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A Genomewide Search for Type 2 Diabetes–Susceptibility Genes in Indigenous Australians

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The prevalence of type 2 diabetes among Australian residents is 7.5%; however, prevalence rates up to six times higher have been reported for indigenous Australian communities. Epidemiological evidence implicates genetic factors in the susceptibility of indigenous Australians to type 2 diabetes and supports the hypothesis of the "thrifty genotype," but, to date, the nature of the genetic predisposition is unknown. We have ascertained clinical details from a community of indigenous Australian descent in North Stradbroke Island, Queensland. In this population, the phenotype is characterized by severe insulin resistance. We have conducted a genomewide scan, at an average resolution of 10 cM, for type 2 diabetes–susceptibility genes in a large multigeneration pedigree from this community. Parametric linkage analysis undertaken using FASTLINK version 4.1p yielded a maximum two-point LOD score of +2.97 at marker D2S2345. Multipoint analysis yielded a peak LOD score of +3.9 <1 cM from marker D2S2345, with an 18-cM 3-LOD support interval. Secondary peak LOD scores were noted on chromosome 3 (+1.8 at recombination fraction [θ] 0.05, at marker D3S1311) and chromosome 8 (+1.77 at $\theta = 0.0$, at marker D8S549). These chromosomal regions are likely to harbor novel susceptibility genes for type 2 diabetes in the indigenous Australian population.

Introduction

Type 2 diabetes (MIM 125853) is characterized by hyperglycemia due to impaired insulin secretion, insulin resistance in muscle, and nonsuppressible hepatic glucose production (DeFronzo 1988). Genetic factors play an important role in the development of diabetes. The monogenic forms of diabetes account for ~5% of cases and are caused by mutations in genes encoding insulin, the insulin receptor, glucokinase, and the transcription factors hepatocyte nuclear factor-1α, (HNF-1α), HNF-1β, HNF-4α, insulin promoter factor-1, and NeuroD1/BETA2 (Steiner et al. 1995; Taylor 1995; Bell et al. 1996; Yamagata et al. 1996*a,* 1996*b;* Horikawa et al. 1997; Stoffers et al. 1998; Malecki et al. 1999). Mutations in mitochondrial genes can cause diabetes, often in association with hearing loss (Maassen and Kadowaki 1996). There has been relatively little progress in identifying the genes responsible for the more common late-onset forms of type 2 diabetes. These late-onset forms do not have a simple Mendelian genetic basis and are thought to result from the joint action of and complex interaction between genetic and environmental factors.

Type 2 diabetes is a major public health problem. The overall prevalence of type 2 diabetes among Australians aged >25 years is 7.5% (Zimmet and Welborn 2001). Prevalence rates up to six times higher have been reported in indigenous Australian communities (Bastian 1979), with a lower average age at onset of type 2 diabetes. The epidemiological and pathophysiological characteristics of type 2 diabetes support the hypothesis of the "thrifty genotype" (Neel 1963), but, to date, the nature of the genetic predisposition is largely unknown. The high prevalence of type 2 diabetes and associated metabolic disturbances in indigenous Australians are major factors contributing to high morbidity and mortality in this group (O'Dea 1992). In the group 35–54 years of age, the prevalence of diabetes in indigenous Australians is 20%–25%. Complications including renal failure, blindness, and foot ulcers leading to amputation are common. The clustering of hyperglycemia with insulin resistance, elevated plasma triglyceride, low HDL cholesterol, hypertension, and central obesity predisposes to macrovascular disease (O'Dea et al. 1990; O'Dea 1991; Guest et al. 1993; Gault et al. 1996; Hayman 1997).

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Epidemiological evidence strongly implicates genetic factors in the susceptibility of indigenous Australians to type 2 diabetes. One line of evidence for genetic influences underlying ethnic differences in diabetes prevalence is the fact that diabetes and insulin resistance are inversely related to the amount of European admixture present in a population. Among indigenous Australians in New South Wales, the prevalence of diabetes was twice as high in inland towns as in coastal towns where European admixture was common (Williams et al. 1987). In a survey in central Australia, glucose intolerance and 2-h insulin levels were inversely related to European admixture (O'Dea et al. 1993). Such genetic effects, however, must depend on interaction with environmental factors, such as weight gain and low physical activity, since type 2 diabetes has remained uncommon among indigenous Australians who are able to continue living as hunter-gatherers (O'Dea 1992).

