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Mexican-American Admixture Mapping Analyses for Diabetic Nephropathy in Type 2 Diabetes Mellitus

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Summary

Diabetic nephropathy is a classic complex trait, whose development in a given individual reflects contributions from multiple genes and whose expression is modulated by environmental factors. Numerous genetic strategies have been used to identify common disease risk loci and genes, including candidate gene analyses, linkage analysis, transmission disequilibrium testing (a family based association test to identify linkage between a genetic marker and a biological trait or disease), and admixture mapping (also referred to as *mapping by admixture linkage disequilibrium*). Choosing the best genetic strategy to identify susceptibility genes in a disease is dependent on knowing whether the disorder is monogenic (the result of one gene), oligogenic (the result of a few genes), or polygenic (the result of many genes). The likelihood of finding risk loci for a disease with a putative genetic contribution is in part owing to the disease recurrence risk ratio (the risk of expressing the disease phenotype in siblings of the proband divided by the risk observed in the general population), the genotypic risk ratio (the risk of expressing the phenotype if the gene is present divided by the risk if the gene is not present), the number of susceptibility genes, how the susceptibility genes interact, how much of the disease risk is contributed by environmental factors, and the disease penetrance (the likelihood that the phenotype will be expressed if the gene is present).

Keywords

Admixture mapping; diabetic nephropathy risk loci; Mexican-Americans

For diabetic nephropathy from type 2 diabetes, despite years of research, a single gene contributing a large effect has not yet been identified. However, there has been some success in replicating risk loci of modest effect for some populations with diabetic nephropathy, including genes in the renin-angiotensin-aldosterone system in many ethnic groups¹; the engulfment and motility-1 (ELMO1) gene in Japanese and African Americans and in Caucasians with type 1 diabetes^{2–4}; carnosinase (CNDP1) in Europeans^{5,6}; and superoxide

dismutase 2 in Europeans, Koreans, and Japanese,⁷⁻⁹ although dissenting data for each of these variants have been published.^{10,11} It is worthwhile to briefly review the history of the search for type 2 diabetic nephropathy genes, which mirrors progress in the field of genetics, to appreciate the potential contribution of the gene-searching methodology called *admixture mapping* or *mapping by admixture linkage disequilibrium* for finding genetic risk loci in admixed populations.

CANDIDATE GENE CASE-CONTROL STUDIES

Initial attempts to identify genetic risk in diabetic nephropathy focused on studies testing candidate genes in case-control association studies comparing unrelated probands and control subjects. Case-control association studies are advantageous in oligogenic and polygenic disorders with low genotypic relative risk and moderate to high allele frequency in the population. However, they are subject to error owing to unrecognized population substructure resulting from systematic differences in allele frequencies between cases and controls. These effects may relate to differential ancestry (population stratification). In addition, differential disease prevalence rates between groups can cause false-positive association results. Candidate genes are chosen on the basis of hypotheses of disease pathogenesis, thus limiting their scope. Literally scores of candidate gene articles have been published for type 2 diabetic nephropathy, and these have been reviewed.¹² For some genes identified by this strategy, particularly those in the renin-angiotensin system, the preponderance of evidence does support a significant role for conferring diabetic nephropathy risk. But for many, the significance of the findings are clouded by numerous limitations, including lack of replication, small cohort and effect size, population stratification, and lack of consistency across studies among individuals of diverse ancestry, although the latter may represent actual differences.

