Genome-Wide Search for Type 2 Diabetes/Impaired Glucose Homeostasis Susceptibility Genes in the Chinese

Significant Linkage to Chromosome 6q21-q23 and Chromosome 1q21-q24

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This genome-wide search for susceptibility genes to type 2 diabetes/impaired glucose homeostasis (IGH) was performed on a relatively homogenous Chinese sample with a total number of 257 pedigrees and 385 affected sibpairs. Two regions showed significant linkage to type 2 diabetes/IGH in the Chinese. The region showing linkage to type 2 diabetes/IGH from the entire sample group analysis was located on chromosome 6q21-q23 (128.93 cM, 1-LOD [logarithm of odds] support interval between 124 and 142 cM, according to the Marshfield genetic map), with a maximum likelihood score of 6.23, a nonparametric linkage (all) score of 4.48, and empirical *P* value <0.001. With a subanalysis based on 101 affected sibpairs with age at diagnosis of type 2 diabetes/IGH <40 years, we detected significant evidence for linkage to chromosome 1q21-q24 (192.1 cM, 1-LOD support interval between 182 and 197 cM), with a maximum likelihood score of 8.91, a nonparametric linkage (all) score of 5.70, and empirical *P* value <0.001. No interaction was observed between these two regions. Our independent replication of the region on chromosome 1q that has been shown to be linked significantly to type 2 diabetes/IGH in Chinese supports the notion that gene(s) in this region may be universally important in the development of human type 2 diabetes.
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ASP, affected sibpair; IA-2, protein tyrosine phosphatase-like protein; IGH, impaired glucose homeostasis; LOD, logarithm of odds; MLS, maximum likelihood score; MODY, maturity-onset diabetes of the young; NPL, nonparametric linkage.

Type 2 diabetes is a complex disease that develops in individuals with genetic susceptibility to impaired insulin secretion, as well as to impaired insulin sensitivity, in the presence of appropriate environmental factors, particularly those leading to obesity (1). Marked increases in the prevalence of type 2 diabetes occur in those societies or countries that have experienced tremendous economic development from a starting point of an impoverished economic base (2). Along with the economic development in China, nationwide surveys have revealed an increase in the prevalence of diabetes in the adult population from 0.9 to 2.4% over the years 1980–1994 (3). In Shanghai, China, the prevalence of diabetes was only 1.0% in 1978 but had reached 9.8% by the turn of the last century, i.e., there has been a 10-fold increase within the last two decades in the Shanghai population alone (4,5).

Genetic heterogeneity of type 2 diabetes has been suggested among ethnic groups (6). This may be one of the reasons for the different locations of susceptibility loci reported to be linked to type 2 diabetes among ethnic groups in genome-wide scans (7–22). In the large geographic area of China, 56 ethnic groups are officially recognized, the Han being the largest. The Chinese of Han ethnicity reside throughout China, mostly in the eastern and central regions. Studies of the origin of the East Asian population revealed that, even within the Han ethnic group, considerable genetic heterogeneity might exist according to geographical location (23–25). Because appropriate definition of a more homogenous sample set is one of the issues for a genome-wide screen for type 2 diabetes susceptibility genes, geographical genetic heterogeneity should be considered when conducting such a study on the Chinese population. Thus, the genome-wide screen reported in this study was performed with Chinese pedigrees recruited from a limited geographic area in China.

RESEARCH DESIGN AND METHODS

Pedigrees for this study were selected from a sampling scheme for the collection of multiplex diabetic families aimed at the genetic studies of type 2

TABLE 1
Characteristics of the sample set

	Set 1	Set 2	Combined
Pedigrees			
Entire group	163	94	257
Age-at-diagnosis <40 years subgroup	40	27	67
Age-at-diagnosis ≥40 years subgroup	123	67	190
Samples			
Entire group	446	256	702
Age-at-diagnosis <40 years subgroup	118	93	211
Age-at-diagnosis ≥40 years subgroup	328	163	491
Affected people			
Entire group	415 (366)	241 (214)	656 (580)
Age-at-diagnosis <40 years subgroup	108 (93)	81 (73)	189 (166)
Age-at-diagnosis ≥40 years subgroup	307 (273)	160 (141)	467 (414)
Parents	76	48	124
Affected parents	45 (35)	33 (30)	78 (65)
Sibs	370	208	578
Affected sibs	370 (331)	208 (184)	578 (515)
Affected sibpairs [s (s − 1)/2]			
Entire group	251 (195)	134 (106)	385 (301)
Age-at-diagnosis <40 years subgroup	62 (46)	39 (31)	101 (77)
Age-at-diagnosis ≥40 years subgroup	189 (149)	95 (75)	284 (224)

