Heritability of Measures of Kidney Disease Among Zuni Indians: The Zuni Kidney Project

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Background: The long-term goal of the GKDZI (Genetics of Kidney Disease in Zuni Indians) Study is to identify genes, environmental factors, and genetic-environmental interactions that modulate susceptibility to renal disease and intermediate phenotypes.

Study Design: A community-based participatory research approach was used to recruit family members of individuals with kidney disease.

Setting & Participants: The study was conducted in the Zuni Indians, a small endogamous tribe located in rural New Mexico. We recruited members of extended families, ascertained through a proband with kidney disease and at least 1 sibling with kidney disease. 821 participants were recruited, comprising 7,702 relative pairs.

Predictor Outcomes & Measurements: Urine albumin-creatinine ratio (UACR) and hematuria were determined in 3 urine samples and expressed as a true ratio. Glomerular filtration rate (GFR) was estimated using the Modification of Diet in Renal Disease (MDRD) Study equation modified for American Indians. Probands were considered to have kidney disease if UACR was ≥0.2 in 2 or more of 3 spot urine samples or estimated GFR was decreased according to the CRIC (Chronic Renal Insufficiency Cohort) Study criteria.

Results: Kidney disease was identified in 192 participants (23.4%). There were significant heritabilities for estimated GFR, UACR, serum creatinine, serum urea nitrogen, and uric acid and a variety of phenotypes related to obesity, diabetes, and cardiovascular disease. There were significant genetic correlations of some kidney-related phenotypes with these other phenotypes.

Limitations: Limitations include absence of renal biopsy, possible misclassification bias, lack of direct GFR measurements, and failure to include all possible environmental interactions.

Conclusions: Many phenotypes related to kidney disease showed significant heritabilities in Zuni Indians, and there were significant genetic correlations with phenotypes related to obesity, diabetes, and cardiovascular disease. The study design serves as a paradigm for the conduct of research in relatively isolated, endogamous, underserved populations.

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INDEX WORDS: Genetics; heritability; American Indians; kidney diseases; risk factors; glomerular filtration rate; urine albumin-creatinine ratio (UACR); creatinine; serum urea nitrogen (SUN); uric acid.

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The Zuni Indians are experiencing an epidemic of chronic kidney disease (CKD). The prevalence of end-stage renal disease is 20.0-, 4.4-, and 5.6-fold higher than in European and African Americans and the composite estimate for American Indians, respectively.[1,2] Earlier studies, which were not population based, attributed most kidney disease to mesangiopathic glomerulonephritis.[3-6] Presently, >95% of end-stage renal disease is attributable to diabetic nephropathy.

To decrease the burden of CKD, the Zuni Pueblo established the Zuni Kidney Project in partnership with the Indian Health Service, University of New Mexico, Southwest Foundation

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for Biomedical Research, and Dialysis Clinic Inc.[2] We conducted a population-based cross-sectional survey that showed high prevalence estimates, age-and sex-adjusted to the Zuni population, for decreased estimated glomerular filtration rate (eGFR),[7] albuminuria, and hematuria.[8] Prevalence estimates for albuminuria and hematuria were higher for diabetic than nondiabetic participants.[8,9]

The GKDZI (Genetics of Kidney Disease in Zuni Indians) Study was initiated to identify genes, environmental factors, and genetic-environmental interactions that modulate susceptibility to CKD and intermediate phenotypes. This report presents heritability estimates and genetic correlations for CKD, diabetes, and cardiovascular disease phenotypes.

METHODS

Study Design

GKDZI is a community-based participatory research project. Institutional review boards from each institution approved the study, and informed consent was obtained. We recruited 821 members of extended families ascertained through probands with CKD and 1 or more affected sibling(s).

Setting

The Zuni Pueblo in rural New Mexico is relatively endogamous. The tribe has approximately 10,000 members, and 80% live in the pueblo. Median age is 26 years.[10] Most adult tribal members work as artisans making jewelry, pottery, and fetishes, which are a contemporary art form that represents animals and icons important to the Zuni.

Participants

Probands were identified from Zuni Kidney Project survey participants.[7-9,11,12] Eligibility criteria for probands and affected siblings included age 18 years or older and evidence of CKD, for example, urine albumin-creatinine ratio (UACR) $\geq$0.2 in at least 2 of 3 urine samples or decreased eGFR.[13] We used parental identities to construct family trees and determine the relatedness of individual pairs. We recruited first-, second-, and third-degree relatives of probands and their spouses. First-degree relatives are parents, siblings, and offspring; second-degree relatives are aunts and uncles, nieces and nephews, grandparents, and grandchildren; and third-degree relatives are first cousins, great aunts, great uncles, etc. All family members with CKD were eligible. We used PEDSYS (Southwest Foundation for Biomedical Research, http://pedsys.sfbrgenetics.org)[14] for data entry, quality control, report generation, and preparation of data files for statistical genetic analysis, and PedigreeDraw,[15] a family tree drawing program (Jurek Software, www.pedigree-draw.com).

Variables

Participants were considered to have diabetes if they met at least 1 of the following conditions: (1) history of diabetes, (2) plasma glucose level $\geq$200 mg/dL, (3) hemoglobin A_{1c} (HbA_{1c}) level >7.0%,[16,17] or (4) receiving diabetes medication(s). Diabetes status in participants with HbA_{1c} level of 6.0%-7.0%, plasma glucose level <200 mg/dL, and no history of diabetes was considered "indeterminate."[7] Participants were classified as hypertensive if they met at least 1 of the following conditions: (1) history of hypertension; (2) systolic or diastolic blood pressure $\geq$140 and $\geq$90 mm Hg, respectively;[18] or (3) using antihypertensive medication(s). Blood was drawn for chemistry profile, HbA_{1c},[17] serum creatinine (SCr),[19] and, in a subset, serum cystatin C (SCysC) measurement.[20] Buffy coats were obtained by centrifugation for DNA isolation. We assessed phenotypes related to CKD (eGFR, UACR, SCr, and serum urea nitrogen [SUN]) or diabetes and cardiovascular disease (weight, body mass index [BMI], HbA_{1c}, diabetes status, hypertension status, serum triglycerides, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and total cholesterol) in artisans and nonartisans.

Data Sources and Measurement

Questionnaire Data and Biological Measurements Made in the Home

We administered a questionnaire[2] that ascertained birth dates, parents' identities, education, occupation, tribal affiliation, language spoken, and medical history. Height and weight were measured.[2] We identified overweight (BMI 25-29 kg/m^2) and obese (BMI $\geq$30 kg/m^2) participants. We measured systolic and diastolic blood pressure 3 times separated by 1-minute intervals and used the respective average values to classify hypertension status.

Reducing Bias in Biological Samples

To minimize classification bias, we attempted to obtain 3 urine samples from each participant. The median interval between urine collections was 2 days. We compared classifications of albuminuria and hematuria using the first versus the mode of 3 urine samples. UACR was classified as normal (<0.03), incipient (0.03-0.19), or overt ($\geq$0.20). If all 3 samples were discordant, we used the median value. Urine albumin was measured using nephelometry.[21-23] The presence of 3 or more red blood cells per high-power field was considered evidence of hematuria.

Reducing Bias in eGFR

We used the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation, modified for use in American Indians,[7,8,24] and a SCysC-based equation (both formulas are given in the notes to the third table in this article) to estimate GFR based on a single serum sample.[25-28] Limitations of these equations include need for race-specific coefficients and lack of widespread calibration in SCr and SCysC assays.[25] SCr level is influenced by muscle mass. eGFR may underestimate GFR in people with near-normal kidney function.[25-28] We categorized eGFR using the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative