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Polymorphisms at the GLUT1 (HepG2) and GLUT4 (muscle/adipocyte) glucose transporter genes and non-insulin-dependent diabetes mellitus (NIDDM)

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Summary. In order to determine the possible contribution of the GLUT1 (HepG2) glucose transporter gene to the inheritance of non-insulin-dependent diabetes mellitus (NIDDM), two restriction fragment length polymorphisms (RFLPs) and the related haplotypes at this locus were studied in 48 Italian diabetic patients and 58 normal subjects. Genotype frequencies for the *Xba*I polymorphism were significantly different between patients and controls (*Xba*I: $\chi^2 = 9.80$, $df = 2$, $P < 0.0079$). A significant difference was also found in the allele frequencies between NIDDM patients and controls ($\chi^2 = 9.39$, $df = 1$, $P < 0.0022$), whereas no differences were found for the *Stu*I RFLP. No linkage disequilibrium was detected between the *Xba*I and *Stu*I RFLPs in this sample. The analysis of the four haplotype frequencies (X1S1, X1S2, X2S1, X2S2) revealed a significant difference between diabetic patients and controls ($\chi^2 = 14.26$, $df = 3$, $P < 0.002$). By comparing single haplotype frequencies, a significant difference between the two groups was found for the X1S1 and X2S2 haplotypes. A two-allele RFLP at the GLUT4 (muscle/adipocyte) glucose transporter gene, detected with the restriction enzyme *Kpn*I, was also examined; no differences were found between patients and controls for this RFLP. The finding of an association between polymorphic markers at the GLUT1 transporter and NIDDM suggests that this locus may contribute to the inherited susceptibility to the disease in this Italian population.

Introduction

Genetic factors contribute a major part to the aetiology of non-insulin-dependent diabetes mellitus (NIDDM). The greater than 90% concordance rate for the disease among monozygotic twins (Barnett et al. 1981) provides strong evidence for a major genetic component, but the gene (or genes) involved are still unknown. Many metabolic defects have been demonstrated in NIDDM, including defects in the binding of insulin to its receptor (Olefsky and Reaven 1974), reduced tyrosine-kinase activity of the insulin receptor β-subunit (Comi et al. 1987; Freidenberg et al. 1987), and impaired glucose transport activity (Kashiwagi 1983; Ciaraldi et al. 1982).

The distinction between inherited defects and defects secondary to metabolic abnormalities can be difficult to elucidate. One method for identifying genetic factors in polygenic disorders such as NIDDM is to use restriction fragment length polymorphisms (RFLPs) as markers for candidate genes and to examine the differences in genotype and allele frequencies between diabetic patients and matched control subjects. Such differences may be demonstrated because of linkage disequilibrium between the alleles at the RFLP site and the alleles involved in the susceptibility to the disease. Candidate genes that have been considered to contribute to the aetiology of NIDDM include the insulin gene, the insulin receptor gene and the glucose transporter genes. Evidence from pathophysiological data suggests the presence of inherited defects of glucose transport, in cases where a reduction in both glucose transporter numbers and activity in adipocytes is observed and when a reduced sensitivity to the action of insulin that is not reversible after insulin treatment is found (Kashiwagi 1987; Ciaraldi et al. 1982; Garvey et al. 1988). Furthermore, a decrease in glucose oxidation in NIDDM patients has been reported (Golay et al. 1988); it has been suggested that a defect in glucose transport may account for this (Butler et al. 1990).

Four different glucose transporter proteins have been recently identified, each of them expressed by a particular gene and considered to have a specific tissue distribution (Mueckler 1990). The best characterized of the glucose transporter genes is the GLUT1 or HepG2 glucose transporter gene (Mueckler et al. 1985); this gene is present on chromosome 1p31.3–p35 (Shows et al. 1987), is ubiquitously expressed, and is the major transporter in brain, placenta and erythrocytes. The transporter was initially considered to be a non-insulin-sensitive glucose

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transporter, mainly involved in the basal glucose uptake of the cells. However, it has been shown that this transporter is translocated after insulin stimulation of adipocytes (Gould et al. 1989; Zorzano et al. 1989), together with the insulin-responsive glucose transporter (GLUT4) (James et al. 1989), raising the question of the relative contribution of the GLUT1 transporter to the action of insulin on glucose uptake. The GLUT4 glucose transporter gene, which has recently been cloned, appears to be another good candidate gene for NIDDM. It is expressed in adipocytes and muscle cells (Joost and Weber 1989), which are sites of insulin-dependent glucose disposal; a defect in this protein should therefore be considered in the aetiology of NIDDM.

