Linkage of Type 2 Diabetes on Chromosome 9p24 in Mexican Americans: Additional Evidence from the Veterans Administration Genetic Epidemiology Study (VAGES)

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Key Words

Type 2 diabetes · Linkage · Chromosome 9p24 · Mexican Americans · VAGES

Abstract

Objective: Type 2 diabetes (T2DM) is a complex metabolic disease and is more prevalent in certain ethnic groups such as the Mexican Americans. The goal of our study was to perform a genome-wide linkage (GWL) analysis to localize T2DM susceptibility loci in Mexican Americans. **Methods:** We used the phenotypic and genotypic data from 1,122 Mexican-American individuals (307 families) who participated in the Veterans Administration Genetic Epidemiology Study (VAGES). GWL analysis was performed using the variance components approach. Data from 2 additional Mexican-American family studies, the San Antonio Family Heart Study (SAFHS) and the San Antonio Family Diabetes/Gallbladder Study (SAFDGS), were combined with the VAGES data to test for improved linkage evidence. **Results:** After

adjusting for covariate effects, T2DM was found to be under significant genetic influences ($h^2 = 0.62$, $p = 2.7 \times 10^{-6}$). The strongest evidence for linkage of T2DM occurred between markers D9S1871 and D9S2169 on chromosome 9p24.2-p24.1 (LOD = 1.8). Given that we previously reported suggestive evidence for linkage of T2DM at this region also in SAFDGS, we found the significant and increased linkage evidence (LOD = 4.3, empirical $p = 1.0 \times 10^{-5}$, genome-wide $p = 1.6 \times 10^{-3}$) for T2DM at the same chromosomal region, when we performed a GWL analysis of the VAGES data combined with the SAFHS and SAFDGS data. **Conclusion:** Significant T2DM linkage evidence was found on chromosome 9p24 in Mexican Americans. Importantly, the chromosomal region of interest in this study overlaps with several recent genome-wide association studies involving T2DM-related traits. Given its overlap with such findings and our own initial T2DM association findings in the 9p24 chromosomal region, high throughput sequencing of the linked chromosomal region could identify the potential causal T2DM genes.

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Introduction

Type 2 diabetes (T2DM) is a complex metabolic disease, characterized by insulin resistance and impaired β -cell function [1–3]. T2DM continues to be a major global public health problem and a large economic burden. Approximately 24 million people in the United States are estimated to have diabetes, and about 48 million people are projected to have diabetes by the year 2050 if current demographic trends continue [4]. Also, the prevalence of T2DM is disturbingly high in US ethnic minorities such as the Mexican Americans [5]. Both genetic and environmental factors play important roles in the development of T2DM [1, 6–9]. There have been continued efforts to localize and characterize T2DM susceptibility genes using genome-wide linkage (GWL) and, most recently, genome-wide association approaches. Although linkage studies have identified various T2DM susceptibility loci [10], subsequent gene discovery successes from such efforts have been limited. In recent years, as an alternative gene localization tool, the genome-wide association study (GWAS) method has become a popular design with several notable successes in localizing several novel T2DM susceptibility genes/variants [11]. This approach is based on the common variant/common disease hypothesis, and generally uses data from large samples of unrelated cases and controls. So far, more than 60 T2DM susceptibility loci have been localized with genome-wide significance [12–16]. Of these loci, only the transcription factor 7-like 2 (*TCF7L2*) gene was localized as a follow-up to the previous report of linkage of T2DM to the 10q chromosomal region in an Icelandic population [17, 18], where we previously found evidence for linkage of T2DM in Mexican Americans [19].

GWASs have contributed greatly to the understanding of the genetic architecture of T2DM. However, for most cases, the identity of the causal genes and the functional relevance of the implicated genetic variants have yet to be established. As has been the case with various GWASs of other complex diseases, the genetic contribution of common variants identified by the GWASs to the overall susceptibility to T2DM is rather modest. These observations have led to thoughts of ‘missing heritability’ and ‘synthetic associations’, in turn highlighting the potential role of rare variants of large effect [20–22]. However, following Gibson [22], it is conceivable that both common and rare variants could be important contributors to complex disease risk. Although most of the T2DM GWASs have involved populations of European ancestry, their relevance to other ethnic groups, such as Mexican Americans, who

are at a high T2DM risk, has been examined with attention, focused on issues such as allele frequency and linkage disequilibrium differences among diverse populations [23]. However, recently, the transferability of previous GWAS findings in multiethnic populations has been reported [24–26].