The number in parentheses is the number of people or sibpairs with diabetes. The number before the parentheses is the number of people or sibpairs with diabetes or IGH.

diabetes and monogenic forms of diabetes. The collections included the following major items: *1*) Information on the proband and family members, including age, sex, ancestral origin of both parents, and age at diagnosis of diabetes (for those with known diabetes). *2*) Detailed pedigree drawings. *3*) Each of the participants (except those with known diabetes) was asked to undergo an oral glucose tolerance test. *4*) GAD and protein tyrosine phosphatase-like protein (IA-2) antibodies and mitochondrial DNA nucleotide 3243 A-to-G mutation were determined in the youngest patients with diabetes in each pedigree. If the results of the antibody tests or mutation detection were positive, all members of that family were checked. *5*) Anthropometrical measurements of body weight, height, and waist and hip circumference were obtained for each participant. BMI and waist-to-hip ratio were calculated. This study was approved by the institutional review board of Shanghai Jiaotong University No. 6 People's Hospital. Written informed consent was obtained from the participants.

Diagnosis and classification of diabetes. Diagnosis of diabetes, impaired fasting glucose, and impaired glucose tolerance was based on the criteria recommended by the American Diabetes Association (26). Because impaired fasting glucose/impaired glucose tolerance, i.e., impaired glucose homeostasis (IGH), is considered an intermediate metabolic state between normal glucose homeostasis and any type of diabetes (26), for purposes of this study, we combined all abnormal glucose tolerance categories into a single category, i.e., considering individuals with diabetes or IGH to be affected. Individuals, including deceased members of pedigrees, were designated as "affected" when clear documentation of a diagnosis and/or treatment of diabetes was available. Any pedigree with members who had positive serum tests for GAD and/or IA-2 antibodies was classified as a suggestive type 1 diabetic family, and any pedigree with members who tested positive for mitochondria nucleotide 3243 A-to-G mutation was considered a mitochondrial diabetic family. Neither of these two forms of diabetic families was used in our analysis. Additionally, we excluded pedigrees that we classified as families with possible maturity-onset diabetes of the young (MODY), wherein diabetes was linearly transmitted in the first-degree relatives through at least three generations and in the affected members not requiring insulin treatment for correction of hyperglycemia for at least 2 years after diagnosis. Because of the situation regarding health insurance policy in China, we did not place much emphasis on the age at diagnosis in the diagnostic criteria of MODY (27), i.e., in all pedigrees meeting the conditions noted above, even if the age at diagnosis was >25 years, we considered them as MODY pedigrees in a broad sense and did not use them in our analysis.

Inclusion and exclusion criteria. From 1996 to 2001, we collected a total of 527 pedigrees of Chinese with Han ethnicity, each of which had at least two diabetic members. We classified 14 pedigrees as type 1 diabetes, 7 as mitochondrial nucleotide 3243 A-to-G mutation diabetes, and 32 as possible MODY; in total, 53 (10.06%) of the collected pedigrees were considered to be other forms of diabetes. The remaining 474 pedigrees were classified as type 2 diabetes only because there was no evidence suggesting any other form of diabetes. To further reduce the genetic heterogeneity of the sample set for our genome-wide screen, we used the following additional selection criteria: *1*) include only those nuclear families with two or three affected siblings because of the higher probability that Mendelian inheritance diabetes, including MODY, may be concealed in those families with more affected siblings due to inadequate clinical information for the clarification of the transmission mode of diabetes in that family; *2*) include only those pedigrees recruited in Shanghai and the nearby area; and *3*) include only those pedigrees for which the affection status for all the participants, except for known diabetic patients, was ascertained by oral glucose tolerance test. These selection criteria yielded a total of 257 pedigrees for study.