We have previously reported a significant association between a genetic variant at the GLUT1 transporter and NIDDM in three distinct ethnic groups (Li et al. 1988); however, a study in a Chinese American population has failed to confirm this association (Xiang et al. 1989). In another study with four restriction fragment length polymorphisms (RFLPs) in Black Americans, there was no significant association between any of these RFLPs and NIDDM, when the results were corrected for multiple comparisons (Kaku et al. 1990). Further work is required to assess the possible contribution of the GLUT1 (HepG2) transporter gene to the inheritance of NIDDM, and we have therefore studied, in a newly recruited Italian diabetic population, two individual RFLPs at this locus, detected with the restriction enzymes *Xba*I and *Stu*I (Shows et al. 1987; Li et al. 1989a), and their related haplotypes. We have also examined a *Kpn*I RFLP (Bell et al. 1989) at the muscle/adipocyte GLUT4 transporter.

Materials and methods

A total number of 106 subjects was newly recruited for the study; 48 unrelated Italian Caucasian patients (21 women, 27 men) were recruited from the diabetic clinic of the II Clinica Medica, University of Rome. All conformed to the World Health Organization criteria for non-insulin-dependent diabetes mellitus (WHO 1980). Unrelated Italian Caucasian normal subjects (36 women, 21 men) were selected for the control group on the basis of their fasting blood glucose levels being less than 6 mmol/l, and their having a negative family history for diabetes in their first degree relatives. Not all subjects were genotyped at each RFLP, and the number of observations at each RFLP are indicated in the relevant tables (see Tables 2, 5). The clinical details of the two groups are described in Table 1.

Analysis of RFLPs

DNA was extracted from 10 ml whole blood as previously described (Kunkel et al. 1977). Briefly, 8 μg DNA was digested with the restriction enzymes *Xba*I, *Stu*I and *Kpn*I according to the manufacturer's instructions (GIBCO-BRL, Uxbridge, UK). The resulting fragments were separated by electrophoresis in 0.85% agarose gel, and subsequently transferred to Hybond-N filters (Amersham International, Amersham, Bucks) by Southern blotting. The filters were then hybridized with a genomic DNA probe labelled with P^{32} by the random priming procedure, and the bands were visualized by autoradiography after incubation at −70°C with "Hyperfilm" (Amersham) for 2–10 days. The GLUT1 probe used for hybridization was prepared from the 3.5-kb genomic GLUT1 transporter probe Pe1a, kindly donated by Dr. M. Mueckler (Washington University, Missouri). This probe was digested with *Sph*I (GIBCO-BRL) to yield a 2.5-kb fragment Pe1a-*Sph*I covering the 5′ region upstream of exon 3 of the GLUT1 gene (Kaku et al. 1990). The GLUT4 cDNA transporter probe used was the 1.7-kb *Eco*RI insert phJHT-3 (Bell et al. 1989) covering a 1326-bp region encoding for amino acids 1-442, kindly donated by Dr. G. I. Bell (University of Chicago, Illinois).

Statistical analysis

Differences in genotype and allelic frequencies were assessed by Chi-square analysis with Yates' correction where indicated. The polymorphism information content (PIC) value was calculated as previously described (Botstein et al. 1980).

Linkage disequilibrium between the *Xba*I and the *Stu*I alleles was assessed by the likelihood ratio test, comparing estimated haplotype frequencies with those expected from the allele frequencies assuming no linkage disequilibrium, and by the disequilibrium statistics Delta (Hill and Robertson 1968) and D' (Lewontin 1984).