There are complexities involved in the mapping of diabetes-susceptibility genes. Different ethnic groups have distinct population histories and, in each population, different genes are likely to be responsible for disease susceptibility. Research efforts to date have largely centered on ethnic groups in the United States, Finland, and Western Europe. The genetic analysis of the indigenous Australian population is likely to make a unique contribution to the understanding of diabetes susceptibility and resistance. The major aim of this research program is the identification of susceptibility genes for type 2 diabetes in Australian indigenous pedigrees. The clinical relevance of this includes (*i*) the development of preclinical screening for at-risk individuals and (*ii*) the discovery of novel drug targets that may prove amenable to new forms of therapy for type 2 diabetes, both in these populations and more generally.

Methods

We have ascertained clinical details from a community of indigenous Australian descent in North Stradbroke Island, Queensland. We have conducted a genomewide scan, at an average resolution of 10 cM, for type 2 diabetes–susceptibility genes and have undertaken linkage and quantitative-trait analysis in a large multigeneration pedigree from this community (fig. 1). The pedigree consists of 232 living members, 56 of whom are affected with type 2 diabetes. To date, 138 individuals from the pedigree who are >18 years of age, including 49 who have diabetes, are participating in the study, with recruitment ongoing. The study protocol was approved by the Princess Alexandra Hospital Ethics Committee, and all participants provided informed consent before the study. These studies have been performed after full consultation with and with the approval of the community.

Clinical Studies

The protocol included an interview that recorded age at onset of diabetes, history of treatment and complications, and measurements of height, weight, body-mass index (BMI), blood pressure, and waist and hip circumference. A fasting blood sample was taken for measurements of glucose, lipids, and C-peptide. The fasting plasma glucose and C-peptide concentrations were integrated by homeostasis-model assessment (HOMA) of beta-cell function and insulin sensitivity (Matthews et al. 1985; Levy et al. 1991). Beta-cell function and insulin sensitivity measured by HOMA have been shown to correlate with measures obtained by hyperglycemic and euglycemic clamp studies (Matthews et al. 1985; Levy et al. 1991). Individuals were considered "affected" for the linkage analysis if they met one of the following criteria (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997): (*i*) previously diagnosed type 2 diabetes being treated with medical therapy or (*ii*) fasting plasma glucose $\geq$7 mmol/liter. Normoglycemia was defined as fasting plasma glucose <6.1 mmol/liter. Subjects with fasting plasma glucose $\geq$6.1 mmol/liter and <7.0 mmol/liter were classified as having impaired fasting glucose. The subjects considered affected with type 2 diabetes had no history of ketosis, had been treated for $\geq$3 mo by diet or by oral hypoglycemic agents, and had measurable C-peptide levels. The mean age of the subjects with diabetes was 54 ± 12 years (± 1 SD), the mean BMI was 32 ± 7 kg/m^2, the median HOMA insulin sensitivity was 16% (interquartile range 11%–29%), and the median HOMA beta-cell function was 166% (interquartile range 89%–237%).

Molecular Studies

DNA was prepared from peripheral lymphocytes. The subjects were genotyped with 474 autosomal markers, with an anticipated average heterozygosity of 0.74 ± 0.11 (mean $\pm$ SD), at the Australian Genome Research Facility. The mean sex-averaged distance between adjacent markers is 8.6 ± 6.5 cM (range 0–34 cM). The pedigree structure was validated by genotypic profiling/haplotyping. Marker-error checking, marker-map evaluation, and allele-frequency estimation were undertaken as described elsewhere (Ewen et al. 2000). The genomewide scan was performed on 97 subjects, of whom 45 had type 2 diabetes. Fine mapping was performed on a total of 136 subjects, of whom 49 had type 2 diabetes.