Characteristics of the sample set. The 257 pedigrees with type 2 diabetes included a total number of 702 individuals and 385 affected sibpairs (ASPs) (Table 1). Because we began our genome-wide scan genotyping before we had accomplished the pedigree collection noted above and because of the limited fund for research, the 257 pedigrees were divided sequentially through recruitment into two sample sets. The first sample set, consisting of 251 ASPs in 163 pedigrees, was used for the genome-wide scan, whereas the second set, with 134 ASPs in 94 pedigrees, was used for genotyping any of those chromosomes having regions with maximal maximum likelihood score (MLS) ≥1.18 as well as with a nominal P value <0.05 from the multipoint linkage analysis of the first set. The same whole-panel markers of those chromosomes of potential interest were genotyped for the second sample set. In addition to the linkage study of the entire group, age-at-diagnosis subgroups, with cutoff at 40 years of age according to the youngest age at diagnosis of the affected siblings, were analyzed. The number of ASPs within the age-at-diagnosis <40 and ≥40 years subgroups was 101 and 284, respectively (Table 1). (The clinical characteristics of the affected siblings are presented in Table A1 in an online appendix available at http://diabetes.diabetesjournals.org.)

Clinical laboratory determinations. Plasma glucose levels were measured by the glucose oxidase–peroxidase method (kit from Shanghai Biological Products Institute, Shanghai, China). GAD and IA-2 antibodies were determined by radioligand assay according to the instruction manual (kit from RSR). The mitochondrial nucleotide 3243 A-to-G mutation was detected as described elsewhere (28).

Genotyping. A fluorescent-labeled human linkage-mapping set (version 8; Research Genetics), comprising a panel of 388 microsatellite markers on autosomes and the X chromosome, was used in this study. Of the 383 markers in the mapping set, 13 markers scattered on chromosomes 4, 5, 14, 16, 17, 18, and 19 were not included in the analysis because of technical problems. The average heterozygosity of these markers calculated from our Chinese samples was 73 ± 9%. The average intermarker spacing was 9.31 cM, with only one gap >20 cM. PCR was performed on the Gene Amp PCR system 9700 thermocycler (PE Applied Biosystems). The PCR products were electrophoresed through 64-well plates of 5% polyacrylamide gels (Long Ranger gel solution; BioWhit-

taker Molecular Applications) with the ABI Prism 377 DNA Sequencer (PE Applied Biosystems). (Details of the genotyping techniques are in the online appendix [available at http://diabetes.diabetesjournals.org].)

Genotype check. Each genotype was reviewed independently by two readers of the research team who were blinded to the phenotype of the sample individual. If there was any inconsistency between readings, the original data were reevaluated for scoring or data-entry errors. Markers were rerun as required. Mendelian incompatibilities were checked by means of the Relative program, version 1.10 (29). If there were any incompatibilities, the original data were reevaluated and the relationships of the incompatible family member were checked through communication with the family and corrected, if required. Thirty-seven pedigrees with errors (0.93%) were detected and automatically deleted during the linkage analysis, which was run with the Genehunter Plus program (see below). The overall dropout rate for the 185,500 genotypes was 1.25%.

Linkage analysis. Nonparametric two-point and multipoint analyses were performed with the computer program Genehunter Plus, version 1.2 (30). Using "increment step 5," scores were calculated at five equally spaced positions between each marker for the multipoint analysis. Map location and distance to the p-terminal end of chromosomes were taken from the Marshfield sex-averaged genetic map (Kosambi distance in centiMorgans) (http://research.marshfieldclinic.org/genetics), along with information from the Genetic Location Database (http://cedar.genetics.soton.ac.uk/public.html), the Genome Database (http://gdbwww.gdb.org/gdb/gdbtop.html), or the National Center for Biotechnology Information (NCBI) Map Viewer (http://www.ncbi.nim.nih.gov/mapview/map_search.cgi). The marker allele frequencies were estimated from the whole dataset by the computer program Splink, version 1.08 (31). The linkage analysis results were reported as the nonparametric linkage (NPL) (all) score, its empirical *P* value (see below), and the logarithm of odds (LOD) score. The LOD score function can resolve the conservativeness of the NPL statistic when the inheritance information is incomplete and can be used to make comparisons among loci and construct confidence/support regions for the gene location (30).

Significance level. We used the cut points recommended by Lander and Kruglyak (32). We also noted any regions with MLS ≥1.18 but <2.19. In addition to the MLS, we determined the 1-LOD support interval (33) for any of the regions with MLS reaching the suggestive linkage level.

