

The localization of type 2 diabetes susceptibility gene loci in northern Chinese Han families

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Abstract We conducted a genome-wide scan, in which 358 well distributed fluorescent dye-labeled microsatellite marker sets were applied in 32 Chinese Han type 2 diabetes families from Northern China to search for the susceptibility gene loci. The data collected from screening all the chromosomes of genome were genotyped by using genescan and genotyping software, then, parametric and non-parametric multipoint test, and affected sib-pair analysis as well, were used to analyze the data. We identified some susceptibility gene loci residing in chromosomes 1,12,18,20, respectively, or precisely, located around D1S214, D1S207, D1S218, D1S235, D12S336, D18S61 and D20S118. The comparison of this result with those from other regions and races reflected the complexity and heterogeneity of type 2 diabetes.

Keywords: Northern Han Chinese, type 2 diabetes, susceptibility gene locus.

Diabetes mellitus is commonly divided into 2 forms: type 1 diabetes or insulin dependent diabetes mellitus (IDDM), and type 2 diabetes or non-insulin dependent diabetes mellitus (NIDDM), which accounts for more than 90% of all diabetes. It is assumed that the interaction between genetic and environmental factors contributes to the pathogenesis of type 2 diabetes. To date, the causes of NIDDM are poorly understood, which lead to the lack of specific preventive ways and remedies. Now nearly 30 candidate genes responsible for metabolism of glucose and signaling pathways of insulin are identified to be associated with the onset of diabetes. Only a few of them, however, have been found to be significantly associated with some specific subtypes (e.g. Maturity-onset diabetes of the young [MODY] and maternal inherited diabetes and deafness [MIDD]) of NIDDM. Type 2 diabetics from different regions or races showed heterogeneity in both inheritance and phenotype, so the localization, cloning and identifying of susceptibility genes of type 2 diabetes play an important role in elucidating the genetic mechanism of pathogenesis. Studies^[1-4] on mapping of NIDDM susceptibility gene loci have been published one by one since the 1990s, unfortunately, none of them comes from China. Now supported by the National Major Basic Research Program, we conducted the localization of type 2 diabetes susceptibility genes in Chinese Han families and reach some success.

1 Materials and methods

(i) Reagents and instruments involved. Fluorescent dye-labeled linkage mapping set, the standard of internal molecular weight, matrix, molecular weight standard kit, ABI 377 DNA sequencer, PE 9600 thermocyclers, 96-plate specific freezing centrifugal machine, Genescan 2.1 or 3.0 software and Genotyper 1.1 were all purchased from PE Company, GENEHUNTER analytical software were purchased from MIT company.

(ii) Collection and genomic DNA extraction from blood samples of NIDDM pedigrees. The protocols are elsewhere described^[5].

(iii) Genotyping of NIDDM pedigrees. Genome-wide scan and analysis of genotypings of microsatellite markers protocols have been described previously^[5].

(iv) Genetic linkage analysis. Non-parametric linkage analysis (NPL) was performed mainly using the GENEHUNTER 2.0 program, which run on the Unix system, to calculate the genotyping data score. We employed both Z value and P value as a criterion to comprehensively assess the data obtained. Z value is consistent with MLS (Maximized LOD score).

2 Results

The genome-wide screening for 22 autosomes in 32 Han families of type 2 diabetes from northern China yielded informative genotypes data in 296 microsatellite markers. Further analysis using both multipoint linkage analysis and affected sib-pair method initially identified chromosomes 1, 12, 18, 20 harboring predisposing genes of type 2 diabetes, respectively (fig. 1).

(i) Susceptibility gene loci on chromosome 1. Most susceptibility gene loci of Northern Chinese Han populations we firstly identified were located on chromosome 1. They are located on 1p36 region, around D1S214 (16.4cM to P terminal), $Z = 2.499$, $P = 0.0018$; 1p31 region, around D1S207 (117.6cM to P terminal), $Z = 1.541$, $P = 0.0355$; 1q22 region, around D1S218 (96.5cM to P terminal), $Z = 2.070$, $P = 0.0085$ and 1q42-43 region, around D1S235 (258.7cM to P terminal), $Z = 1.541$, $P = 0.0356$, respectively.

(ii) Susceptibility gene locus on chromosome 20. A susceptibility gene locus was identified which is located on 20p12 region, around D20S118 (39.3 cM to P terminal), $Z = 2.899$, $P = 0.000413$.

(iii) Susceptibility gene locus on chromosome 12. A susceptibility gene locus was identified which is located on 12p12 region, around D12S336 (3.9 cM to P terminal), $Z = 1.908$, $P = 0.0142$.