When Delta is calculated, complete linkage disequilibrium between two sites is detected when Delta = ±1, and complete random association when Delta = 0, using $n\text{Delta}^2$ (n = sample size) as the variable with 1 df to test the null hypothesis (Delta = 0). D' provides an indication of the linkage disequilibrium relative to its theoretical maximum. Linkage disequilibrium between the *Xba*I and *Stu*I sites was assessed in the whole population studied, and for each group individually.

Comparison of haplotype frequencies was performed by the likelihood ratio test. In the absence of family data, it is not possible unambiguously to haplotype subjects who are heterozygous at both sites; to overcome this problem, we have estimated the frequency of the haplotypes by maximum likelihood from the number of unambiguous haplotypes obtained (Hill 1974), assuming that the genotype frequencies for the double heterozygote class are the same as those computed for the other classes. Comparable results were obtained when the haplotype frequencies were estimated with the method described by Morgan et al. (1990). Control and NIDDM patients haplotypes were estimated separately for each group.

Results

RFLPs at the GLUT1 transporter

Two RFLPs were identified at the GLUT1 transporter with the genomic DNA probe Pe1a-*Sph*I: one with the restriction enzyme *Xba*I (Shows et al. 1987), resulting in

Table 1. Clinical details of the Italian Caucasian population studied, FH, family history; NIDDM, non-insulin-dependent diabetes mellitus

	n	Age[a] (years)	BMI[a] (w/h^2)	Fasting blood glucose[a] (mg/dl)	Duration[a] (years)	Positive FH
NIDDM	48	60.2 ± 11	27.4 ± 3.9	9.4 ± 0.4	10 ± 8	22 (45%)
Controls	58	53.3 ± 10	25.7 ± 3.1	–	–	0

[a] Values are expressed as mean ± standard deviation, BMI, weight/height^2

Table 2. Genotype distributions and allele frequencies of *Xba*I and *Stu*I RFLPs at the GLUT1 glucose transporter gene. NS, Not significant

	n	Genotypes			Allele frequencies	
		X1X1	X1X2	X2X2	X1	X2
*Xba*I[a]						
NIDDM	46	12 (26%)	23 (50%)	11 (24%)	0.51	0.49
Controls	58	4 (6%)	27 (47%)	27 (47%)	0.30	0.70
	n	Genotypes			Allele frequencies	
		S1S1	S1S2	S2S2	S1	S2
*Stu*I[b]						
NIDDM	46	5 (10%)	25 (55%)	16 (35%)	0.38	0.62
Controls	55	3 (6%)	26 (47%)	26 (47%)	0.29	0.71

[a] NIDDM vs control comparisons: genotypes $\chi^2 = 9.80$, $df = 2$, $P < 0.0073$; allele frequencies $\chi^2 = 9.39$, $df = 1$, $P < 0.0022$

[b] NIDDM vs control comparisons: genotypes $\chi^2 = 2.11$, $df = 2$, $P < 0.34$ (NS); allele frequencies $\chi^2 = 1.81$, $df = 1$, $P < 0.17$ (NS)

Table 3. Analysis of *Xba*I/*Stu*I haplotypes at the GLUT1 glucose transporter locus. Values are numbers found, with frequencies in parentheses NIDDM vs control haplotypes comparison: $\chi^2 = 14.26$, $df = 3$, $P < 0.002$

Haplotypes	NIDDM	Controls
X1S1	15 (0.17)	6 (0.05)
X1S2	29 (0.33)	23 (0.21)
X2S1	15 (0.17)	21 (0.19)
X2S2	29 (0.33)	60 (0.55)
Total	88	110

Table 4. Comparison between estimated and expected haplotype frequencies at the GLUT1 glucose transporter gene. Values in parentheses are number of haplotypes. Expected frequencies were calculated assuming no linkage disequilibrium. Likelihood ratio $\chi^2 = 0.93$, $df = 3$, $P < 0.81$ (NS); $D' = -0.18$; *Delta* = 0.107, $\chi^2 = 2.281$, $df = 1$, $P < 0.5$ (NS)