Simulation test. To confirm that those regions that showed evidence of linkage to type 2 diabetes/IGH were not false-positive results from multiple testing, the simulation test for obtaining an unbiased empirical *P* value was performed. Simulated datasets were generated by the program Simulate (34) under the null hypothesis of no linkage and according to the structure, size, and affection status of our sample set as well as the map distance and allele-frequency distribution of the markers from our sample set. For the simulation test of the results obtained from the first sample set, 1,000 simulated genome-wide datasets for the entire group and for each of the age-at-diagnosis subgroups were generated. These simulated datasets were analyzed with Genehunter Plus, under the same conditions that we set for the analysis of our sample sets. Empirical genome-wide *P* values were calculated from the number of times that the NPL scores obtained from analyzing the replicates reached or exceeded the NPL scores of those regions obtained from the analysis of our sample sets. For those linkage loci observed from the entire group analysis and from the age-at-diagnosis subgroups analysis of the first sample set, the empirical genome-wide *P* values were obtained from the simulation analysis of 1,000 genome-wide replicates of the respective group. Accordingly, for the simulation test of the combined results of the first and second sample sets, 1,000 replicates for the entire group or 1,000 replicates for the respective age-at-diagnosis subgroup of the individual chromosomes were analyzed, and appropriate empirical chromosomal *P* values were calculated.

Interaction analyses between regions. To control for the number of tests, conditional analyses were only performed between regions with MLS ≥1.18 observed from the combined analysis. The contribution from each family on the conditioned regions was weighted according to the methods described by Cox et al. (35).

RESULTS

Results from the linkage analysis of the entire group. In the two-point analysis of the first sample set, no locus was observed reaching the suggestive linkage level (Table A2, online appendix [available at http://diabetes.diabetesjournals.org]). Using multipoint analysis of the first sample set, two regions, on 6q21-q23 and 16p13, respectively, had an MLS ≥1.18; only the former reached the suggestive linkage level (Fig. 1). The MLS and NPL score of the locus on chromosome 6q were 3.51 and 3.36, respectively, and located at 128.9 cM (Table 2). The empirical genome-wide *P* value of this locus obtained from the simulation analysis of 1,000 of the entire group replicates was 9.0E-03.

Extended study of the second set of samples on chromosome 6 showed that the peak of the MLS was located at 137.7 cM (Table 2). But with the combined analysis of the first and second set of samples, the peak of the region was relocated at 128.9 cM and reached the significant linkage level (MLS 6.23, NPL 4.48, and empirical chromosomal $P <$ 1.0E-03). The 1-LOD support interval was 14 cM, between 126 and 140 cM. No linkage could be observed on chromosome 16 with the extended study of the second set of samples and with the combined analysis of the entire group.

Results from the linkage analysis of the age-at-diagnosis subgroups. In the two-point analysis of the first sample set, the locus of D1S1589 (192.1 cM) on chromosome 1q in the age-at-diagnosis <40 years subgroup reached the suggestive linkage level (LOD 3.98, NPL 3.78) (Table A2, online appendix [available at http://diabetes.diabetesjournals.org]).

Using multipoint analysis of the first sample set, six regions located on chromosomes 1, 6, 12, and 16 in the age-at-diagnosis <40 years subgroup and one region on chromosome 6 in the age-at-diagnosis ≥40 years subgroup had MLS ≥1.18 (Fig. 1). Of these regions, only the region on chromosome 1 in the age-at-diagnosis <40 years subgroup had a peak reaching the suggestive linkage level. The peak of this region was located at 192.1 cM, had an MLS of 3.26, and had an NPL score of 3.39 (Table 3). The empirical genome-wide *P* value of this locus obtained from the simulation analysis of 1,000 of the age-at diagnosis <40 years subgroup replicates was 7.0E-03.

From the second set age-at-diagnosis <40 years subgroup analysis on chromosome 1, several large peaks were observed. Two of these peaks were on the short arm of chromosome 1, located at 37.1 and 109.0 cM, respectively, and reached suggestive linkage levels; whereas one peak on the long arm, located at 192.1 cM, as it was observed in the first set analysis, reached significant linkage levels (MLS 6.06, NPL 4.84) (Table 3) (Fig. A1, online appendix [available at http://diabetes.diabetesjournals.org]). Combined analysis of the first and second sample sets revealed that the two peaks on chromosome 1p were no longer statistically significant, whereas the region located on 1q, at 192.1 cM, reached highly significant linkage levels (MLS 8.91, NPL 5.70, and empirical chromosomal $P <$ 1.0E-03). The 1-LOD support interval was 16 cM, between 182 and 198 cM.

