

Genome-wide Scan for Type 2 Diabetes Loci in Hong Kong Chinese and Confirmation of a Susceptibility Locus on Chromosome 1q21-q25

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We conducted an autosomal genome scan to map loci for type 2 diabetes in a Hong Kong Chinese population. We studied 64 families, segregating type 2 diabetes, of which 57 had at least one member with an age at diagnosis of ≤ 40 years. These families included a total of 126 affected sibpairs and 4 other affected relative pairs. Nonparametric linkage analysis revealed seven regions showing nominal evidence for linkage with type 2 diabetes (logarithm of odds [LOD] > 0.59 , $P_{\text{pointwise}} < 0.05$): chromosome 1 at 173.9 cM (LOD = 3.09), chromosome 3 at 26.3 cM (LOD = 1.27), chromosome 4 at 135.3 cM (LOD = 2.63), chromosome 5 at 139.3 cM (LOD = 0.84), chromosome 6 at 178.9 cM (LOD = 1.91), chromosome 12 at 48.7 cM (LOD = 1.99), and chromosome 18 at 28.1 cM (LOD = 1.00). Simulation studies showed genome-wide significant evidence for linkage of the chromosome 1 region ($P_{\text{genome-wide}} = 0.036$). We have confirmed the results of previous studies for the presence of a susceptibility locus on chromosome 1q21-q25 (173.9 cM) and suggest the locations of other loci that may contribute to the development of type 2 diabetes in Hong Kong Chinese. *Diabetes* 53:1609–1613, 2004

Type 2 diabetes is a heterogeneous disease characterized by insulin resistance and pancreatic β -cell dysfunction (1). Genetic factors play an important role in the development of type 2 diabetes. Despite considerable effort, there has been relatively little progress in identifying the genes that affect risk. This may be due, at least in part, to phenotypic heterogeneity; i.e., type 2 diabetes is not one disease but

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GIT, glucose intolerance; LLR, independent linked region; LOD, logarithm of odds.

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many, each characterized by hyperglycemia. Genome scans to map type 2 diabetes susceptibility loci have been conducted in many different populations (2–4). Some of the mapped loci have been observed in multiple populations, including those on chromosomes 1q21-q24, 12q, and 20. Other regions, however, may be unique to specific populations, e.g., Mexican Americans and chromosome 2q37.3 and the Amish and chromosome 14q11. It is unclear if this reflects underlying phenotypic heterogeneity, racial/ethnic differences in susceptibility allele frequencies, or differences in sample size, study design, and analytical methods.

The prevalence of diabetes in Hong Kong is among the highest in Asia, with an age-adjusted rate of 8.9% in 1995 (5). This high prevalence is thought to be due to the affluent and westernized lifestyle of Hong Kong Chinese, resulting from rapid socioeconomic development over the last few decades. This is compatible with the thrifty genotype hypothesis, in which favorable genetic traits that facilitate energy storage and mobilization in times of famine are detrimental during time of plenty, leading to the development of modern diseases such as diabetes (6).

We carried out an autosomal genome scan in 64 families with type 2 diabetes (126 affected sibpairs and 4 other affected relative pairs). We also considered glucose intolerance (GIT) as a trait (defined as type 2 diabetes, impaired fasting glucose, or impaired glucose tolerance) because impaired fasting glucose and impaired glucose tolerance may be precursors to type 2 diabetes. We carried out an autosomal scan for GIT in 102 families (306 affected sibpairs and 46 affected relative pairs). The clinical characteristics of affected subjects involved in linkage analyses were similar except for the higher BMI and fasting glucose levels in the type 2 diabetes group (Table A1 in the online appendix [available at <http://diabetes.diabetesjournals.org>]).

Seven regions showed nominal evidence for linkage with type 2 diabetes (logarithm of odds [LOD] > 0.59 , $P_{\text{pointwise}} < 0.05$) (Table 1, Fig. 1, and online appendix Table A2). The region showing the strongest evidence was on chromosome 1q21-q25 at 173.9 cM (LOD = 3.09, $P_{\text{pointwise}} = 0.00008$, 1-LOD CI = 164–180 cM). The LOD scores in these seven regions were not increased when we used GIT as the trait.