LINKAGE ANALYSIS

Candidate gene studies were followed by attempts to identify risk loci by the classic method of family based linkage analysis.¹³⁻²² Concordant sibling-pair analyses provide strong linkage data when the recurrence risk ratio of individual susceptibility loci is high. This strategy is dependent on identifying and collecting a large number of affected sibling pairs. Estimates for the recurrence risk ratio in diabetic nephropathy range from 1.7 to 3.5.^{23,24} Discordant sibling pairs also have been used to find risk loci, and may provide increased power,²⁵ but this strategy is sensitive to low penetrance, and therefore may be problematic when penetrance is not well defined, which is the case for diabetic nephropathy. The power of linkage analysis is optimal when a relatively small number of risk loci contribute a moderate to large risk effect. Unlike candidate gene analysis, linkage analysis represents a more unbiased approach to gene hunting because the genome-wide approach for searching is independent of preconceived ideas regarding pathogenesis. Risk loci for diabetic nephropathy from linkage analysis studies have been reported on chromosomes 3, 7, 9, and 20 in Pima Indians¹⁸; chromosomes 2q, 3q, 10p, 18q and 19q in Caucasians^{16,17,19,20}; and chromosomes 12 and 20 in African Americans. 26 Preliminary linkage data were reported from the National Institutes of Health-funded Family Investigation of Nephropathy and Diabetes (FIND) study in abstract form indicating risk loci on chromosomes 1q, 10p, 15q, and 18p in Native Americans; 6p in Caucasians; and 1p in Mexican Americans.²¹ However, more often than not, even these studies show limitations similar to those observed in candidate gene studies, including smaller sample size than would be optimal for adequate power (despite relatively larger numbers in more recent years), large expense, and lack of replication.

Transmission disequilibrium testing (TDT) is a genetic strategy for the identification of genetic risk loci. It is based on showing disproportionate transfer of a risk locus from a parent with a particular trait or disease to affected children compared with the transfer of the locus to

unaffected children. This strategy may have greater power than classic linkage analysis.²⁷ However, in the context of diabetic nephropathy from type 2 diabetes, this strategy has proven to be impractical. TDT is robust to false-negative associations owing to differences in population substructure. Because diabetic nephropathy has an older age of onset, the simultaneous identification and recruitment of affected parents and children with diabetic nephropathy has proven difficult, and most if not all studies that use these mapping strategies are not powered adequately to identify variants with the small effect sizes expected for diabetic nephropathy.

GENOME-WIDE ASSOCIATION STUDIES

The low yield of reproducible findings derived from linkage analysis studies for diabetic nephropathy resulted in a shift back toward case-control populations, searching for chromosomal risk loci by genome-wide association studies (GWAS). GWAS have been more effective in identifying reproducible chromosomal risk loci than linkage analysis in complex disorders, with diabetes as a case in point.²⁸ All of the following genes that confer a risk for diabetes mellitus identified by GWAS have been replicated, including but not limited to TCF7L2 (transcription factor 7-like2); JAZF1 (nuclear protein JAZf zinc finger); CD123 (interleukin-3 receptor); TSPAN8 (tetraspanin 8); THADA (thyroid adenoma associated; death-receptor interacting protein); ADAMTS9 (a disintegrin-like and metalloproteinase 9); Notch2; DCD (dermicidin); Calpain 10; PTPN1 (protein tyrosine phosphatase N1); CDKAL1 (CDK5 regulatory subunit associated protein 1-like 1); Syn2 (Synapsin 2); peroxisome proliferator activated receptor γ ; BCL11A (B-cell CLL [chronic lymphocytic leukemia] zinc finger protein); ADAM30 (metalloproteinase); KCNJ11 (adenosine triphosphatase-sensitive inward rectifier potassium channel 11, a sulfonylurea target); IGF2BP2 (insulin-like growth factor 2 binding protein 2); CDKN2A/B (maintains stem cellness); SLC30A8 (β -cell specific zinc transporter); FTO (obesity gene, accounts for 1% variance in body mass index); and HHEX (homeobox gene involved in pancreas development) have been replicated. Despite the obvious success of this methodology, it should be appreciated that relatively large patient cohorts are required and classic single nucleotide polymorphism (SNP) markers numbering from 200,000 to several million are needed to identify risk loci. GWAS studies are subject to false-positive results because of unrecognized population stratification. However, several different methods have been developed to statistically address issues of population structure and substructure in the context of whole-genome association studies.^{29–34}

ADMIXTURE MAPPING

Another genetic approach, admixture mapping, or mapping by admixture linkage disequilibrium, is a special type of case-control association study. Admixture mapping can fill a niche between linkage analysis and GWAS, especially if the genes determining phenotypes have been subject to selection or drift when human populations were small. Stated simply, admixture mapping is a useful analytic tool in ethnic groups in whom the genetic inheritance is represented by a composite, usually derived from two separate continental origins. A few major requirements apply for admixture mapping to confer power in genetic analyses. Admixture mapping requires that the origin of the parental genomes that contribute to the hybrid population is known and that the genetic contributions from the parental populations be distinguishable at the genetic level at many loci. The genetic admixture must have been present in the population for several to many generations. Individuals of very recent admixture (last 2 generations) do not confer analytic advantage. The susceptibility genes for the two parental populations must be different and ideally the disease prevalence or severity profiles of the disease in question in the two parental population groups must differ. The easier it is to distinguish between the two parental contributor populations, the greater the power of the method. This method assumes that one of the parental populations has a higher risk for disease