None of the regions on chromosomes 12 and 16 showed linkage to age-at-diagnosis subgroups in the second set analysis or in the combined analysis of the first and second sample sets.

Interaction between regions on chromosomes 1q and 6q. Weighted on the locus of chromosome 1q at 192.1 cM or on the locus of chromosome 6q at 128.9 cM, no evidence of interactions was observed between these loci, neither in the entire group nor in the subgroup analysis (Table A3, online appendix [available at http://diabetes.diabetesjournals.org]).

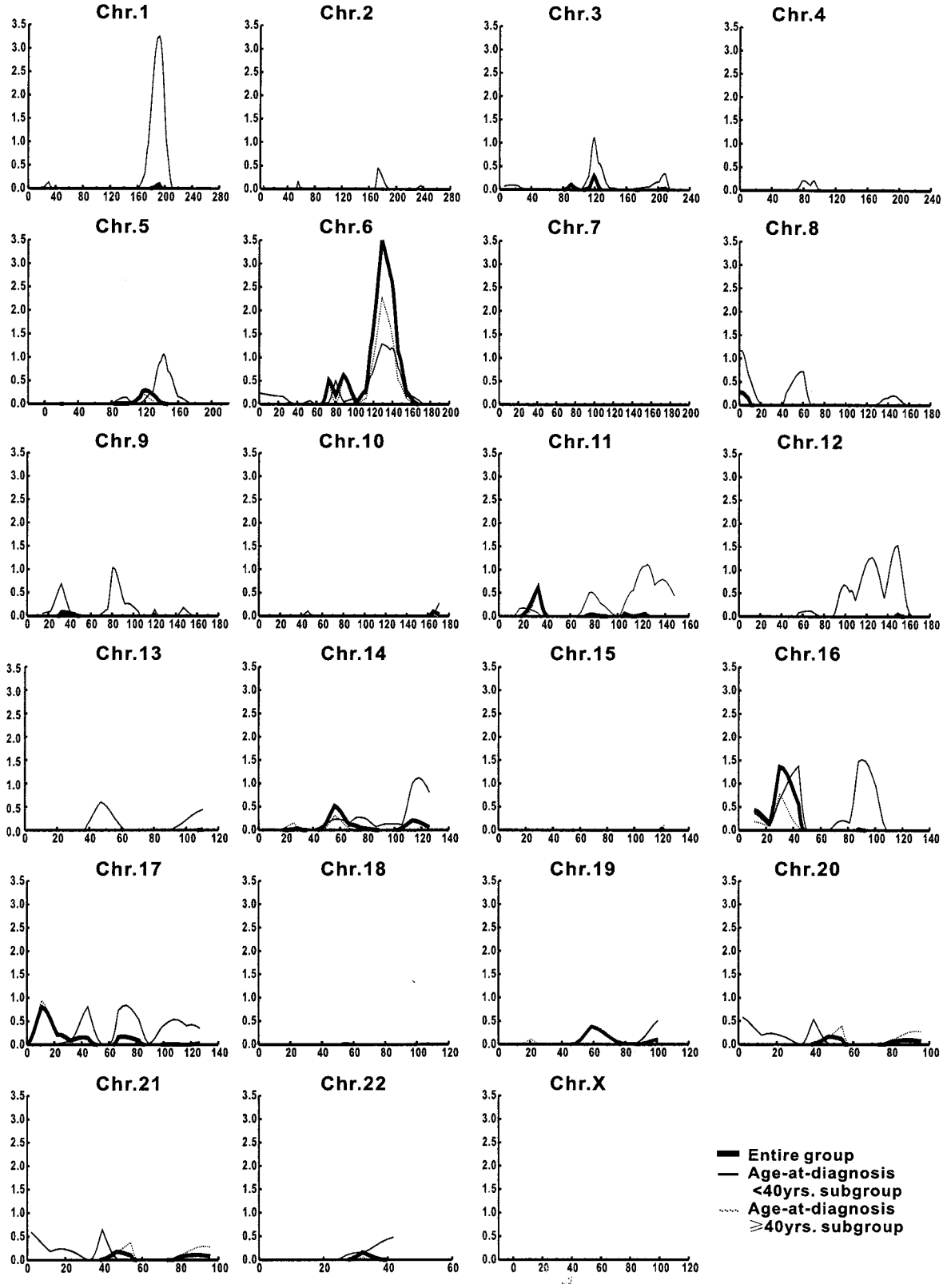

FIG. 1. The multipoint linkage analysis results for the genome-wide scan with the first sample set. The vertical and horizontal axes of each graph indicate the LOD score and length of chromosome in centiMorgans from the p-terminal, respectively.