Haplotypes	Estimated frequencies	Expected frequencies
X1S1	0.11 (21)	0.13 (25)
X1S2	0.26 (52)	0.26 (52)
X2S1	0.18 (36)	0.20 (40)
X2S2	0.45 (89)	0.41 (81)
Total no. of haplotypes	198	198

fragments of 6.2 kb (X1 allele) and 5.9 kb (X2 allele), and one with the enzyme *Stu*I (Li et al. 1989a), giving fragment sizes of 3.2 kb (S1 allele) and 2.6 kb (S2 allele). Both the *Xba*I and *Stu*I sites are located in a 2.5-kb region upstream of exon 3 of the GLUT1 transporter. A total number of 208 alleles for the *Xba*I polymorphism and of 20 alleles for the *Stu*I RFLP were examined: the frequency of the X1 allele was 0.39 with a heterozygosity of 0.47, and the frequency of the S1 allele was 0.33, with a heterozygosity of 0.44. The PIC values for the *Xba*I and *Stu*I RFLPs were 0.36 and 0.34, respectively, and the combined PIC value was 0.70, making this locus informative for linkage studies. The genotype distributions for these two polymorphisms did not differ from that expected from the Hardy-Weinberg equilibrium.

Genotype and allelic frequencies at the GLUT1 transporter

A total number of 106 subjects (diabetics and controls) was studied. The *Xba*I polymorphic site was evaluated in 46 NIDDM patients and 58 normal controls; the *Stu*I RFLP was evaluated in 46 diabetic patients and in 55 normal controls. The genotype distributions and allele frequencies at these two sites were compared between the two groups (Table 2). For the *Xba*I RFLP, the genotype distributions differed significantly between NIDDM patients and normal controls. A significant difference was found when comparing the allele frequencies between the two groups.

At the *Stu*I RFLP, the genotype distributions did not differ significantly between the two groups, and no differences were found in the allele frequencies between the two groups (Table 2).

Haplotype frequencies at the GLUT1 transporter

Haplotype frequencies for the *Xba*I and *Stu*I alleles were estimated for the diabetic and control groups by maximum likelihood estimation (Hill 1974). Four haplotypes were observed (Table 3): the frequencies of these haplotype were significantly different between diabetics and controls. A significant difference was also found by comparing the two groups for the individual haplotypes: in particular, a significant difference was found comparing the X1S1 and the X2S2 haplotype frequencies (X1S1: $\chi^2 = 6.92$, $df = 1$, $P < 0.008$; X2S2: $\chi^2 = 9.21$, $df = 1$, $P < 0.0024$).

The significance of these results was still present after the Bonferroni correction for multiple comparisons with a P value < 0.0125.

Table 5. Genotype distributions and allele frequencies of the *Kpn*I RFLP at the GLUT4 glucose transporter. NIDDM vs control comparisons: genotypes: $\chi^2 = 1.61$, $df = 2$, $P < 0.44$ (NS); allele frequencies: $\chi^2 = 1.44$, $df = 1$, $P < 0.23$ (NS)

	n	Genotypes			Allele frequencies	
		K1K1	K1K2	K2K2	K1	K2
NIDDM	45	5 (11%)	15 (33%)	25 (56%)	0.27	0.73
Controls	56	8 (14%)	24 (43%)	24 (43%)	0.36	0.64

Linkage disequilibrium between RFLPs

To assess the linkage disequilibrium between the *Xba*I and *Stu*I sites, a total of 198 alleles was examined. No significant differences were found comparing the haplotype frequencies estimated and those expected from the respective allele frequencies using the likelihood ratio test, nor by calculating the disequilibrium statistics Delta and D′ (Table 4). No linkage disequilibrium was found when patients and controls were assessed separately (data not shown). The alleles at these two sites therefore appear to be in linkage equilibrium in this sample.

RFLP at the GLUT4 transporter

A two allele RFLP was identified at the GLUT4 transporter locus with the cDNA probe phJHT-3 using the *Kpn*I restriction enzyme (Bell et al. 1989). The allele sizes were 6.5 kb (K1) and 5.8 kb (K2); the frequency of the K1 allele was 0.32 with a heterozygosity of 0.43 and a PIC value of 0.34. The genotype distributions were in Hardy-Weinberg equilibrium.

Genotype and allele frequencies at the GLUT4 transporter

The *Kpn*I genotype and allele frequencies at the GLUT4 transporter did not differ significantly between NIDDM patients and normal subjects (Table 5).

