A genome-wide search for Type II diabetes susceptibility genes in Chinese Hans

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Abstract

Aims/hypothesis. The aim of the study was to search for Type II (non-insulin-dependent) diabetes mellitus susceptibility genes in a Chinese population.
Methods. A genome-wide scan was carried out using non-parametric linkage analyses. We studied 102 families (478 family members) who were Chinese Hans residing in east and south-east China, including 282 diabetic patients, among them 142 independent affected sibpairs were available for genotyping. A total of 247 fluorescence labelled microsatellite markers, with an average resolution of 15 cM, were amplified. GENEHUNTER was used for the non-parametric linkage analyses.
Results. Two loci on chromosome 9 D9S171 and D9S175 showed suggestive evidence for linkage, with an NPL-score of 3.286 and 2.939 respectively,

and a *p* value of $1.19 \cdot 10^{-4}$ and $4.47 \cdot 10^{-4}$. A locus on the long arm of chromosome 20, D20S196 showed a rise in the non-parametric-linkage score (from 1.517 to 2.922) and a corresponding decrease in the *p* value from 0.04 to $6.5 \cdot 10^{-4}$ when families with lower BMI were analysed alone. Other loci with weaker evidence for linkage were also observed.
Conclusions. Our results suggest that chromosome 9 contains genes involved in the susceptibility to Type II diabetes in an eastern and southeastern Chinese Han population, and chromosome 20 could hide genes linked to Type II diabetes in families with a lower BMI. Other regions could also hide susceptibility genes with minor effects. [Diabetologia (2001) 44: 501–506]

Keywords Type II diabetes, genome-wide scan, linkage analysis, susceptibility, candidate gene.

Type II (non-insulin-dependent) diabetes mellitus is a major health problem in many developed countries. In developing countries, like China, the prevalence of Type II diabetes has statistically significantly increased in recent years, especially along with economic growth. In China, the prevalence has almost tripled within the last 15 years, from 1% to about 3% [1–4]. Although many efforts have been made to explain the cause of Type II diabetes, we still do not completely understand its pathogenesis. It is now generally accepted, however, that genetic susceptibil-

ity plays an important part in the development of Type II diabetes, in addition to environmental influences. Probably, in most cases, a number of genes are involved in the susceptibility to Type II diabetes. In some rare forms of Type II diabetes, such as the maturity onset diabetes of the young (MODY) single mutations have been identified of *HNF-4α* in MODY1 [5], *Glucokinase* in MODY2 [6], *HNF-1α* in MODY3 [7], *insulin promoter factor-1* in MODY4 [8] and *HNF-1β* in MODY 5 [9]. Identification of the susceptibility genes for the more common form of Type II diabetes has proved much more difficult. Not only could the phenotype be largely influenced by many environmental factors such as nutrition and life style but the susceptibility to Type II diabetes is also affected by the heterogeneity and ethnic variation of the relevant genes. Recently many researchers

have used family or sib-pair-based linkage analyses and genome-wide scans to detect loci or chromosome regions that are linked to Type II diabetes and obtained some interesting results. One study found locus D2S125, on chromosome 2q37, to be linked to Type II diabetes in a Mexican-American cohort [10]. Other investigators reported that a locus near D12S1349 on chromosome 12 was linked to Type II diabetes in a cohort of Finnish families with the lowest insulin concentrations [11]. Evidence has been found for a linkage on chromosome 20q12–13.1, which was not caused by MODY1 gene [12]. Other loci on different chromosomes have also been reported to be associated with Type II diabetes [13–18]. These results show that the susceptibility genes could vary considerably between populations. Comparison of data from different ethnic groups will thus add to our understanding of the genetic causes of Type II diabetes. Until now, however, most genome-wide scan data have come from Caucasian or American-Indian populations. There is still very little data from east and south east Asian populations. We report results of a study in search of Type II diabetes susceptibility genes in a Chinese Han population using the genome-wide scan method. Our results show that loci on chromosome 9 and 20 could contain genes that contribute to the susceptibility to Type II diabetes.