DISCUSSION

In this study, we found two regions, one on chromosome 6q21-q23 and the other on chromosome 1q21-q24, that exhibit significant linkage to type 2 diabetes/IGH and an early age-at-diagnosis subgroup, respectively, in our Chinese subjects. Though some other regions on chromosomes with nominally significant evidence for linkage were observed in the first or second sample set analyses,

TABLE 2
Results of regions of MLS ≥1.18 from the multipoint linkage analysis on chromosome 6

Group	Cytogenetic location	Distance from p-terminal (cM)	Marker genotyped at the peak	MLS	NPL score	Empirical chromosomal *P**
Entire group						
First set	6q21–q23	128.9	D6S1040	3.51	3.36	0.003
Second set	6q22–q23	137.7	D6S1009	2.71	2.97	0.003
Combined set	6q21–q23	128.9	D6S1040	6.23	4.48	<0.001
Age-at-diagnosis <40 years subgroup						
First set	6q21–q23	128.9	D6S1040	1.29	2.00	0.013
Second set	6q15–q21	102.8	D6S1056	1.74	2.26	0.010
Combined set	6q22–q23	137.7	D6S1009	2.47	2.84	0.011
Age-at-diagnosis ≥40 years subgroup						
First set	6q21–q23	128.9	D6S1040	2.29	2.73	0.008
Second set	6q22–q23	137.7	D6S1009	1.79	2.43	0.001
Combined set	6q21–q23	128.9	D6S1040	4.33	3.74	<0.001

*Results from analysis of 1,000 replicates of the respective sets.

results from the combined set analysis did not support linkage of any of these regions to type 2 diabetes/IGH in our Chinese sample.

In another genome-wide screen study on the Chinese, with 102 families and 142 ASPs, Luo et al. (17) found suggestive evidence for linkage at chromosome 9q21 to type 2 diabetes and at chromosome 20q13.3 to a lower BMI subgroup of type 2 diabetes. Empirical significance of linkage was not reported by these authors. Neither of these two regions showed evidence for linkage in our sample set. The potential genetic heterogeneity of the different Chinese study groups may account for the inconsistency. Although both of these sample sets were Chinese of Han ethnicity, the samples reported by Luo et al. were recruited in east and southeast China, at locations >900 km apart, and our samples were recruited from only Shanghai and nearby areas.

From the first sample set analysis, we only observed results with suggestive linkage levels on chromosomes 6q and 1q, but with the combined analysis of the first and second sample sets, we obtained results with significant and highly significant linkage levels on chromosomes 6q and 1q, respectively. One of the possibilities for these high LOD scores is the relatively homogenous sample set used for this study. Because of the genetic heterogeneity that may exist geographically in the Chinese population within China, we sampled only those pedigrees collected in a limited area. In addition, we collected as much clinical evidence as possible to rule out other forms of diabetes and used only those pedigrees with a small number of affected siblings, i.e., two or three, in the nuclear families for this genome-wide search. Moreover, we used only those pedigrees with the affection status of all of the participants ascertained by oral glucose tolerance test. Although the posterior odds for the presence of Mendelian inheritance diabetes, including MODY, versus type 2 diabetes is determined by the pattern of the transmission of diabetes within a family rather than by the absolute number of affected members in the family, using the same screening protocol for diabetes, it may be that families with a limited number of affected siblings have a lower probability of having Mendelian inheritance diabetes than those with more affected siblings. Of course, we are fully aware of the abundant genetic information that could be retrieved from those pedigrees with more affected siblings. However, considering that genetic heterogeneity even existed in type 2 diabetes, we believe it to be more appropriate to perform a genome-wide screen separately for families with more affected siblings versus families with a small number of affected siblings. In addition to the relatively stringent selection criteria of families for this study, our definition of the age-at-diagnosis <40 years

TABLE 3
Results of regions with MLS ≥1.18 from the multipoint linkage analysis on chromosome 1