Therefore, the purpose of this study was to perform a GWL analysis to localize T2DM susceptibility loci in Mexican Americans residing in San Antonio, Texas, for potential subsequent efforts of fine-mapping for identifying the causal variants, both rare and common, which could be specific for the Mexican-American population. To meet our objective, first, we used data from the Veterans Administration Genetic Epidemiology Study (VAGES) and performed a GWL analysis using variance components linkage analytical techniques implemented in the program SOLAR [27]. Second, since we previously reported T2DM linkage signals from another Mexican-American family study in San Antonio, the San Antonio Family Diabetes/Gallbladder Study (SAFDGS) [19, 28], the present study has also combined the VAGES data with those from SAFDGS and a second Mexican-American family study in San Antonio, the San Antonio Family Heart Study (SAFHS), to perform a GWL analysis for examining whether the use of the combined data would yield improved evidence for linkage at any of the genetic locations found to be linked with T2DM in our SAFDGS and/or VAGES data sets.

Research Design and Methods

The Veterans Administration Genetic Epidemiology Study

The demographic, genotypic, and phenotypic data were collected from Mexican-American individuals who had been enrolled in VAGES. The study procedures have been described elsewhere [29]. In this study, we used data from 1,122 participants from 307 Mexican-American families for whom the diabetic status was known (table 1). The VAGES families were ascertained based on at least 2 siblings and 1 parent affected with T2DM. These 1,122 study participants generated a total of 1,950 relative pairs with varying degrees of genetic relationships. Of these 1,950 pairs, 350 were unaffected-unaffected pairs, 847 were unaffected-affected pairs, and 753 were affected-affected pairs (table 2). The study protocol was approved by the Institutional Review Board of the University of Texas Health Science Center at San Antonio, and written informed consent was obtained from all subjects.

Phenotypic Data

The phenotypic data for various metabolic and anthropometric traits, including information on medical history, were collected for the study participants [29]. In addition to the fasting plasma glucose concentration, plasma glucose levels were

Table 1. Clinical characteristics of the individuals from VAGES, SAFDGS, SAFHS, and the combined data

	VAGES	SAFDGS	SAFHS	Combined data
Sample size, n	1,122	557	1,407	3,086
Age, years	49±13	42±17	39±17	43±16*
Females, %	65	59	60	62*
T2DM ^a , %	65	26	16	36**
Age at T2DM onset, years	44±12	49±14	48±15	45±13**
BMI	33.2±7.8	30.1±6.6	29.3±6.6	30.8±7.3**
Waist circumference, mm	1,036.2±169.6	975.2±174.7	948.0±171.7	984.5±176.0**

^a Diagnosed according to the WHO criteria [30].

* $p < 0.01$; ** $p < 0.0001$. p value was not corrected for non-independence.

Table 2. Number and types of relative pairs generated from 1,122 VAGES participants distributed across 307 families in the present study

Type of relative pairs	Relationship coefficient ^a	Unaffected-unaffected pairs, n	Unaffected-affected pairs, n	Affected-affected pairs, n
Parent-offspring	0.5000	52	194	200
Siblings	0.5000	203	489	484
Grandparent-grandchild	0.2500	3	13	2
Avuncular	0.2500	62	111	34
Half-siblings	0.2500	10	25	22
Third degree	0.1250	20	14	11
Fourth degree	0.0625	–	1	–
Total		350	847	753

^a The relationship coefficient is 2× the coefficient of kinship of 2 individuals.

measured during a 2-hour oral (75 g) glucose tolerance test. The subjects were classified as having T2DM, if they had a fasting glucose concentration ≥ 126 mg/dl and/or a glucose level after 2 h of ≥ 200 mg/dl according to the 1999 criteria of the World Health Organization [30]. Participants who did not meet these criteria, but reported to be under treatment with either oral antidiabetic agents or insulin, and those who gave a history of diabetes were also considered to have T2DM. Anthropometric data (i.e., height, weight, and waist circumference) were collected using standardized procedures. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). For the analyses, the BMI was log transformed to provide an approximately normal distribution.