(eg, diabetic nephropathy) than the other for a specific locus, and that the locus (or loci) contributing to this excess risk tracks with the ancestry of the chromosomal segments in the hybrid population (Fig. 1). Finally, admixture mapping requires a specially designed genomic scanning marker set with ancestry-informative markers with large allele frequency differences in the two parental populations to optimally identify SNPs that distinguish the two parental groups and that cosegregate with the disease state. Thus, admixture mapping can confer several advantages in the search for disease risk genes in admixed populations.^{35,36} It confers increased power over other widely used gene mapping techniques. It requires several thousand rather than several hundred thousand markers. Finally, it is less affected by other mutational effects that are unrelated to the ancestral differences.

In the United States, African Americans and Mexican Americans are groups in whom admixture mapping analyses can contribute favorably to the identification of risk loci in various clinical disorders. More commonly used in African Americans at this point in time because of marker availability, admixture mapping has been successful in contributing to the identification of chromosomal loci and/or genes contributing to increased risk in African Americans for multiple sclerosis,³⁷ obesity,^{38–40} peripheral arterial disease,⁴¹ prostate cancer,⁴² hyperlipidemia,³⁸ type 2 diabetes,⁴³ coronary artery calcification,⁴⁴ and nondiabetic end-stage renal disease.⁴⁵ Although not as commonly used to find genes and/or chromosomal loci in the Mexican American population as in African Americans, admixture is nevertheless a powerful tool for this purpose in this group.

THE DEVELOPMENT OF A MARKER SET FOR ADMIXTURE MAPPING IN MEXICAN AMERICANS

The large linkage disequilibrium (linkage of markers with ancestral information) in admixed populations translates into smaller requirements for both marker saturation and sample size than standard association studies. Today's Mexican American population is a nearly ideal admixed population for this type of analysis. In contrast to the large experience with admixture mapping in African Americans, the relative paucity of data in the Mexican American population is attributable to the relative lack of appropriate ancestry informative markers with which to perform genotyping in this group. Three marker sets recently were developed for Hispanic admixed populations. Panels of 2,100 and 1,649 were developed for Hispanic/Latino populations,^{46,47} and 8,144 were identified for Mexican Americans.⁴⁸

For admixture mapping studies in Mexican Americans,⁴⁸ it was necessary to develop a genome-wide SNP panel that can distinguish between chromosomal segments of Amerindian and European ancestries, called *ancestry informative markers*. In our studies, genotypes for more than 400,000 SNPs defined in European, Pima, and Mayan populations were used to start. The use of two Amerindian populations was necessary to remove a subset of SNPs that distinguished genotypes of only one Amerindian subgroup from European genotypes, so the resultant SNPs would maximally distinguish the Amerindian inheritance from the European inheritance, and at the same time would minimize differences among Amerindian groups. Differences and similarities between SNPs of different geographic origins were defined statistically by an F-statistic (F_{st}). The marker set developed had SNP F_{st} values greater than 0.30 (mean F_{st} , 0.48) distinguishing the European from Amerindian SNPs. In addition, differences between Mayan and Pima SNPs were minimized (F_{st} values, <0.05 ; mean F_{st} , <0.01).

Two statistical methods (STRUCTURE [<http://pritch.bsd.uchicago.edu>] and ADMIXMAP [http://homepages.ed.ac.uk/pmckeigu/admixmap/manual_desc.html]) were used to estimate the overall number of generations since initial admixture in the Mexican American population. The average number of generations varied for each chromosome, probably owing to the small

sample size because the admixture mapping information was similar for each chromosome. STRUCTURE and ADMIXMAP algorithms showed a mean of 15.7 ± 3.15 (standard deviation) and 13.3 ± 4.1 generations, respectively. The number of generations for each chromosome estimated using these two algorithms were highly correlated ($r^2 = 0.60$, $P = .0004$, paired t test). The difference between the STRUCTURE and ADMIXMAP estimations probably is owing to the difference between these algorithms: STRUCTURE estimates the admixture generation for each individual, whereas ADMIXMAP estimates the number of generations for each gamete separately.