Linkage Analysis

Two-point and multipoint parametric analyses were performed using FASTLINK version 4.1p (Cottingham et al. 1993; Schaffer et al. 1994) with an autosomal

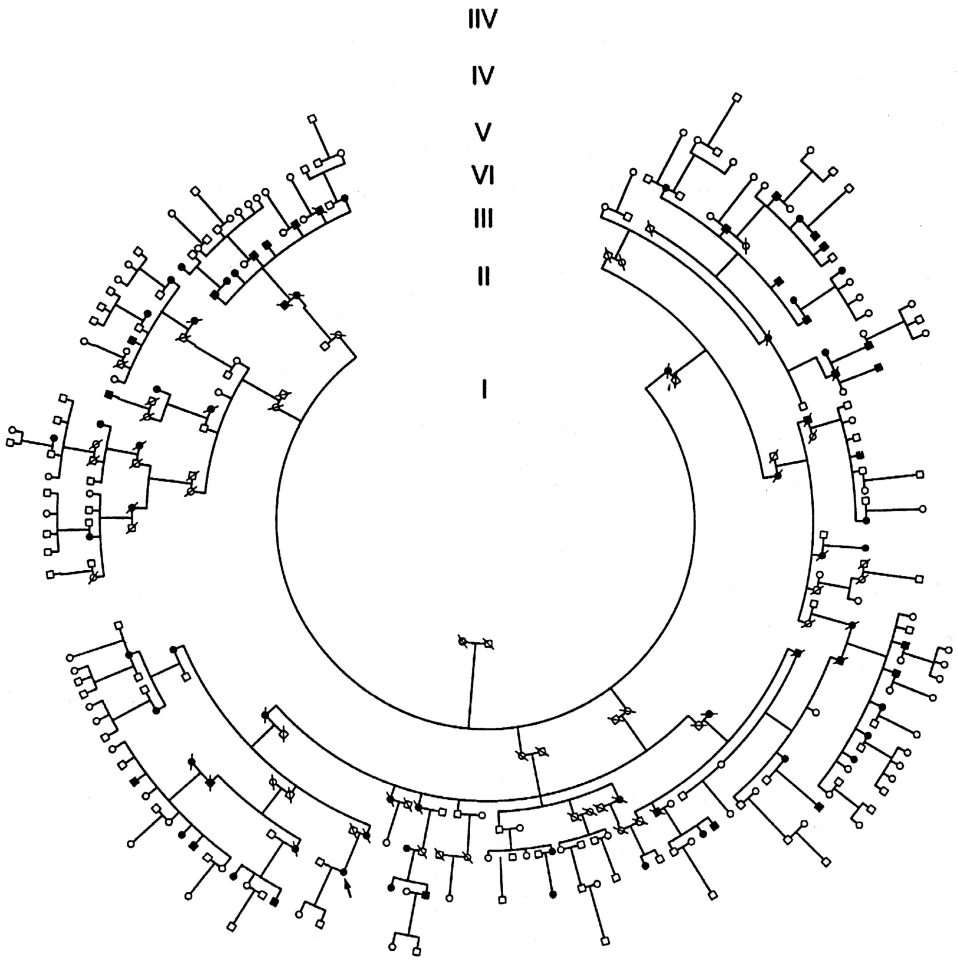

Figure 1 Pedigree structure. Blackened symbols denote individuals with type II diabetes. Unblackened symbols denote unaffected individuals. The arrow indicates the proband.

dominant, three-liability-class model and age-dependent penetrance factors. For ease of computation, the large pedigree was split into two. Simple counting estimates were used to calculate allelic frequencies within the pedigree. The genetic model used for the linkage analysis was an ad hoc model chosen to approximate the high cumulative incidence and recurrence risks of diabetes in this sample and was selected prior to these linkage analyses. We have not used a MOD (i.e., maximized-over-trait-model) approach. A dominant model was chosen, because of the density and pattern of disease in the pedigree. The penetrances in the three age classes were chosen to match the empiric Kaplan-Meier age-at-onset curves for the pedigree, bearing in mind that diagnosis in the earlier generations was delayed or absent. The three liability classes defined on the basis of age were as follows: class 1, age >65 years; class 2, age 45–65 years; and class 3, age <45 years. Phenocopy rates used in each liability class to accommodate potential heterogeneity were 0.2, 0.05, and 0.0001, respectively, and heterozygous and homozygous dominant penetrance factors were 0.99, 0.7, and 0.1, respectively. The disease-allele frequency is necessarily high, because of the high lifetime risk. Disease-gene frequency was set to define a 30% population prevalence, with a maximum sporadic (noninherited) frequency of 40%. This model leads to high baseline population rates of 20–30% and a sibling recurrence ratio of 1.8–2.5 and is consistent with prevalence data from the community (Shaw et al. 2000). The original analysis was performed with only overt diabetes classed as "affected." A secondary analysis was carried out including impaired fasting glucose subjects in the "affected" classification.