Genotypic Data

The Center for Inherited Disease Research (CIDR) performed an approximately 10-cM genome scan (i.e., 385 highly polymorphic autosomal STR markers) using the DNA samples from the VAGES participants [29]. The genetic map obtained from these data was used to localize T2DM susceptibility loci.

Briefly, the program PREST was used to resolve pedigree discrepancies. The programs PRESWALK and SimWalk2, as implemented in PEDSYS, were used to clean the genotype data of Mendelian inconsistencies and spurious double recombinants which may inflate map distances. Multipoint identical-by-descent matrices were estimated using Markov chain Monte Carlo methods implemented in the program Loki using SOLAR, as described previously [29]. To facilitate a comparison with other studies, the locations of our linkage findings were placed on the Marshfield genetic map.

Statistical Analysis

A variance components approach was used to evaluate the genetics of T2DM [31]. In a simple model, variances or covariances between relatives as a function of the genetic relationships can be specified, and the proportion of phenotypic variance that is attributed to additive genetic effects (i.e., heritability: h^2) can be estimated from the components of variance. We used an extension of the variance components method to a threshold model to test for linkage between genetic markers and the discrete trait T2DM [32].

Table 3. Genetic locations linked to T2DM with LOD scores ≥ 1.2 based on multipoint linkage analyses of VAGES and combined data sets

Marker region	Distance from p-ter, cM	Chromosomal location	Maximum LOD	
			VAGES	combined data
D5S807	19	5p15.31	–	1.2
D5S2494	59	5p13.1	–	1.7
D5S629-D5S424	77–82	5q13.1-q13.3	–	1.2
D9S1779-D9S2169	0–14 ^a	9p24.3-p24.1	1.8	4.3
D11S1999-D11S1981	17–21	11p15.3-p15.1	1.5	(1.0) ^b
D21S1254-D21S1440	31–37	21q22.11-q22.13	–	2.0

^a Combined data = D9S1779-D9S1871 (0–8 cM), and VAGES = D9S1871-D9S2169 (8–14 cM); ^b shown for the purpose of comparison with the VAGES finding.

Fig. 1. Findings from a multipoint linkage analysis of T2DM in the combined data. Genetic locations with potential evidence ($\text{LOD} \geq 1.2$) for T2DM linkage have a LOD scale next to them. The 11p chromosome finding is associated with a LOD score of 1.0, and shown for the purpose of discussion.

The variance components (i.e., heritability attributed to the susceptibility locus and heritability attributed to the residual additive genetic effects) and covariates for T2DM (e.g., age and sex) were estimated simultaneously in likelihood terms. A hypothesis testing of no linkage versus linkage was performed using the likelihood ratio test. Twice the difference in the ln likelihoods of these models yields a test statistic that is asymptotically distributed as 1/2:1/2 mixture of χ^2_1 and a point mass at 0, denoted by χ^2_0 , where the degree of freedom (d.f.) is equal to the difference in the number of parameters estimated between the 2 competing models. LOD scores were obtained by converting the ln likelihood values into values of log to the base 10. A LOD score of ≥ 3.0 was considered as significant evidence in support of linkage. For the purpose of discussion, LOD scores ≥ 1.2 were considered as evidence for potential linkage. Given the VAGES family ascertainment scheme, all genetic analyses including the estimation of heritability were performed by correcting for the ascertainment, as described previously [29]. The program SOLAR was used to perform the statistical, genetic, analytical procedures described above [31].

Combined Data from VAGES, SAFHS, and SAFDGS for Linkage Analysis

Since VAGES, SAFHS, and SAFDGS are part of our ongoing San Antonio Family Birth Weight Study, the combined genetic maps, generated based on marker data from these 3 family studies, were used for this study [33]. For consistency with VAGES, the baseline phenotypic data from SAFHS and SAFDGS were used (table 1). SAFHS's and SAFDGS's study procedures have been described previously [19, 28, 34, 35]. Briefly, the phenotypic data from 1,407 SAFHS participants from 42 large families and from 557 SAFDGS participants from 31 large families were utilized for the present study (table 1). T2DM and other phenotypic data were obtained using methods similar to the procedures in VAGES. All genetic analyses were performed using methods described previously. For the combined linkage analysis, 2 dummy variables were generated as additional covariates to account for the study effects. To verify our major T2DM linkage finding on chromosome 9p24, we performed a simulation analysis to determine the empirical p value, using information obtained from 100,000 replicates. In addition, to address the issue of multiple testing, we estimated the genome-wide p value for the strongest T2DM linkage finding, following the method of Feingold et al. [36].