We used simulation to assess the significance of the

TABLE 1
Regions showing nominal evidence of linkage to type 2 diabetes in Hong Kong Chinese*

| Chromosome | Flanking markers | Position (cM)† | LOD | $P_{\text{pointwise}}$ |
|------------|------------------|----------------|------|------------------------|
| 1 | APOA2–D1S194 | 173.9 | 3.09 | 0.00008 |
| 3 | D3S4545 | 26.3 | 1.27 | 0.008 |
| 4 | D4S2394–D4S1644 | 135.3 | 2.63 | 0.0003 |
| 5 | D5S816 | 139.3 | 0.84 | 0.02 |
| 6 | D6S1277–D6S1027 | 178.9 | 1.91 | 0.002 |
| 12 | D12S1042 | 48.7 | 1.99 | 0.0012 |
| 18 | D18S843 | 28.1 | 1.00 | 0.02 |

*Evidence of linkage is determined as $\text{LOD} > 0.59$, $P_{\text{pointwise}} < 0.05$; †marker positions are indicated in Haldane centimorgans from the p-terminus obtained from the Marshfield Medical Research Foundation.

results and found the LOD score threshold of 2.93 for ≥ 1 independent linked regions (ILRs) for type 2 diabetes, yielding an estimated $P_{\text{genome-wide}} < 0.05$. The chromosome 1q region demonstrated genome-wide significant linkage for type 2 diabetes ($\text{LOD} = 3.09$, $P_{\text{genome-wide}} = 0.036$). Chromosomes 4q ($\text{LOD} = 2.63$), 6q ($\text{LOD} = 1.91$), and 12p ($\text{LOD} = 1.99$) showed suggestive evidence for linkage based on observation in our simulations of an average of one ILR per genome scan (7) at a LOD score of 1.59 (Table 1).

We also used locus-counting methods to evaluate the linkage results (8). We observed seven, five, and two loci with $\text{LOD} > 0.59$ ($P_{\text{pointwise}} < 0.05$), > 1.18 ($P_{\text{pointwise}} < 0.01$), and > 2.08 ($P_{\text{pointwise}} < 0.001$), respectively. The simulations showed that 392 of the 500 replicates (78%) had seven or more loci at $\text{LOD} > 0.59$, whereas 56 (11%) had five or more loci at $\text{LOD} > 1.18$, and 21 (4%) had two or more loci at $\text{LOD} > 2.08$. Overall, the results suggest that there may be one or more susceptibility loci in the other six regions with nominal evidence for linkage.

Could our results be due to the presence of genotyping error or missing data? In general, these problems are believed to reduce the power to detect linkage (9). Our genotyping error rate as assessed by blind duplicates is comparable with that of previous genome screens for type 2 diabetes (10). LOD scores obtained before and after removal of Merlin-derived potential genotyping errors were similar in the seven regions with nominal evidence for linkage (chromosome 1, 3.07 vs. 3.09; chromosome 3, 1.27 vs. 1.27; chromosome 4, 2.42 vs. 2.63; chromosome 5, 0.88 vs. 0.84; chromosome 6, 2.08 vs. 1.91; chromosome 12, 1.99 vs. 1.99; and chromosome 18, 1.00 vs. 1.00). Our missing data rate is comparable with that observed in another type 2 diabetes genome scan (11), where it was demonstrated that 15% missing data did not substantially decrease the power to detect linkage. It should be noted that our moderately sized pedigrees allow recovery of some missing information through haplotype reconstruction. Finally, our study assessed significance through simulation, and thus the consequences of the observed missing data patterns are appropriately taken into account.

In this study, we used both strict (type 2 diabetes) and loose (GIT) criteria of glucose homeostasis to define affection status. The former should yield a more homogeneous sample with respect to disease, whereas the latter provides a larger sample size. Our results generally indicate overlapping linkage signals for type 2 diabetes and GIT (chromosomes 1, 3–5, and 12) but the linkage signals for type 2 diabetes tended to be stronger than those for

GIT (chromosomes 1, 4, and 12) (Fig. 1), despite the fact that the sample size for type 2 diabetes was smaller. The higher signals for type 2 diabetes suggest that the reduced heterogeneity is important for detecting the larger signals.