Group	Cytogenetic location	Distance from p-terminal (cM)	Marker genotyped at the peak	MLS	NPL score	Empirical chromosomal *P**
Entire group						
Second set	1p35–p34	45.3	D1S552	1.37	2.09	0.078
	1q21–q24	192.1	D1S1589	1.83	2.54	0.057
Combined set	1q21–q24	192.1	D1S1589	1.16	2.00	0.043
Age-at-diagnosis <40 years subgroup						
First set	1q21–q25	192.1	D1S1589	3.26	3.39	0.001
Second set	1p36–p34	37.1	GATA29A05	4.36	4.10	<0.001
	1p22–p13	109.0	D1S1728	3.39	3.31	0.005
	1q21–q24	192.1	D1S1589	6.06	4.84	<0.001
Combined set	1p36–p35	29.9	D1S1597	2.17	2.55	0.028
	1q21–q24	192.1	D1S1589	8.91	5.70	<0.001

*Results from analysis of 1,000 replicates of the respective sets.

subgroups and the designation of both family members with diabetes and with IGH as affected may also contribute to our strong linkage results from a moderate sample size.

The MLS of the locus on chromosome 6q with significant linkage to Chinese type 2 diabetes/IGH was located at 128.9 cM. In the literature, nearby loci (for comparison purposes, locations reported in the literature were reestimated from the Marshfield genetic map) on chromosome 6q indicated linkage with type 2 diabetes subsets. These were ~D6S287 (104 cM), linked to early age-at-diagnosis subset (MLS 2.48) and ~D6S262-D6S292 (117 cM), linked to a low fasting plasma glucose level subset (MLS 3.17) in Finns (10), and ~D6S1056-D6S1021 (102.8–112.2 cM), which had evidence of significant sharing of maternally derived alleles in ASP before age 25 years (MLS_{mother} 3.0) in Pima Indians (16). It is interesting to note that Arya et al. (36) reported that regions D6S403 and D6S264 (142.9 and 179.1 cM) were linked to the clustered factors fasting insulin/leptin/BMI (MLS 4.2 and 4.9, respectively) in nondiabetic Mexican Americans.

The MLS of the locus on chromosome 1q, which we discovered had significant linkage to the Chinese type 2 diabetes/IGH early age-at-diagnosis subgroup, was located at 192.05 cM. More results of nearby loci showing linkage to type 2 diabetes or related metabolic traits in other ethnic groups have been reported: D1S2858 (159.3 cM) linked to type 2 diabetes/IGH (MLS 2.35) in the Old Order Amish (13); CRP-APOA2 (165.6–170.8 cM) linked to type 2 diabetes (MLS 2.96) in Utah Caucasians (9); APOA2-D1S484 (169.7–170.8 cM) linked to type 2 diabetes with BMI <27 kg/m^2 subset (MLS 3.04) in French Caucasians (20); D1S1677 (175.6 cM) linked to type 2 diabetes (MLS 2.50) and D1S2127 (200.3 cM) linked to type 2 diabetes early-onset subset (MLS 4.10) in Pima Indians (12); D1S1589 (192.1 cM) linked to HbA_{1c} (MLS 2.81) in U.S. Caucasians (37); and D1S2799-D1S452 (203.8–206.0 cM) linked to type 2 diabetes (MLS 3.07, resulting from the interaction with those loci on chromosome 10q23.3) in U.K. Caucasians (21). Independent replication of susceptibility loci to type 2 diabetes is essential before proceeding with further positional cloning studies. Independent replication of the same location indicating linkage to type 2 diabetes among diverse ethnic groups, such as the current aggregated data on chromosome 1q21-q24, suggests that a gene or genes in this location may universally contribute to the development of human type 2 diabetes. Moreover, the variation of the gene or genes at this location responsible for type 2 diabetes may arise very early during human evolutionary history. Our independent replication of the linkage of these loci to type 2 diabetes/IGH at significant levels in the Chinese adds further support to this notion. Productive and fruitful results may be achieved from exploring these regions with further linkage disequilibrium fine mapping.

In conclusion, we found two regions on chromosomes 6q21-q23 and 1q21-q24, respectively, showing significant linkage to type 2 diabetes/IGH in the Chinese. Our study suggested that making every effort in defining a more homogenous sample set is one of the most important issues in searching for type 2 diabetes susceptibility genes.

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