Preliminary Association Analysis of the T2DM-Linked Region on Chromosome 9p24

We screened for the potential common genetic variants influencing T2DM in the 1.5-LOD support interval using data from 2 (i.e., SAFHS and SAFDGS) of the 3 studies used for our linkage analysis (table 1). The 1.5-LOD support interval refers to the critical chromosomal region surrounding the linkage peak with an approximately 95% probability of containing the susceptibility locus [37]. We used our existing genome-wide genotypic data obtained from SAFHS and SAFDGS to select 5,329 single nucleotide polymorphisms (SNPs) representing the T2DM-linked region for the association analysis [38]. In addition, we also carried out similar analyses for fasting glucose and insulin data related to nondiabetic individuals only. The details of the genome-wide genotypic data involving approximately 950,000 SNPs, which were generated using several versions of Illumina's BeadChip microarrays and the Illumina Infinium protocol and processed using standard quality

control procedures, were previously reported [38]. We used an additive measured genotype approach within the variance components framework to conduct an association analysis as implemented in the program SOLAR.

Results

The study-specific clinical characteristics of the participants are reported in table 1. The VAGES data analyses involved information from 1,122 individuals (females: 65%, mean age: 49 years, T2DM: 65%, and mean BMI: 33), and the combined data analyses were based on information from 3,086 individuals (females: 62%, mean age: 43 years, T2DM: 36%, and mean BMI: 31). Initially, the heritability ($h^2 \pm SE$) of T2DM in the VAGES data was determined to be 0.62 ± 0.16 after adjusting for the significant ($p \leq 0.05$) covariate effects of age, sex, age^2 , $age^2 \times sex$, and ln BMI, which was highly statistically significant ($p = 2.7 \times 10^{-6}$). These covariates explained 12% of the total phenotypic variation in T2DM. Subsequently, we performed multipoint linkage analyses to localize the susceptibility loci for T2DM. There was no evidence in favor of significant T2DM linkage. However, as reported in table 3, 2 genetic locations exhibited potential linkage with T2DM. The stronger of the 2 suggestive signals (LOD = 1.8, nominal $p = 2.1 \times 10^{-3}$) occurred between markers D9S1871 and D9S2169 (9p24.2-p24.1; 8–14 cM), the other suggestive linkage signal (LOD = 1.5, nominal $p = 4.7 \times 10^{-3}$) involved markers D11S1999-D11S1981, at a region on chromosome 11p (11p15.3-p15.1; 17–21 cM).

Following these linkage findings and our previous SAFDGS T2DM linkage results, we performed a GWL analysis of T2DM using our combined larger data set ($n = 3,086$) to examine whether it would yield improved evidence for linkage at any of the genetic locations found to be linked with T2DM in our SAFDGS and/or VAGES data sets. After accounting for the significant ($p \leq 0.05$) covariate effects of age, sex, age^2 , $age^2 \times sex$, ln BMI, and study, which explained 24% of the total phenotypic variation in T2DM, the heritability of T2DM was estimated to be highly significant ($h^2 \pm SE = 0.57 \pm 0.09$, $p = 8.3 \times 10^{-15}$). As shown in figures 1 and 2 and table 3, the GWL of the combined data yielded the strongest, most significant, and improved linkage evidence (LOD = 4.3, nominal $p = 4.3 \times 10^{-6}$, empirical $p = 1.0 \times 10^{-5}$, genome-wide $p = 1.6 \times 10^{-3}$) at the 9p24 chromosomal region between markers D9S1779 (9p24.3) and D9S1871 (9p24.2). The estimated heritability ($\pm SE$) due to this susceptibility locus is 0.55 ± 0.12 ($p = 4.3 \times 10^{-6}$) of the total phenotypic

Fig. 2. T2DM linkage profiles on chromosome 9 from the VAGES and the combined data sets.

variation in T2DM after adjusting for the covariate effects. It should be noted that, even after allowing for parameter heterogeneity by obtaining study-specific findings, the LOD score and the location were found to be similar. The observed LOD score of 4.3 with 3 d.f. (i.e., the mixture for the χ^2) would have a p value of 4.5×10^{-5} , which would be equivalent to a LOD score of approximately 3.33. Thus, the linkage finding at the 9p24 region continues to be significant even after allowing for additional d.f.