Subjects and methods

Population studied. We studied Hans families with at least two siblings affected by Type II diabetes who attended a diabetic clinic in one of five hospitals in east and south-east China. Only families in which either of the siblings were over 35 years of age at onset of diabetes and with only one parent affected were included in the study. Families with both parents or relatives of both parents affected, or families with parents whose status was not identified were not included. Affected status was defined according to the World Health Organization (WHO) criteria (fasting plasma glucose > 7.8 mmol/l and/or > 11.1 mmol/l at 2 h after a 75 g glucose load) [19]. Where affected family members were already treated by diet or with a diet combined with hypoglycaemic agents, diagnosis was confirmed by the first OGTT result before the beginning of their treatment. We excluded MODY, Type I (insulin-dependent) diabetes mellitus and maternally inherited diabetes on the basis of personal and family history. Family members with glutamic acid decarboxylase autoantibodies exceeding the normal range were also excluded. Non-diabetic subjects were defined as having a fasting plasma glucose of less than 6.1 mmol/l and a plasma glucose of less than 7.8 mmol/l at 2 h after glucose load. Subjects having fasting plasma glucose between 6.1 and 7.8 mmol/l or a plasma glucose between 7.8 and 11.1 mmol/l at 2 h after a glucose load were not included in the study. Non-diabetic family members younger than 40 years of age were excluded from the study. Informed consent was obtained from all participants. The protocol of the study was approved by the Human Subjects Committee of the Chinese Human Genome Centre.

Genotyping. Genomic DNA was extracted from peripheral blood leucocytes by the standard procedure [20]. Highly polymorphic microsatellite markers were provided by Perkin-Elmer Biosystem Division (ABI Prism Linkage mapping set version 2, Foster City, Calif., USA) which were packaged in a commercially available reaction kit. Originally, 328 microsatellites provided by LMS2 set were used, but for technical reasons, 48 microsatellites were not amplified in more than 90 % of the subjects. A further 33 microsatellites were excluded because of their low heterogeneity in this population (the heterogeneity provided by Genethon was drawn from a Caucasian population and could be very different in other populations such as the Chinese). All the markers were subdivided into 28 panels following the guidelines of the kit and were amplified using a multiplex PCR reaction with a touch-down algorithm to meet the different annealing temperatures of these markers. Briefly, PCR reactions were carried out in a cocktail of 5 ul, including 10 mmol/l TRIS-HCl, pH 8.3 50 mmol/l KCl, 0.1 mg/ml gelatin, 3.0 mmol/l $MgCl_2$, 200 umol/l deoxyribonucleoside triphosphates (dNTPs), 0.25 U *Taq* polymerase, 1.1ug/ml /*Taq* Start antibody, 0.5 u mol/l each pair of primer and 50 ng genomic DNA. Thermo cycling was done in a Perkin-Elmer 9600 Thermocycler. The PCR condition was: denaturation at 94 °C for 12 min, followed by 39 cycles, each having denaturation at 94 °C for 1 min, annealing at 56 °C for 1 min and extension at 72 °C for 1 min, except that in the first 14 cycles, the annealing temperature decreased from 63 °C to 56 °C by 0.5 °C per cycle, the final extension was 10 min. The PCR products were then denatured and loaded on 6 % denatured polyacrylamide gel, and the electrophoresis was done on a 377 fluorescence-based DNA sequencer (Applied Biosystem, Foster City, Calif., USA). Genescan 3.0 and Genotyper 2.1 software (Applied Biosystem) were used for lane tracking and size calculation of all the alleles. All genotypes were verified for Mendelian segregation among pedigree members using PedCheck [21]. Genotypes of each locus were reviewed and scored independently by two observers and retyped in case of discrepancy. The statistical power to detect linkage was evaluated by simulation using the computer program SIMLINK (University of Michigan, Ann Arbor, Mich., USA).

Statistical analyses. Single-point and multi-point non-parametric linkage analyses using GENEHUNTER (Whitehead Institute for Biomedical Research, MIT, Mass., USA), which calculates the non-parametric linkage (NPL) score at each position, comparing the observed IBD sharing among all affected family members with that expected under the null hypothesis of no linkage [22], were carried out. According to the suggested guidelines for interpreting results of linkage analysis in a whole genome scan using a dense map, a *p* value of $7.4 \cdot 10^{-4}$ or less corresponds to "suggestive" linkage and a *p* value of $2.2 \cdot 10^{-5}$ or less corresponds to "significant" linkage [22]. Only loci that reached the threshold for suggestive evidence ($p \leq 7.4 \cdot 10^{-4}$) for linkage are described in detail.