Results

Peak two-point LOD scores from the genomewide scan are presented in figure 2. Suggestive linkage was indi-

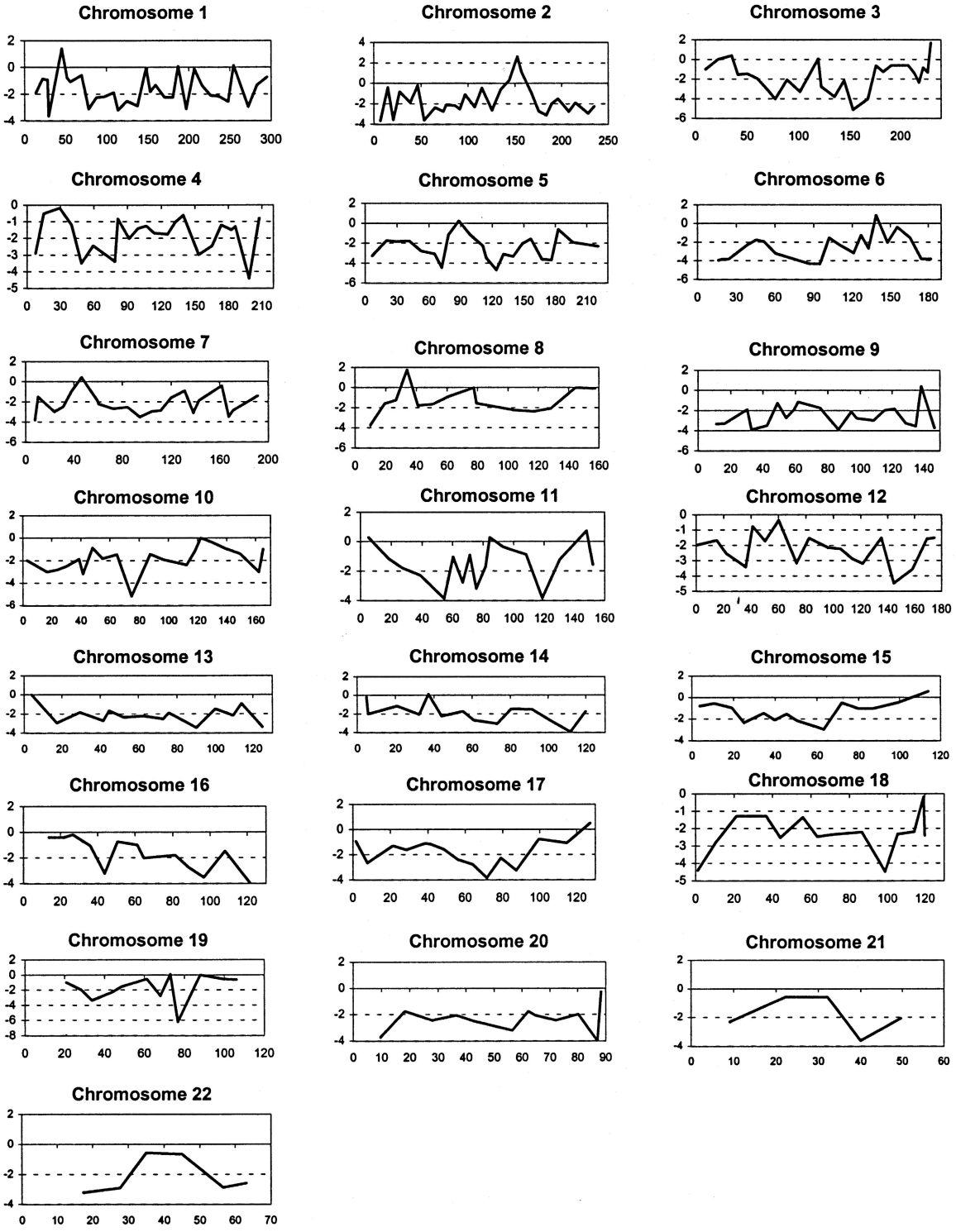

Figure 2 Graphs of two-point LOD scores at $\theta = 0.01$, for each autosome from the genomewide scan. The *x*-axes represent distance in centimorgans, and the *y*-axes represent two-point LOD scores.