The number of ancestry informative markers required for admixture mapping is in part a function of the number of generations since admixture in the study population. Based on estimates of the number of generations since admixture, a calculation can be performed to estimate the power of the admixture mapping information from a given marker set. An estimation of admixture mapping information was calculated for a set of 8,144 SNP ancestry informative markers that met the European/Amerindian F_{st} greater than 0.30, Pima/Mayan F_{st} less than 0.05 criteria, and for smaller subsets of ancestry informative markers from this group of 8,144. The complete panel of 8,144 SNP ancestry informative markers extracted more than 50% of the admixture information for more than 99% of the genome and more than 60% of the admixture information for more than 85% of the genome. A subset of 5,287 SNPs selected for informativeness only marginally decreased these levels of extracted admixture information.

The admixture ratios in Mexican Americans show nearly an equal representation of European and Amerindian ancestry, on average, which distinguishes this population from African Americans, in whom the African representation is much greater than the European component. In addition, the average number of generations since admixture is greater in Mexican Americans compared with African Americans. Although the larger number of generations leads to a requirement for a larger set of markers in Mexican Americans than African Americans, this tends to be offset by the near equal admixture of parental populations, suggesting that the admixture mapping strategy in Mexican Americans should be at least as powerful as in African Americans. Although the panel created provides reasonable admixture mapping information when the parental admixture proportions deviate from 50:50, the power will decrease when the contribution from either of the parental populations deviates from 50:50 substantially. The effect on power is greatest when the ethnicity relative risk is modest, the admixture ratios more extreme, and the susceptibility gene derives from the parental population with the larger contribution.^{35,49}

Together, these strategies identified large numbers of SNP ancestry informative markers, providing a marker set that is useful for admixture mapping in European/Amerindian admixed populations. The full marker set developed of 8,144 SNPs were separated by a minimum of 50 kb with only three intermarker intervals more than 1 Mb. Analysis of a subset of these SNP ancestry informative markers suggested that this panel also may distinguish ancestry between European and other Amerindian groups including the Quechuans from South America. Realistic simulation parameters that were based on analyses of Mexican American genotyping results showed that this panel of SNP ancestry informative markers provides good power for detecting disease-associated chromosomal segments for genes with modest ethnicity risk ratios. A reduced set of 5,287 SNP ancestry informative markers captured almost the same admixture mapping information. Smaller SNP sets show substantial drop-off in admixture mapping information and power. This marker set will enable studies of type 2 diabetes, rheumatoid arthritis, and other diseases in which epidemiologic studies suggest differences in the distribution of ancestry-associated susceptibility. The marker set initially was tested in a case-control cohort of Mexican American patients with type 2 diabetes with and without diabetic nephropathy.

USING THE MEXICAN AMERICAN ADMIXTURE MAPPING MARKER SET TO IDENTIFY CHROMOSOMAL RISK LOCI FOR DIABETIC NEPHROPATHY

Diabetic nephropathy from type 2 diabetes is more common in ethnic groups with a large percentage of African or Amerindian ancestry than in Europeans. Because the prevalence and incidence of diabetic nephropathy is well known to differ among ethnic groups, a strategy that uses special genetic markers in an attempt to link disease risk to ancestral inheritance of particular polymorphisms is a particularly powerful tool in the approach to identify these risk loci. The National Institutes of Diabetes, Digestive and Kidney Diseases–sponsored FIND study is a consortium with the goal of identifying diabetic nephropathy, diabetes, and diabetic retinopathy risk genes. Its design has been reviewed.⁵⁰ Overall, FIND used linkage analysis, GWAS, and admixture mapping in African Americans and Mexican Americans to identify diabetic nephropathy risk loci. The diabetes and diabetic nephropathy phenotypes in the separate studies were nearly identical, and are summarized in Table 1. There were two major differences between the phenotypes in the FIND linkage analysis and the Mexican American admixture mapping study. In the latter, there was a requirement for both diabetic nephropathy probands and controls to have two parents and all four grandparents of Mexican American ancestry. In addition, in the Mexican-American admixture mapping study, no control was to have a known first-degree relative with end-stage renal disease or known kidney disease.