Results

A total of 102 families (74 with 2 affected siblings, 18 with 3 affected siblings, 10 with 4 affected siblings), including 282 diabetic patients, were available for genotyping. Among these families, both parents' DNA were available in 35 families, DNA from only 1 parent was available in 31 families and in 36 families DNA was not available from either parent. The clinical characteristics of all subjects studied are shown in Table 1. Non-diabetic subjects were also included in

Table 1. Clinical characteristics of the subjects studied

Clinical characteristics	Type II diabetic patients	Non-diabetic subjects
Male/Female	144/138	100/96
Current age	56.4 ± 12.2 (36–83)	57.8 ± 13.5 (40–85)
Age at diagnosis	51.7 ± 10.9 (35–74)	
Body mass index (BMI) (kg/m^2)	23.9 ± 4.3	22.4 ± 4.1
Fasting plasma glucose (mmol/l)	12.6 ± 6.7	5.1 ± 2.6

Table 3. Non-parametric linkage analysis result of D20S196, D9S171 and D9S175 in families with lower BMIs and families with higher BMIs

	Families with lower BMIs		Families with higher BMIs	
	NPL-score	p value	NPL-score	p value
D20S196	2.922	$6 \cdot 10^{-4}$	0.023	0.483
D9S171	2.316	0.005	2.368	0.004
D9S175	1.674	0.031	2.420	0.003

the study if they were siblings of diabetic patients. A total of 247 microsatellite markers were typed, with the mean resolution of 15 cM. The largest gap was 41.8 cM on chromosome 6 between D6S276 and D6S460. The average heterogeneity of these loci was 0.72. Using D20S196 as an indicator which was genotyped twice in 58 families, our genotyping error rate was 1.1%. All the loci with "nominal" evidence for linkage ($p < 0.05$) under non-parametric linkage analyses using GENEHUNTER are shown in Table 2, with the relevant NPL-score and p value. Among these loci, only D9S175 and D9S171 which were 67.8 and 42 cM from the pter of chromosome 9, reached the threshold of suggestive evidence ($p < 7.4 \cdot 10^{-4}$) for linkage using non-parametric linkage analyses, with the NPL-score of 3.286 and 2.939 and the corresponding p value of $1.19 \cdot 10^{-4}$ and $4.73 \cdot 10^{-4}$. The multipoint linkage analyses also showed a peak NPL-score of 3.351 and 3.112 at 33.4 cM and 59.2 cM (from D9S288), which locate D9S171 and D9S175, respectively (Fig. 1). The rest of the loci listed in Table 2 did not reach the generally accepted threshold of suggestive evidence for linkage but we reported

these results because of their potential biological interest. We then stratified each family according to the mean BMI of affected family members to see if this intermediate trait contributes to the evidence of linkage. We ranked all the families on the basis of their BMI and partitioned families into lower BMI (BMI ≤ 23) and higher BMI groups (BMI > 23). A total of 33 families with a BMI of less than 23 (range 18.4–23.0, mean 21.8), including 47 independently affected sibpairs, were partitioned into the lower BMI group. Our results show that the lower BMI group yielded a rise in the NPL-score at D20S196 from 1.517 to 2.922, with a corresponding decrease in the p value from 0.04 to $6.53 \cdot 10^{-4}$ compared with that yielded overall from the families. Families with higher BMIs did not contribute to the evidence for linkage (Fig. 2). As for D9S171 and D9S175, both families with lower and higher BMIs contributed to the evidence for linkage (Table 3), although at D9S175, families with higher BMI yielded an NPL-score and Lod-score more relevant than families with lower BMIs.
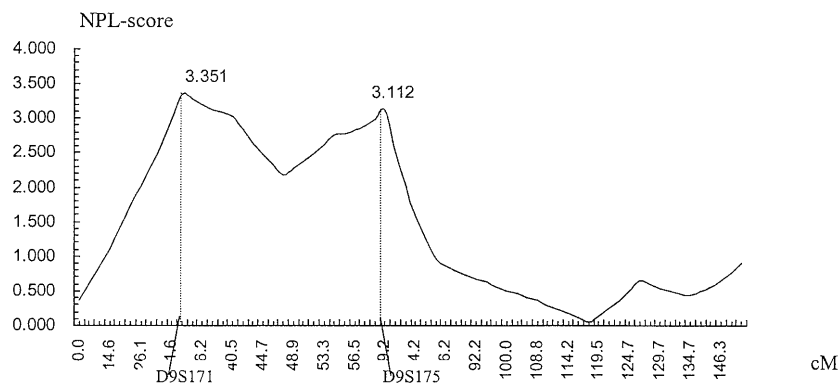
Table 2. Loci with a p value of less than 0.05 using non-parametric linkage analyses by GENEHUNTER