cated on chromosome 2, with a peak two-point LOD score of 2.61 at marker D2S2330 (recombination fraction [θ] 0.01). Fine mapping in the expanded data set was performed in this region, with a maximum two-point LOD score of +2.97 at D2S2345 ($\theta = 0.01$) (table 1). Multipoint analysis yielded a peak multipoint LOD score of +3.9, <1 cM from marker D2S2345, with a 3-LOD support interval of 18 cM (fig. 3). Secondary peak two-point LOD scores on the genomewide scan were noted on chromosome 8p (LOD score +1.77 and $\theta = 0$ at D8S549) and chromosome 3q (LOD score +1.8 and $\theta = 0.05$ at D3S1311). Two-point analysis of the genomewide scan data, when individuals with impaired fasting glucose were considered to be "affected," did not remove these peaks, with peak two-point LOD scores of +1.79 at D2S2330 ($\theta = 0.05$), +1.51 at D3S1311 ($\theta = 0.05$) and +1.81 at D8S549 ($\theta = 0$). Analysis of the fine-mapping data in the chromosome 2 region gave a peak two-point LOD score of +1.96 at D2S2345 ($\theta = 0.05$) and a peak multipoint LOD score of +2.72 at marker D2S2345.

Table 1

Peak Two-Point LOD Scores for Chromosome 2q Markers

Marker	LOD Score	θ	Location[a] (Mb)
D2S2313	−.11	.1	156.4
D2S142	.57	.1	166.3
D2S2157	.51	.05	175.1
D2S2330	2.61	.01	175.5
D2S2345	2.97	.01	177.2
D2S335	1.27	.05	182.5
D2S364	−.12	.1	192.9

[a] Location is according to Genethon Database and is taken from the Genome Browser Oct 2000 freeze.

Discussion

The genetic analysis of type 2 diabetes is challenging because of the disease's etiological complexity and genetic heterogeneity. Positive linkages with type 2 diabetes have been identified in a number of populations. Hanis et al. (1996) reported linkage with type 2 diabetes in Mexican-American affected sib pairs, at marker D2S125, in a region termed *NIDDM1* (MIM 601283). The evidence for linkage was associated with a common G→A polymorphism (UCSNP-43) within the calpain-10 gene (*CAPN10* [MIM 605286]) (Horikawa et al. 2000). Pima Indians with normal glucose tolerance who have a G/G genotype at UCSNP-43 were found to have decreased rates of postabsorptive and insulin-stimulated glucose turnover, resulting from decreased rates of glucose oxidation, and G/G homozygotes were found to have reduced *CAPN10* mRNA expression in skeletal muscle (Baier et al. 2000). Mahtani et al. (1996) described linkage of *MODY3*-linked markers with type 2 diabetes in a subset of families from an isolated population in western Finland, in the absence of mutations in HNF-1α. Those authors inferred the presence of a gene in this region (*NIDDM2* [MIM 601467]) that affects susceptibility to adult-onset diabetes associated with low insulin secretion. Shaw et al. (1998) identified positive linkage with the *NIDDM2* region in a large pedigree of admixed European/Pacific Islander descent. Elbein et al. (1999) conducted a genomewide scan in Utah families of northern European ancestry, and a locus on chromosome 1q21-23 met genomewide criteria for significant linkage. Sib-pair analyses in the Pima Indian population indicated a diabetes-susceptibility locus on chromosome 1 (LOD score +4.1 at D1S127) (Hanson et al. 1998). A number of studies of different populations have found evidence for linkage on 20q in the *MODY1* region, in the absence of mutations in HNF-4α (Bowden et al. 1997; Ji et al. 1997; Zouali et al. 1997; Malecki et al. 1998; Ghosh et al. 1999). These data indicate that type 2 diabetes is a heterogeneous disorder, with different genetic regions implicated in different populations. There has been replication of positive results in the regions of the *MODY1* and *MODY3* genes and on chromosome 1q, adding weight to the hypothesis that novel diabetes-susceptibility genes relevant to a number of populations are located in these regions.