(iv) Susceptibility gene locus on chromosome 18. A susceptibility gene locus was identified which is located on 18p23 region, around D20S118 (102.8 cM to P terminal), $Z = 1.911$, $P = 0.0131$.

3 Discussion

As a result of complexity and heterogeneity of pathogenesis of type 2 diabetes, the studies published so far have shown significant diversity in localizing the susceptibility loci of diabetes mellitus of different ethnic groups (table 1), as mentioned below. The one susceptibility gene locus in Mexican-American is located around D2S125^[1], within the band 2q37; susceptibility locus is proximal to D12S1349^[11], 20q (57cM to P-terminal) and 20p (19.5 cM to P-terminal) in Finnish^[4]; another study located susceptibility gene locus of Pima Indians on 11q, 1q and 7q^[3]. The note here shows that susceptibility loci of Northern Han Chinese type 2 diabetes families are rich in chromosome 1, in which several loci are included. Some of them are in agreement with the findings from other races (e.g. 1p31, 1q22)^[7,8], others are not, which appeared only in Northern Han Chinese. The identical or highly equivalent results, that is, the susceptibility loci appear in chromosome 1 in some different human race, confirmed the validity of these results, which implicates that some susceptibility genes may surely locate on these loci.

Also some NIDDM susceptibility gene loci are reported being mapped on chromosomes 12 and 20, respectively. Most papers focus on the regions around MODY3 and MODY1^[2,4,11,15,16] along the chromosomes mentioned above. Recently, Ghosh et al.^[4] reported that the NIDDM susceptibility gene locus of Finnish was located on 20q (19.5cM to P-terminal), which is relevant to what we found that a

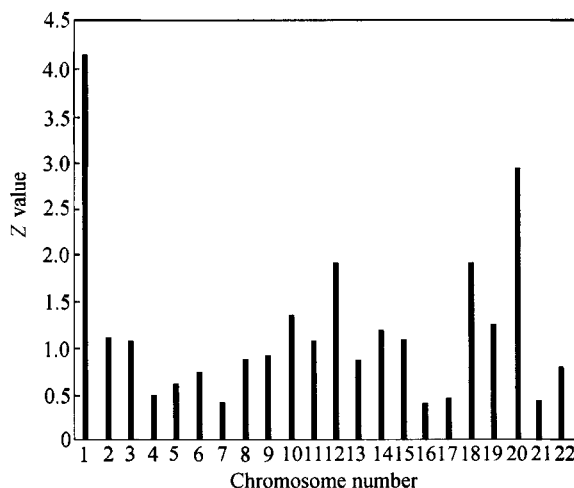


Fig. 1. Multipoint linkage analysis for chromosomes 1—22 in Chinese Han population type 2 diabetes.

NOTES

Table 1 NIDDM susceptibility gene loci preliminarily determined in different races

Locus	Race	Reference
1q(D1S2127)	Pima Indians	[3]
1q ²¹⁻²³	Utah Caucasians, Chinese Han population, Pima Indians	[6,7], this study
1p ³⁶ (D1S214)	Chinese Han population,	this study
1p ³¹ (D1S207)	Chinese Han population, Old Order Amish	this study
1q ⁴²⁻⁴³	Chinese Han population	this study, [8]
2q ³⁷ (D2S125)	Mexican Americans	this study
7q(D7S1799)	Pima Indians	[1]
7p ¹³⁻¹⁴ (MODY2)	French	[3]
10q(D10S587)	Mexican Americans	[9]
11q(D11S4464)	Pima Indians	[10]
12q(D12S1349)	Finnish	[3]
12q ^{24,2} (MODY3)	Americans	[11]
12p ¹² (D12S336)	Chinese Han population	[12]
13q ^{12,1} (MODY4)		this study
18q ²³ (D18S61)	Chinese Han population	[13]
20q(MODY1)		this study
20q(MODY1)		[14]
20q(D2S197)	Finnish	[2]
20q	Finnish	[4,11]
20p ¹² (D20S118)	Chinese Han population	this study
20p	Finnish	[4]

possible type 2 diabetes susceptibility gene locus of Chinese was located in 20p12 around D20S118 (39.3 cM to P-terminal) , $P=4 \times 10^{-4}$, $MLS=4.6787$, $Z=2.899$. The criterion suggested by Lander et al.^[17] is also met by our study. Interestingly, we also identified a moderate linkage relation in the region ~20cM toward the P-terminal of chromosome 20 (adjacent to D20S115, $P=0.05$, $Z=1.35$). For the sake of too broad interval between the marker D20S115 and P-terminal, a further test must be performed to take a fine-scale mapping by increasing the number of type 2 diabetes pedigrees and density of markers.

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