Chromosome	Locus	Cytogen etic location	Distance	NPL	p value
2	D2S2382		221.6	1.549	0.037
2	D2S126	2q33 ~ 2q37	232	2.108	0.008
4	D4S2964		95	1.943	0.013
4	D4S1534	4q21	101	1.670	0.028
5	D5S426		53.8	1.674	0.027
5	D5S408		203.3	1.595	0.033
6	D6S289	6p23	31.2	1.614	0.032
6	D6S276	6p22.3 ~ 6p21.3	45.3	2.066	0.009
6	D6S264	6q25.2 ~ 6q27	173	1.443	0.048
6	D6S446		183	1.846	0.017
9	D9S171	9p21	42	3.286	$1.19 \cdot 10^{-4\,a}$
9	D9S161	9p21	49.1	2.220	0.006
9	D9S273	9p21	62.3	1.620	0.031
9	D9S175	9q13 ~ 9q21	67.8	2.939	$4.73 \cdot 10^{-4\,a}$
11	D11S935	11p13 ~ 11p12	46.9	1.463	0.046
11	D11S987		68.2	1.676	0.027
16	D16S423	16p13.3	8.4	1.507	0.039
20	D20S117	20p13	2.9	1.641	0.030
20	D20S889	20p13	11	1.959	0.013
20	D20S196	20q13. 3	73.5	1.517	0.040

[a] value reached the threshold of suggestive evidence for linkage ($\leq 7.4 \cdot 10^{-4}$)

Fig. 1. Multipoint linkage analysis of chromosome 9 showed two peaks of NPL-score at 33.4 cM and 59.2 cM from D9S288
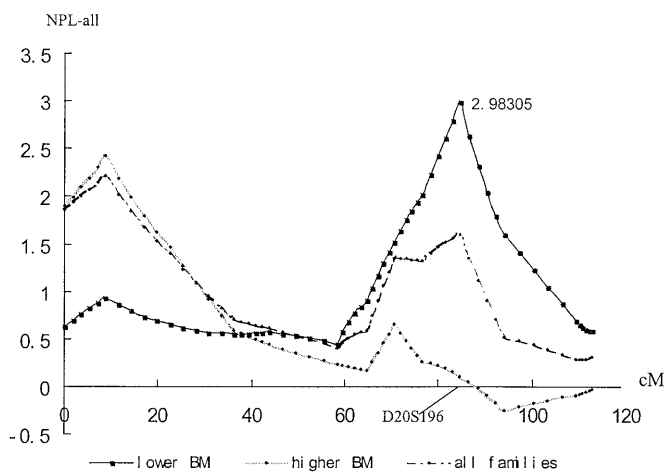

Fig. 2. Multipoint non-parametric linkage analyses of lower BMI family group, higher BMI family group and all families. The result showed a rise in the NPL-score at D20S196 when the lower BMI family group was analysed alone compared with the NPL-score yielded from analyses overall of the families, whereas the NPL-score of D20S196 yielded from the higher BMI group was around 0, indicating that these families did not contribute to the evidence for linkage at this locus. (distance is calculated from D20S117)

Discussion

Which genes contribute to the susceptibility to the common form of Type II diabetes is still not known. Many studies on different populations have shown evidence for linkage on different regions of a given chromosome or on different chromosomes, implying an ethnic variation in the genetic susceptibility to Type II diabetes. We report the result of a genome-wide scan for the Type II diabetes susceptibility genes in a Chinese Han population residing in east and south-east China using non-parametric linkage analyses by GENEHUNTER. Our study suggests evidence for linkage of D9S171 and D9S175 on chromosome 9 with Type II diabetes. These two loci were 42 cM and 67.8 cM, respectively, from pter of chromo-