Discussion

In the present study, we have examined two different polymorphic sites of the GLUT1 (HepG2) glucose transporter gene and the only RFLP reported at the GLUT4 (muscle/adipocyte) glucose transporter gene in Italian NIDDM patients and unrelated normal controls. The findings confirm our previous observation that an allele (X1) of the *Xba*I RFLP shows an association with NIDDM (Li et al. 1988).

The *Xba*I RFLP showed significant differences in allele frequencies and genotype distributions between NIDDM patients and normal subjects. At the *Stu*I site, a higher frequency of the minor allele (S1) was seen in the patient group, but this did not reach statistical significance; there was also no significant difference in the genotype distributions. A significant difference was also found between the four haplotypes defined by the *Xba*I and *Stu*I RFLPs in the two groups; in particular, when comparing single haplotype frequencies, it appears that the X1S1 haplotype is significantly more frequent in NIDDM patients, whereas the X2S2 haplotype is significantly more frequent in normal subjects.

The lack of linkage disequilibrium between these two RFLPs requires some comment: it may be speculated that a higher rate of recombination is present between these two sites, and that the differences found in the haplotype frequencies are probably a reflection of the difference at the *Xba*I site alone. Alternatively, our sample size may not be large enough to detect linkage disequilibrium. A previous report in a West Indian and a North European Caucasian population did not show linkage disequilibrium at these two sites (Li et al. 1989b). Interestingly, the frequency of the observed haplotypes in our population differed significantly from that reported in the West Indian population ($\chi^2 = 12.57$, $df = 3$, $P < 0.006$), suggesting that either natural selection or genetic drift may be operating to account for this difference.

No differences were found between our control haplotype frequencies and previously reported values in Northern European Caucasians (Li et al. 1989b), which suggests that our control group results may not be accounted for by sampling bias.

In a recent report, Kaku et al. (1990) concluded that there was no association between four polymorphic markers at the GLUT1 transporter, including the *Xba*I RFLP, and NIDDM in an American Black population. The existence of racial differences in the genetic susceptibility to NIDDM or a different evolutionary history of these RFLPs might explain the differences found between this study and ours.

Moreover, the possibility that NIDDM might be an heterogeneous disease, with few major genes contributing most of the susceptibility in some families, has to be considered. For example, in one pedigree study (O'Rahilly et al. 1989), co-segregation for the *Xba*I RFLP was not found in a family with NIDDM, but the authors could not exclude linkage at diabetogenic gene frequencies of 0.05 and 0.01, which are similar to the frequency of the disease in Caucasian populations. Furthermore, the existence of sub-groups of patients with sporadic (environmental) and familial forms of NIDDM has to be considered; if this is the case, the characterization of the patients studied becomes critical, and it may be important in the future to enter only patients with a positive family history in genetic studies.

A defect in the regulation of basal glucose uptake by the GLUT1 transporter can be considered with respect to the aetiology of NIDDM. It might be speculated that a defect in the primary sequence or in the regulation of the GLUT1 transporter could cause impaired glucose transport in the fasting state, resulting in reduced glucose tolerance and insulin resistance. A defect at the GLUT1 transporter could also be associated with defects of other glucose transporter genes; the muscle/adipocyte

GLUT4 transporter (James et al. 1989), for example, remains a good candidate gene for NIDDM, despite the negative findings for the *Kpn*I RFLP. A defect of the β-cell/hepatocyte GLUT2 transporter (Mueckler 1990) leading to impaired glucose sensitivity of the β-cells with diminished insulin secretion should also be considered in the aetiology of NIDDM.

In conclusion, the confirmation of the positive association of the *Xba*I RFLP at the GLUT1 transporter with NIDDM, and the finding of a significant difference in the frequencies of the haplotypes at the GLUT1 transporter between NIDDM patients and normal controls suggest that genetic variation at this locus may be involved in the susceptibility to the disease in this population. However, as discussed by Cox and Bell (1989), association studies should be considered as exploratory and preliminary; therefore, sib-pair analysis in families and DNA sequence studies of critical exons are in progress in order to elucidate whether the GLUT1 glucose transporter gene has a role in susceptibility to NIDDM.

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