The region on chromosome 1q (173.9 cM from p-terminus) has also been linked to type 2 diabetes and related traits in Chinese from Shanghai, Pima Indians, and Europeans (2–4, 10–14) (Table 2). There are > 100 known genes in this region. Results from association studies on genes encoding for potassium inwardly rectifying channel J9 (*KCNJ9*) (15), C-reactive protein (*CRP*) (16), and phospholipase A2 4A (*PLA2G4A*) (17) suggest there are associations that require confirmation. This region is the focus of an international collaborative project to positionally clone the gene(s) that affect type 2 diabetes risk. At least one or more of the six other regions showing nominal evidence for type 2 diabetes may harbor true susceptibility loci based on the results of locus-counting methods (8) and linkage to these regions in other studies (Table 2). The identification of the genes and alleles that affect risk to type 2 diabetes may lead to a better understanding of the genetic basis of type 2 diabetes in Hong Kong Chinese and other populations.

RESEARCH DESIGN AND METHODS

Since 1995, all patients attending the diabetes clinic of the Prince of Wales Hospital have been documented for detailed phenotypes and family history (parents, siblings, and offspring), which formed the Prince of Wales Hospital Diabetes Registry (18). Through this registry, Hong Kong Family Diabetes Study ascertained families through a diabetic proband with available first-degree relatives for screening at two stages. At the first stage, 161 families were recruited through a diabetic proband with age at diagnosis ≤ 40 years (early-onset group). At the second stage, an additional 30 families were recruited through a diabetic proband with age at diagnosis > 40 years and with positive family history of diabetes (late-onset group). The second cohort aimed to increase the sample size for gene-mapping study. A total of 191 families were recruited. Among the young-onset families, 100 of the families were screened for antibodies to GAD. Individuals with clinical type 1 diabetes (diabetic ketoacidosis or heavy ketonuria [> 3] or required continuous insulin treatment within 1 year of diagnosis) or with antibodies to GAD were excluded. Subsequently, families without any GIT or diabetic members remaining were excluded. In addition, 48 of the probands with positive family history had participated in a previous study to screen for mutations in the *MODY2* and *MODY3* genes and in the mitochondrial DNA nucleotide 3243 A \rightarrow G mutation (19). Families with these gene mutations were also excluded. A total of 179 families remained. From these 179 families, studies on the dichotomous traits of type 2 diabetes and GIT included 64 and 102 families, respectively, due to the requirement for at least two affected (nonparent offspring) relatives. The probands, all of their first- and second-degree relatives, and the probands' spouses were recruited between January 1998 and March 2002. The clinical characteristics, family structure, and distribution of the affected relative pairs of these families are summarized in Tables A1, A3, and A4, respectively, in the online appendix. Of special note, 57 of the 64 families used in the type 2 diabetes studies and 86 of the 102 in the GIT studies