Our data represent the first full-genome linkage analysis performed in an indigenous Australian pedigree. Type 2 diabetes in the indigenous Australian population is characterized by severe and predominant insulin resistance (Guest et al. 1993). Indigenous Australians have a sixfold increased risk of diabetes compared with Australians of European descent, and this risk is modulated by European admixture (Williams et al. 1987; O'Dea et al. 1993). Our hypothesis is that the indigenous Australian population harbors unique susceptibility genes for type 2 diabetes; however, the pathways involved may also have relevance to other ethnic groups, in terms of etiology and therapeutic potential. The advantages of studying this population include the availability of large pedigrees arising from a limited number of founders, giving statistical power to the analysis and reducing potential genetic heterogeneity.

The strongest evidence for multipoint linkage was found on chromosome 2q24.3 at D2S2345, with a two-point LOD score of +2.97 and a multipoint LOD score of +3.9 <1 cM centromeric to D2S2345. D2S2330, which gave the original peak two-point LOD score in this region, has previously been implicated by Vionnet et al. (2000), who found linkage with a maximum-binomial-likelihood LOD score and maximized LOD score of +1.25 and +1.22, respectively, at marker D2S2330. This linkage was in French whites, with affected status including both overt diabetes and glucose

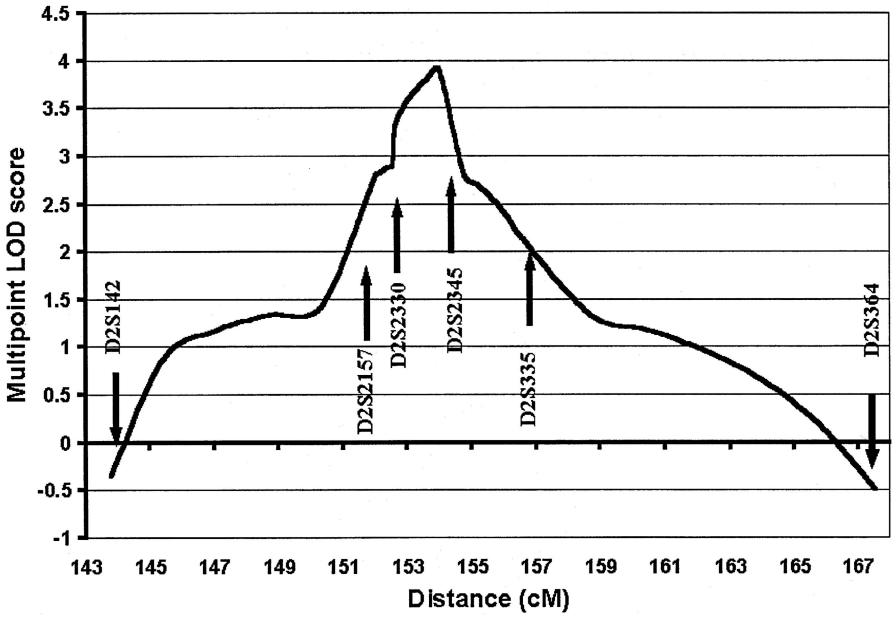

Figure 3 Graph of multipoint LOD scores for chromosome 2q. Marker positions are sex-averaged and are calculated on the basis of The Genetic Location Database.

intolerance with a BMI <27 kg/m^2. This is in contrast with the diagnostic criteria used and the clinical features of affected subjects in the present study, who have BMI of 32 ± 7 kg/m^2. Duggirala et al. (2001) found suggestive linkage to fasting-specific insulin in nondiabetic Mexican Americans, with a LOD score of 2.7 at marker D2S142. D2S142 is ~10 Mb centromeric to D2S2330. These data give further support to the location of a type 2 diabetes–susceptibility gene in this region, across a number of different ethnic groups. The region is located ~66 Mb centromeric to marker D2S362, for which positive linkage has been demonstrated in Mexican American subjects (Ehm et al. 2000), and ~87 Mb centromeric to the *NIDDM1* locus (Hanis et al. 1996).