As reported in figure 1 and table 3, however, using the combined data, a similar improvement in the linkage signal at the genetic location on chromosome 11p was not observed (LOD = 1.0, nominal $p = 1.4 \times 10^{-2}$). In addition to the significant linkage signal on chromosome 9p24, 4 chromosomal regions (i.e., 5p15.31, 5p13.1, 5q13.1-q13.3, and 21q22.11-q22.13) representing 2 chromosomes across the genome exhibited potential evidence for link-

age with T2DM (i.e., LOD ≥ 1.2), and the LOD scores ranged from 1.2 (nominal $p = 9.1 \times 10^{-3}$) to 2.0 (nominal $p = 1.1 \times 10^{-3}$) (table 3, fig. 1).

We performed a preliminary T2DM association analysis of the 5,329 SNPs in the 1.5-LOD support interval surrounding the 9p24 linkage signal [~ 22 cM or ~ 10 -Mb region between markers D9S1779 (9p24.3) and GATA187D09 (9p23)] using data from 2 (i.e., SAFHS and SAFDGS, $n = \sim 2,000$) of the 3 studies used for our linkage analysis (table 1), for which we now have genome-wide genotypic data. In addition to the covariates considered for the GWL analysis, the first 3 principal component-based values (PC1, PC2, and PC3), obtained using a subset of SNPs (that are not in linkage disequilibrium) from the GWAS genotypic data [38], were also considered for the association analysis as covariates to adjust for potential population structure influences. No attempt was made to adjust for multiple testing. The

Table 4. GWL and association findings on chromosome 9p for T2DM and its related traits