some 9, according to the genetic map of Genethon. One study on a prediabetic population of Pima Indians provided evidence that 9q21, a region that contains D9S903 (69.3 cM) and D9S1120 (76.1 cM), is linked to fasting and 2-h OGTT insulin concentration [18]. This region is very close to D9S175 which also mapped to 9q21 (59 cM) in a cytogenetic map. Recently, it has been reported that a region on chromosome 9 (9p13-q21) is linked to Type II diabetes in families from the Botnia region in Finland and almost the same chromosome region (9p12–9q12) linked to the metabolic syndrome [24]. This region is very close to that reported in this study. The D9S1874 locus, with peak NPL reported in the Botnia study was only 8.9 cM to D9S175 according to the genetic map of Genethon. This region contains an important candidate gene: the *X25* gene, which, located on chromosome 9q13–21, encodes frataxin, the mitochondrial protein. A decreased expression of this protein will cause Friedreich's ataxia, a common hereditary disease, transmitted in an autosomal recessive mode. This disease is frequently associated with disturbances of glucose metabolism. Homozygous expansion of an intronic GAA repeat in the first intron on X25 inhibits frataxin expression and is associated with clinical manifestations of the disease [25]. Recently, investigators found that intermediate expansions (10 to 36 repeats), which are longer than normal but not sufficient for the appearance of the ataxia phenotype, were associated with Type II diabetes (p < 0.001) [26]. In two other studies, the association of intermediate expansions of the GAA repeat in the frataxin gene with Type II diabetes was, however, not found [27, 28].

Another finding of our study is a rise of Lod-score and NPL of D20S196 after stratification of families according to the average BMI of the affected family members. The families with the lowest BMIs showed stronger evidence for linkage at D20S196 whereas the rest of the families did not contribute to linkage. In another study stratification of families on the basis of the insulin secretion response unmasked a locus (D12S1394) on chromosome 12q which showed no evidence for linkage when all the families were analysed together but a suggestive evidence for linkage

was found when the families in the quartile with the lowest insulin concentrations were analysed alone [11]. This result showed that stratification of families could in some cases dissect heterogeneous families with complex diseases like Type II diabetes into some more homogeneous groups of families, thus increasing the power to detect linkage. Because of the great variation in blood glucose concentration, duration of disease and modality of treatment, which could greatly disturb the insulin response to glucose loading, we did not use the insulin response as an indicator to rank families but rather chose BMI, which is less variable, as the indicator for partitioning families into lower and higher BMI groups. The reason we used 23 kg/m^2 instead of 25 kg/m^2 as a threshold for partitioning families into lower and higher BMI groups is because in a previous report [29] it was found that about 1/8 of the non-overweight and obese Chinese subjects with BMI 23 ~ 25 kg/m^2 could have metabolic syndrome which could be associated with insulin resistance. We found suggestive evidence in the lower BMI group for D20S196 linkage with Type II diabetes whereas there was no evidence for linkage for families in the higher BMI group. This result indicates that low BMI itself, or some factors associated with low BMI, acts on 20q13.3 and yields linkage of D20S196 whereas factors other than BMI yield linkage of D9S171 and D9S175. Clinically, it has been found that general as well as regional adiposity can be closely related to insulin resistance [29, 30]. Thus our result suggested that factors other than insulin resistance (possibly deficiency in insulin secretion) could have an action on 20q13.3. At least four other research groups have found evidence for linkage in this region, although the precise locus is somewhat different among these results [12, 14–16]. The 20q 13.3 location contains many candidate genes, among them the *HNF4α* (MODY1) gene is the most important. We have screened for the mutation of all the exons and part of the promotor region of this gene in families with higher NPL-score at D20S196, but we did not find any mutation in exons and promotor regions (data not shown) in these families. Therefore, *HNF4α* is not likely to be the susceptibility gene for families analysed in this study. Other important candidate genes in the 20q13.3 location include: The *PLCG1* gene, encoding an intracellular second messenger involved in signal transduction pathways [31, 32]; the *CCAAT/enhancer binding protein β gene* (*C/EBP-β*), encoding a transcription factor that regulates cAMP-induced expression of the PCK-1 gene in the liver [33, 34] and the *agouti signalling protein* (*ASP*); mutation of the murine *agouti* gene is associated with obesity-related Type II diabetes [35]. In conclusion, using a genome-wide scan method, we have found suggestive evidence for linkage with Type II diabetes on chromosome 9 and suggestive evidence for linkage on the long arm of chromosome 20

in diabetic families with lower BMIs. In addition loci with weaker evidence for linkage on other chromosomes were also observed in this study.

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