Candidate genes within the region of interest on 2q include the gene encoding growth-receptor–binding protein 14 (Grb14 [MIM 601524]). Grb14 belongs to the Grb7 family and binds to receptor tyrosine kinases and tyrosine-phosphorylated proteins. Grb10 and Grb14 have been shown to bind the insulin receptor and are negative regulators of insulin signalling. Overexpression of Grb14 in Chinese hamster ovary cells stably expressing the insulin receptor results in decreased insulin stimulation of glycogen synthesis, accompanied by decreased tyrosine phosphorylation of insulin substrate-1. This would result in dysregulation of the downstream signalling component of insulin-mediated pathways (Kasus-Jacobi et al. 1998; Hemming et al. 2001). Another candidate in the region is the gene encoding islet-specific glucose-6-phosphate catalytic subunit–related protein. The activity of the glucose-6-phosphatase catalytic subunit is elevated in islets isolated from ob/ob mice, leading to increased glucose cycling and reduced glucose-stimulated insulin secretion (Khan et al. 1995; Ebert et al. 1999). Close to D2S142 and ~10 Mb from our peak LOD score are the genes for mitochondrial glycerol-3-phosphate dehydrogenase 2 (MIM 138430), which possibly has a role to play in glucose-stimulated insulin secretion (Ferrer et al. 1996), and the inwardly rectifying potassium channel KCNJ3 (MIM 601534), which has been implicated in the regulatory pathways of insulin secretion (Vionnet et al. 1997).

To identify additional chromosomal regions that are likely to harbor genes affecting susceptibility to type 2 diabetes, we adopted more-liberal criteria than those proposed by Lander and Kruglyak (1995) to identify regions with positive results. Following the recommendations of Rao and Province (2000) we considered a P value of <.0023 as "highly suggestive" evidence for linkage and a P value <.01 as "suggestive" evidence for linkage. These P values correspond to LOD scores of 1.75 and 1.18, respectively. These more liberal criteria maximize the detection of genomic regions to be considered for further investigation while allowing true negative results to be reported. On chromosomes 3q29 and 8p22 there was highly suggestive evidence for linkage, with LOD scores of +1.8 at $\theta = 0.05$ for marker D3S1311 and +1.77 for marker D8S549. Whereas the region on chromosome 8p22 has not previously been

linked to type 2–diabetes susceptibility, several studies have found the region on chromosome 3q27-qter to have positive linkage to metabolic traits and type 2 diabetes (Hegele et al. 1999; Kissebah et al. 2000; Vionnet et al. 2000). Kissebah et al. (2000) reported linkage of six quantitative traits representative of the metabolic syndrome to 3q27, in 507 white nuclear families. These traits gave peak LOD scores of 2.37–3.54 between markers D3S2427 and D3S2418. An indication of linkage between type 2 diabetes and D3S2418 was also reported by Hegele et al. (1999), in a genomewide scan in Canadian Oji-Cree. Vionnet et al. (2000) also reported linkage to 3q27-qter in French nuclear families and sib pairs with a relatively early age at onset (age <46 years). These reports are all within 20 cM of our peak LOD score at D3S1311 and support the presence of a diabetes-susceptibility gene in this region. Fine mapping will be undertaken in both the 8p and 3q regions. Several candidate genes of potential interest have been identified in the region of these secondary peaks, including lipoprotein lipase on chromosome 8p, which has been associated with insulin resistance in Mexican Americans (Yang et al. 2001), and type 1 protein phosphatase inhibitor 2 (MIM 601792), which reversibly inhibits and facilitates the correct conformational arrangement of the catalytic subunits of type 1 protein phosphatase, an activator of glycogen synthase (Alessi et al. 1993).

In conclusion, on the basis of a genomewide scan, we have identified a region of significant positive linkage with type 2 diabetes on chromosome 2q. Several candidate genes have been identified in the region, and we plan to continue fine mapping, haplotype analysis, and sequence analysis, to identify the nature of the causative gene. The identification of genetic markers for type 2 diabetes is fundamental for understanding the cause of the disease, for identifying subjects at risk at a preclinical stage, and for the development of more-effective preventative and therapeutic strategies for the management of the condition.

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Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Genethon, http://www.genethon.fr/ (for marker locations)
Genetic Location Database, The, http://cedar.genetics.soton.ac.uk/public_html/ldb.html (for marker and chromosome locations)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for type 2 diabetes [MIM 125853], *NIDDM1* [MIM 601283], *NIDDM2* [MIM 601467], *CAPN10* [MIM 605286], Grb14 [MIM 601524], glycerol-3-phosphate dehydrogenase 2 [MIM 138430], KCNJ3 [MIM 601534], and type 1 protein phosphatase inhibitor 2 [MIM 601792])

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