Phenotype	Marker region	Chromosomal location	Position		LOD score or p value	Analysis type	Population	Reference
			cM ^a or gene/region	bp ^b				
T2DM	D9S1871-D9S2169	9p24.2-p24.1	8–14	3,859,167–5,200,390	1.8	Linkage	Mexican Americans (VAGES)	This study
T2DM	D9S1779-D9S1871	9p24.3-p24.2	0–8	516,800–3,859,167	4.3	Linkage	Mexican Americans (combined data)	This study
T2DM	D9S288-D9S925	9p24.2-p22.2	10–32	3,951,639–18,289,052	2.4	Linkage	Mexican Americans	Duggirala et al. 1999 [19]
T2DM	rs7041847	9p24.2	<i>GLIS</i>	4,277,466	2×10^{-14}	Association	Asian	Cho et al. 2012 [41]
HOMA-B, fasting plasma glucose, and fasting insulin	rs7034200	9p24.2	<i>GLIS3</i>	4,279,050	1×10^{-13} , 1×10^{-12} , 7×10^{-7}	Association	Caucasians	Dupuis et al. 2010 [42]; Manning et al. 2012 [43]
Type 1 diabetes	rs7020673	9p24.2	<i>GLIS3</i>	4,281,747	5×10^{-12}	Association	Caucasians	Barrett et al. 2009 [44]
T2DM	rs10814916	9p24.2	<i>GLIS</i>	4,283,150	6×10^{-12}	Association	Chinese	Li et al. 2013 [45]
Insulin sensitivity index	D9S2169	9p24.1	14	5,200,390	2.0	Linkage	Pimas	Hanson et al. 2001 [46]
T2DM	rs17584499	9p24.1	<i>PTPRD</i>	8,869,118	9×10^{-10}	Association	Chinese	Tsai et al. 2010 [47]
T2DM	rs649891	9p23	<i>PTPRD</i>	10,420,602	6×10^{-6}	Association	Mexican Americans	Below et al. 2011 [48]
LDL-C (size)	D9S921	9p23	22	10,509,421	3.7	Linkage	Caucasians	Badzioch et al. 2004 [49]
Adiponectin	D9S168-D9S925	9p23-p22.2	22–32	10,588,156–18,289,052	3.5	Linkage	Pimas	Lindsay et al. 2003 [50]
HDL-C	D9S921	9p23		10,509,421	2.1	Linkage	Finnish-Dutch	Pajukanta et al. 2003 [51]
HDL-C	D9S925-D9S741	9p22.2-p21.3	32–42	18,289,052–24,534,138	3.4	Linkage	Mexican Americans	Arya et al. 2002 [52]
Lipid factor (HDL/TG)	D9S925-D9S741	9p22.2-p21.3	32–42	18,289,052–24,534,138	2.0	Linkage	Mexican Americans	Arya et al. 2002 [53]
T2DM	rs564398	9p21.3	<i>CDKN2A/CDKN2B</i>	22,019,547	1×10^{-6}	Association	Caucasians	Zeggini et al. 2007 [54]
T2DM	rs2383208	9p21.3	<i>CDKN2A/CDKN2B</i>	22,122,076	2×10^{-29} , 3×10^{-17}	Association	Japanese; Chinese	Takeuchi et al. 2009 [55]; Li et al. 2013 [45]
T2DM	rs10965250	9p21.3	<i>CDKN2A/CDKN2B</i>	22,123,284	1×10^{-10}	Association	Caucasians	Voight et al. 2010 [13]
T2DM, fasting insulin, and fasting glucose	rs10811661	9p21.3	<i>CDKN2A/CDKN2B</i>	22,124,094	5×10^{-8} , 7×10^{-7} , 8×10^{-15} , 7×10^{-6}	Association	Caucasians	Saxena et al. 2007 [56]; Scott et al. 2007 [57]; Manning et al. 2012 [43]
T2DM	rs1333051	9p21.3	<i>CDKN2A/CDKN2B</i>	22,126,489	10×10^{-10}	Association	Hispanics and Caucasians	Parra et al. 2011 [58]
T2DM	rs7018475	9p21.3	<i>CDKN2B</i>	22,127,685	3×10^{-8}	Association	Caucasians	Huang et al. 2012 [59]
T2DM	D9S171	9p21.3	43	24,534,209	3.3 ^c	Linkage	Chinese	Luo et al. 2001 [60]

^a Marshfield distance; ^b base pair location at the beginning of the marker (NCBI Genome Build 36.3; dbSNP build 130); ^c nonparametric linkage score.

strongest T2DM association was found with rs10976093 ($\beta = 1.140$; $p = 7.3 \times 10^{-5}$; 7.17 Mb) near the lysine (K)-specific demethylase 4C (*KDM4C*) gene. The minor allele A was the risk allele, it was a low-frequency variant (MAF = 0.009). Using the data from nondiabetic individuals only, the strongest associations for fasting glucose ($\beta = -0.475$; $p = 1.7 \times 10^{-3}$; MAF (C) = 0.015; 3.14 Mb) and fasting insulin ($\beta = 0.132$; $p = 6.4 \times 10^{-5}$; MAF (A) = 0.473; 3.77 Mb) were found with rs1570286 [near the coactivator-associated arginine methyltransferase 1 pseudogene 1 (*CARM1P1*) gene] and rs7033034 [near the GLIS family zinc finger 3 (*GLIS3*) gene]. rs1570286 was also nominally associated with T2DM ($p = 6.8 \times 10^{-3}$) and fasting insulin ($p = 1.3 \times 10^{-2}$).

As reported in table 4, several SNPs in the *GLIS3* gene (rs7041847 and rs10814916) and the protein tyrosine phosphatase, receptor type, D (*PTPRD*) gene (rs17584499 and rs649891), whose locations correspond to the chromosomal region of interest, were reported to be associated with T2DM. None of these markers were found to be associated with T2DM in our data, although suggestive evidence of T2DM association in terms of direction could be seen with rs7041847 (one-sided $p = 0.065$) and rs10814916 (one-sided $p = 0.072$). However, several other SNPs in these 2 genes exhibited some evidence for association with T2DM, the strongest being rs2027394 in *GLIS3* ($p = 2.2 \times 10^{-3}$; MAF (G) = 0.395) and rs10977825 in *PTPRD* ($p = 2.9 \times 10^{-4}$; MAF (G) = 0.141).