Preliminary results of the FIND Mexican-American admixture mapping study have been published in abstract form.⁵¹ A total of 664 probands and 490 controls were studied. The participants were genotyped with a lithographic array using a subset of the genome-wide panel of ancestry informative markers developed that distinguish European and Amerindian ancestry.⁴⁸ Analyses were performed using ADMIXMAP software, which uses a Markov Chain Monte Carlo statistical algorithm to assign probability of ancestry, applying a score test for assessing the strength of ancestry linkage with the trait. The data were analyzed taking into account age, sex, diabetes duration, and recruitment site as covariates.

The analysis revealed a locus in the region of chromosome 2q36.3–37.1 arising from the Amerindian ancestral genome associated with diabetic nephropathy and reaching genome-wide statistical significance by permutation testing. Candidate genes in this region include, but are not limited to, delta and notch-like EGF repeats (DNER); the Sp100 family of promyelocytic leukemia protein oncogenic domain (POD) proteins Sp100, 110 and 140; CCL20 (also known as *macrophage inflammatory protein 3 alpha*); PID1 (also known as *phosphotyrosine interaction domain containing 1*); and collagen IV alpha 3 and 4 peptide chains. This region also has been reported to bear a locus associated with glomerular filtration rate changes in Mexican American subjects with type 2 diabetes.⁵² Replication and fine mapping studies, as well as a demonstration of biological relevance, will be required to ascertain the significance of this finding. However, the FIND linkage analysis did not identify chromosomal loci for diabetic nephropathy that reached genome-wide significance in Mexican American participants despite a larger cohort for analysis and a denser marker set used. Thus, although these data are preliminary and require substantiation, the data nevertheless support the proposition that admixture mapping is a powerful tool in the search for genetic risk loci in admixed populations such as Mexican Americans.

There are some limitations of admixture mapping. If a region in the genome undergoes selection for another cause (eg, an infectious disease), it is possible that unidentified differences in the parental population that are unrelated to disease risk per se could lead to spurious results in admixture mapping. Ultimately, the best means to protect from false-positive errors, for example, identification of genes (loci) unrelated to disease, is to perform replication in an independent sample. For the finding on chromosome 2q in Mexican Americans with diabetic nephropathy, this process is under way.

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Figure 1.

Admixture mapping is a method for genome-wide linkage studies based on association with ancestral heritage. Conceptually pictured, a SNP in the affected group of Mexican Americans (MAs) is ancestrally derived from the parental group with the higher disease prevalence, whereas a SNP in the control group is ancestrally derived from the parental group with the lower disease prevalence.

Table 1**Phenotypic Characteristics of the Subjects Studied in the Mexican American Admixture Mapping Cohort of the FIND Study**

Type 2 diabetes as per FIND ²¹
Diabetic nephropathy probands
Subjects with ESRD
DM duration ≥ 5 years before ESRD + retinopathy; or
DM duration ≥ 5 years before ESRD + ≥ 3 g proteinuria either by 24-hour or protein/cr ratio or albuminuria equivalent (historical values accepted); or
Proteinuria + retinopathy
Subjects with CKD but not ESRD
Retinopathy + DM duration ≥ 5 years + ≥ 1 g proteinuria either by 24-hour or protein/cr ratio or albuminuria equivalent (historical values accepted); or
If no retinopathy, DM duration ≥ 10 years + ≥ 3 g proteinuria either by 24-hour or protein/cr ratio or albuminuria equivalent (historical values accepted);
Biopsy-proven DN + ≥ 500 mg proteinuria or albuminuria equivalent
Diabetic controls
DM duration ≥ 10 years
Normoalbuminuria (ACR < 0.03 g/g albumin/creatinine)
Serum creatinine
<1.6 mg/dL for males
<1.4 mg/dL for females
No history of renal disease (except hypertension)
No first-degree relative with known kidney disease*

Abbreviations: ESRD, end-stage renal disease; cr, creatinine; DM, diabetes mellitus; CKD, chronic kidney disease; ACR, albumin/creatinine ratio.

* Applicable only to the Mexican American admixture mapping study.