensitivity in Amerindians (6.14% of the ancestral effect) (H.-Q.Q., unpublished data). However, a limitation of our current study is the limited number of AIMs genotyped. Admixture mapping using AIMs at high density in this cohort is warranted to further investigate genetic variants contributing to the ancestral effect. Additional study efficiency may be acquired by the combined usage of association mapping (15).

Acknowledgments—This work was supported by the National Center on Minority Health and Health Disparities (MD-000170-P20) and by the National Center for Research Resources (Centers for Translational Science Award 1U54-RR-023417-01). H.-Q.Q is supported by intramural funding from The University of Texas School of Public Health. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

No potential conflicts of interest relevant to this article were reported.

H.-Q.Q. conceived the study, researched the data, and wrote the manuscript. Q.L. researched data and reviewed and edited the manuscript. Y.L. performed the experiments. C.L.H. provided advice on study design. S.P.F.-H. and J.B.M. developed the CCHC, conceived the study, and wrote the manuscript. H.-Q.Q. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors appreciate Dr. Constantin Polychronakos's instructive comments on this paper. The authors thank the cohort

recruitment team, particularly Rocio Uribe, Elizabeth Braunstein, and Julie Ramirez (The University of Texas School of Public Health, Brownsville Regional Campus [UTSPH-BRC]) and Dr. Anne Rentfro (The University of Texas at Brownsville). The authors also thank Marcela Montemayor (UTSPH-BRC) and other laboratory staff for archiving specimens and performing insulin assays and Christina Villarreal (UTSPH-BRC) for administrative support. The authors thank Valley Baptist Medical Center (Brownsville, TX) for providing space for the Center for Clinical and Translational Science Clinical Research Unit and the community of Brownsville and the participants in our cohort, who so generously participated in this study in their city.

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