Discussion

In this study, we first screened the genome for T2DM susceptibility loci in Mexican Americans using the data from VAGES ($n = 1,122$) and a GWL approach, which resulted in potential linkage evidence for T2DM at genetic locations on chromosomes 9p24.2-p24.1 and 11p15.3-p15.1. Both of these chromosomal regions have previously been implicated as influencing T2DM-related traits by various GWL studies including our own [19, 28, 39, 40, see also table 4 for additional studies related to chromosome 9]. Recently, certain variants/genes [*PTPRD* and *GLIS3* on 9p24.3-p23 and the UDP-N-acetyl- α -D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 18 (*GALNT18*) gene/LOC729013 and the potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*) gene on 11p15.3-p15.1] have been localized as T2DM susceptibility loci in these chromosomal regions by GWASs [16, 25, 61].

Following these observations, we performed a GWL of T2DM using an enlarged data set consisting of individu-

als from VAGES, SAFHS, and SAFDGS. We found the significant and increased evidence for linkage of T2DM at the 9p24.3-p24.2 chromosomal region (LOD = 4.3, empirical $p = 1.0 \times 10^{-5}$, genome-wide $p = 1.6 \times 10^{-3}$, 0–8 cM). As reported in tables 3 and 4, the peak LOD score on chromosome 9p24.2-p24.1 in the VAGES data (LOD = 1.8) occurred at 8–14 cM. Previously, the SAFDGS (baseline) data exhibited suggestive linkage evidence (LOD = 2.4) at 10–32 cM on 9p24.2-p22.2. It should be noted that the current SAFDGS genotypic data were generated by CIDR, using genetic markers which are different from those used at baseline, and that the BMI was not used as a covariate in the baseline data analysis. However, the combined data analysis greatly improved the evidence for T2DM linkage as noted above.

Although the linkage evidence on 11p15.3-p15.1 was attenuated compared to the VAGES finding, new potential evidence for T2DM linkage in our data was found at 3 different locations on chromosome 5 (i.e., 5p15.31, 5p13.1, and 5q13.1-q13.3) and at the 21q22.11-q22.13 chromosomal region. Several previous studies found some evidence for linkage of T2DM-related traits at these regions [62–64]. Interestingly, the chromosomal regions 5q13.3 and 21q22.11 exhibit a close correspondence with recent T2DM GWAS findings involving the zinc finger, BED-type containing 3 (*ZBED3*) gene region (5q13.3) and the hormonally up-regulated Neu-associated kinase (HUNK) gene region (21q22.11) [13, 65].

The major linkage finding of our study, however, is the T2DM susceptibility locus on chromosome 9p24, which explains about 55% of the total phenotypic variation in T2DM after adjusting for the covariate effects. It is plausible that the observed linkage signal refers to potential T2DM functional variants, both rare and common, in a genetic location representing one or more genes on chromosome 9p24. The 1.5-LOD support interval on the centromeric side of the linkage peak (i.e., combined data) is flanked by the marker GATA187D09 (9p23, ~22 cM, ~10 Mb). Aside from the information from GWL studies of T2DM-related traits on chromosome 9p (table 4), as noted earlier, some recent GWASs have localized variants/genes within the 10-Mb chromosomal region from p-ter that influence susceptibility to T2DM or its related traits (table 4).

One of the most interesting genes in this region that has been reported to play a key role in the pancreatic β cell development and insulin gene expression is *GLIS3* (9p24.2, 3.8–4.3 Mb). Two SNPs in the intronic region of *GLIS3*, namely rs7041847 and rs7034200, showed significant associations with T2DM in Asians and with HOMA-B levels, fasting plasma glucose and fasting insulin in Caucasians

[41–43]. Another intronic polymorphism (rs7020673) in the same gene was found to be associated with T1DM in Caucasians [44]. Tsai et al. [47], using data from a Chinese population, reported that a variant rs17584499 in the intron region of the *PTPRD* gene (9p24.3-p23, 8.3–10.6 Mb) was significantly associated with T2DM. Interestingly, rs649891 (9p23), yet another intronic SNP in the same gene, showed an association with T2DM in Mexican Americans [48]. It is important to note that GWAS-identified variants in the regions of the cyclin-dependent kinase inhibitor 2A/2B genes (*CDKN2A/CDKN2B*) are located at approximately 22.1 Mb from p-ter, and that this chromosomal region is approximately 12 Mb away from the marker GATA187D09 region that flanks the 1.5-LOD support interval on the centromeric side in our data. It is worth noting that our previous HDL cholesterol linkage signal within the approximately 18.3–24.5-Mb chromosomal region strongly overlaps with the *CDKN2A/CDKN2B* gene regions (i.e., 22.1 Mb, table 4).