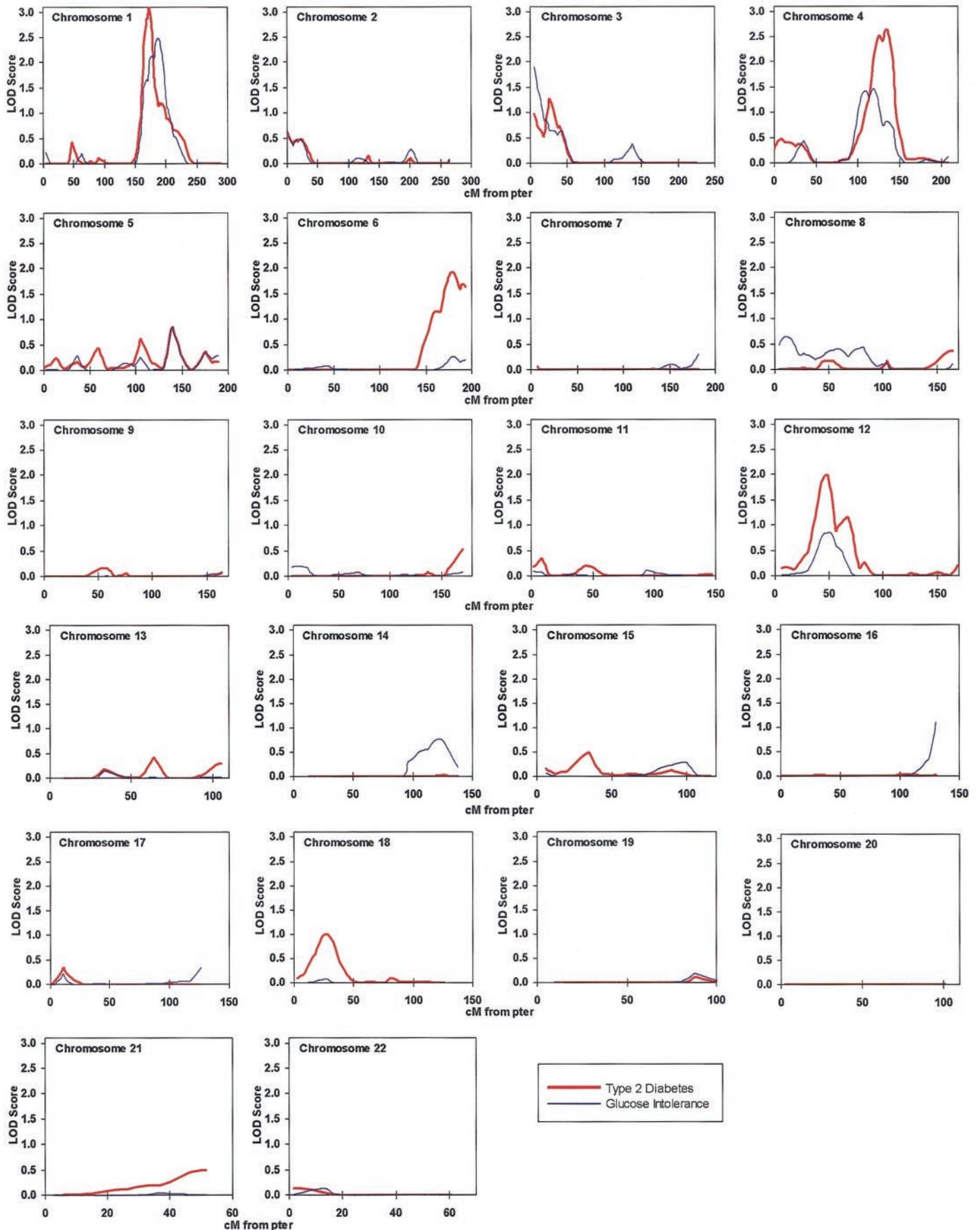


FIG. 1. Multipoint linkage analyses for diabetes and glucose intolerance. The horizontal axis is centimorgans from the p-terminus.

TABLE 2
Regions showing nominal evidence for linkage with type 2 diabetes in Hong Kong Chinese and their replications in other studies

| Chromosome | Location (cM from pter) | Study/trait (reference) |
|------------|-------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | 173.9 | Chinese (Shanghai)/young-onset GIT (12) Old Order Amish/GIT (13) Caucasian (Utah)/type 2 diabetes (2–4) Pima Indian/young-onset type 2 diabetes (10) Caucasian (U.K.)/type 2 diabetes (11) Caucasian (France)/lean type 2 diabetes (14) Caucasian (Framingham)/HbA _{1c} (4) |
| 3 | 26.3 | Caucasian (Scandinavian)/young-onset type 2 diabetes (26) |
| 4 | 135.3 | Old Order Amish/GIT (13) |
| 5 | 139.3 | Chinese (Shanghai)/GIT (12) Caucasian (Finland/Sweden)/young-onset type 2 diabetes (27) |
| 6 | 178.9 | African American/type 2 diabetes (28) |
| 12 | 48.7 | Caucasian (France)/young-onset GIT (14) |
| 18 | 28.1 | Chinese (Shanghai)/GIT (12) Caucasian (Finland/Sweden)/obese type 2 diabetes (27) Caucasian (Netherlands)/obese type 2 diabetes (29) |

had at least one affected member diagnosed before age 40 years. Informed consent was obtained for each participating subject. This study was approved by the clinical research ethics committee of the Chinese University of Hong Kong.

