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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).

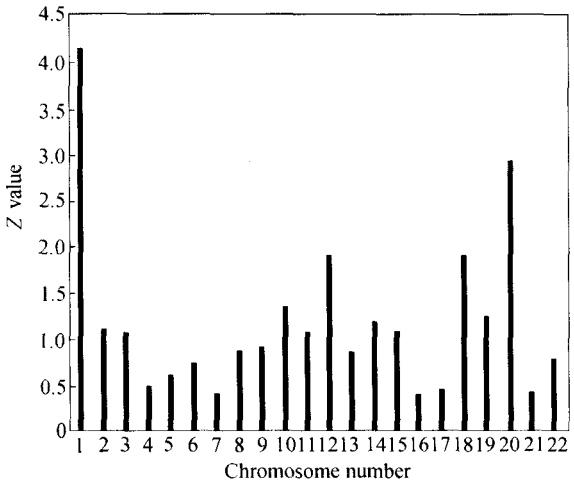

Fig. 1. Multipoint linkage analysis for chromosomes 1—22 in Chinese Han poputation type 2 diabetes.

(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[11], within the band 2q37; susceptibility locus is proximal to D12S1349[111], 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

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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), $P=4\times10^{-4}$, 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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Distributions of dissolved rare earth elements during estuarine mixing at the Changjiang River mouth

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Abstract The first data on the concentrations of dissolved REE in surface waters collected from the north passage of the Changjiang Estuary where the salinity ranges from 0.15 to 19 mg/g were determined by ICP-MS after preconcentration with solvent extraction and back-extraction techniques. Relative to other estuaries, the river-water end-member concentrations of dissolved REE are very low, ranging from 11.963 (Y) to 0.098 ng/kg (Lu). Dissolved REE removed markedly from water in the Changjiang Estuary where salinity lies within the range of 0.15—1 mg/g, but the percent removal is low, ranging only from 47%(La) to 25%(Lu). Strong water-sediment interaction due to shallow water depth in the Changjiang Estuary leads to remarkable concentration peaks of dissolved REE in the location where the salinity varies from 1 to 8 mg/g. In the moderate and high salinity regions from 8 to 19 mg/g, the concentrations of dissolved REE gradually increase as a result of desorption or partial dissolution of particles.

Keywords: Changjiang Estuary, rare earth elements, distributions, removal, desorption.

Estuaries are both chemical and physical dynamic systems that act as buffers between the land and the ocean. The net flux of riverine materials to the open ocean depends on their geochemical behavior at the estuary. Geochemical studies of the REE in an estuary always involve several objectives: (i) to elucidate the geochemical processes that determine the fate of the REE; (ii) to discuss the fractionation behavior of the REE; and (iii) to estimate the net riverine contribution to the REE budget of the world oceans. Large-scale removal of the REE has been evidenced by both field investigations and laboratory experiments, and about 70%—90% or nearly 100% of the dissolved REE are removed in the processes[1~4]. The Changjiang River is the third biggest river in the world, studies on REE distributions in the Changjiang River and Changjiang Estuary are of great significance in interpreting the geochemistry of the REE in the East China Sea and the West Pacific, and in getting a better understanding of many microscopic processes such as water-particle interaction during estuarine mixing.

1 Sampling and analysis

Water samples were collected in surface waters starting from Waigaoqiao to the location at E122°28′ and N31°2′, with the salinity varying from 0.15 to 19 mg/g via the north passage of the Changjiang Estuary on November 4—5, 1998. Sampling was made by using a 10L nitric acid-cleaned