We performed a preliminary T2DM association analysis within the 1.5-LOD support interval on chromosome 9p24.3-p23, using a subset of data (SAFHS and SAFDGS) that contributed to the 9p24 linkage signal. Of the available SNPs in this critical region in our data, the strongest T2DM association involved a low-frequency variant (rs10976093, intergenic, 7.1 Mb, MAF = 0.009) near the *KDM4C* gene. Markers rs7041847 and rs10814916 (*GLIS3*), and rs17584499 and rs649891 (*PTPRD*), which were part of the analysis, failed to exhibit association with T2DM, although suggestive evidence of association with T2DM in terms of direction was found with rs7041847 and rs10814916. However, several other SNPs in these 2 genes exhibited some evidence of association with T2DM, including rs2027394 in *GLIS3* and rs10977825 in *PTPRD*. In nondiabetic individuals, marker rs7033034 (intergenic, 3.8 Mb) near the *GLIS3* gene was strongly associated with fasting insulin, and marker rs1570286 (intergenic, 3.1 Mb) near the *CARM1P1* gene was strongly associated with fasting glucose, which was also nominally associated with T2DM and fasting insulin.

The above observations highlight the relative significance of the *GLIS3* and *PTPRD* genetic regions as well as other regions related to the *KDM4C* and *CARM1P1* genes in the 9p-linked region, as they relate to a potential T2DM risk. Given the attention to the nature of these associations and the magnitude of the linkage signal, a thorough search of the 9p chromosomal region for rare variants, in addition to the common variants that may correspond to the T2DM linkage signal, appears to be a promising approach. As reported in table 4, several metabolic syndrome-related

traits are linked or associated with the 9p chromosomal region besides T2DM. It is possible that the 9p chromosomal region could harbor genes that may have pleiotropic influences on metabolic syndrome-related traits. However, we have recently reported linkage findings of metabolic syndrome (as defined by the NCEP/ATPIII criteria) using our SAFDGS data, and there was no evidence for linkage of metabolic syndrome on chromosome 9 [66].

In summary, this study has identified the strongest linkage evidence for T2DM at 9p24 in Mexican Americans. Although the independent T2DM linkage evidence based on VAGES and SAFDGS data sets would be considered potential or suggestive, the large combined family data set used in this study yielded improved and significant evidence for a linkage of T2DM on chromosome 9p24. In addition, some recent GWASs have also unveiled certain variants/genes associated with T2DM and related traits in this chromosomal region. Importantly, we have found preliminary evidence for an association of T2DM and its related traits with sequence variants (both common and low-frequency) representing distinct genetic locations within the 9p chromosomal region of interest. In comparison to GWL studies, the chromosomal regions of interest identified by GWASs usually involve small confidence interval regions (~500 kb to 1 Mb). Collectively, these studies together with our current findings provide strong evidence for the presence of susceptibility loci for T2DM on chromosome 9p24, while in turn making the case for the performance of high throughput sequencing of this linked chromosomal region to ultimately capture the causal variants, including the rare ones, responsible for the original linkage/association signals. In fact, large family-based studies like ours have a high likelihood of detecting the rare or very rare variants, given that multiple individuals in large families can be associated with such sequence variants.

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Erratum

In the article by Farook VS et al., entitled 'Linkage of type 2 diabetes on chromosome 9p24 in Mexican Americans: additional evidence from the Veterans Administration Genetic Epidemiology Study (VAGES)' [Hum Hered 2013;76:36–46, DOI:10.1159/000354849], the name of the institute has changed from 'Southwest Foundation for Biomedical Research, San Antonio, Tex.' to 'Texas Biomedical Research Institute, San Antonio, Tex.'.