Clinical studies. All available family members were assessed for blood pressure and standard anthropometric parameters and completed a questionnaire on demographic data, family and medical histories, and lifestyle. Fasting blood samples were collected for measurement of plasma glucose, insulin, C-peptide, lipid profile, liver and renal function, and DNA extraction. Family members with no known history of type 2 diabetes were tested with a 75-g oral glucose tolerance test. Type 2 diabetes, impaired glucose tolerance, and impaired fasting glucose were diagnosed using the 1998 World Health Organization criteria (20). Plasma glucose was measured by a glucose oxidase method (Diagnostic Chemicals, Charlottetown, PEI, Canada). Plasma insulin and C-peptide were measured by enzyme-linked immunosorbent assay (Dako Diagnostics, Glostrup, Denmark).

Genotyping. A total of 355 autosomal microsatellite markers (Research Genetics, Huntsville, AL) were typed. These included 320 markers from the Human Screening Set, version 10, and an additional 35 markers that replaced 58 discarded markers from the screening set due to lack of amplification, monomorphism, or significant departure from Hardy-Weinberg equilibrium ($P < 0.05$). The average intermarker distance was 10 cM, and average heterozygosity was 71%. The largest gap was 27.3 cM between D18S1357 and D18S1371 due to removal of two markers not in Hardy-Weinberg equilibrium. Microsatellite markers were amplified with fluorescent-labeled primers using a universal multiplex PCR protocol. Genotypes were performed by capillary electrophoresis (ABI 3100 DNA analyzer). Alleles were called and scored using the Genescan 3.51 and Genotyper 3.6 software (ABI) followed by manual checking. Sixteen percent of genotype data were missing. Blind duplicates were included, with an allele-wise genotyping error rate of 1.2%. Genetic relationships among family members were checked by Relpair (21) and Prest (22). After correction of family relationships and removal of unrelated individuals, Mendelian incompatibilities for all markers were identified by PedCheck (version 1.1) (23). The genotypes that were most likely to have errors within a family were removed, if possible. Otherwise, the genotypes of the incompatible marker were removed in all subjects within the family. Potential genotyping errors observed in 0.17% of the data using Merlin (version 0.9.12b) were removed (24).

Linkage analyses. Marker allele frequencies were estimated from all subjects in 179 families, including those involved in type 2 diabetes and GIT studies. Marker position was based on the sex-average maps from the Marshfield Medical Research Foundation (http://research.marshfieldclinic.org/genetics/Map_Markers/maps/IndexMapFrames.html). Nonparametric multipoint linkage analyses were performed with Merlin (version 0.9.12b) using the score-pairs statistic (24). LOD scores with associated pointwise P values are reported (25). Two linked regions were defined as independent if their maximum LOD score positions differed by ≥ 40 cM. Simulation studies were conducted to assess the significance of the observed linkage signals. Five hundred simulated genotype datasets were generated by gene dropping with Merlin under the null hypothesis of no linkage. The maps, marker allele frequencies, pedigree structures, and missing genotype patterns used in these simulations were identical to those in the actual data. The linkage analyses

were then conducted on the simulated datasets. In each simulation, the number of ILRs greater than a particular LOD score threshold was tallied. $P_{\text{genome-wide}}$ for n ILRs at a LOD score threshold was calculated as the proportion of simulations with $\geq n$ ILRs at that particular LOD score. A significant excess of ILRs in the observed dataset was defined as $P_{\text{genome-wide}} < 0.05$.

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This work is dedicated to the memory of Professor Julian Critchley.

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