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PRELIMINARY REPORT

Polymorphism of the Glycogen Synthase Gene and Non–Insulin-Dependent Diabetes Mellitus in the Russian Population

Gulja Babadjanova, Bruno Allolio, Felix Beuschlein, Alexander Chuchalin, and Martin Reincke

Recently, a polymorphism in the glycogen synthase gene was shown to be associated with the development of non–insulin-dependent diabetes mellitus (NIDDM) and identified patients with a strong family history of diabetes and hypertension in the Finnish population. However, no association was found in French and Japanese populations. We investigated the possible association between the *Xba*I polymorphism of the glycogen synthase gene and NIDDM in the Russian population. One hundred fifty NIDDM patients and 109 healthy controls were studied. In 16 of 150 Russian NIDDM patients (10.7%), the *Xba*I polymorphism was found, and 17 of 109 controls (15.6%) showed the *Xba*I polymorphism ($P > .05$). These results suggest that the *Xba*I polymorphism of the glycogen synthase gene cannot be used as a marker for NIDDM in the Russian population.

GENETIC FACTORS contribute to the development of non–insulin-dependent diabetes mellitus (NIDDM), and genes involved in regulating pancreatic β-cell function and insulin effects on glucose metabolism are good candidates for NIDDM susceptibility loci. However, testing candidate genes for linkage to NIDDM depends on the identification of highly informative DNA polymorphisms in or near the candidate locus. The glycogen synthase gene is a prime candidate for a genetic mutation in NIDDM. Interest has focused on glycogen synthase as the site of the mutation because defects in the synthesis and activation of the enzyme have been found in NIDDM.[1,2] There are two glycogen synthases coded for by separate genes: a skeletal muscle glycogen synthase (GYS1) and a liver glycogen synthase (GYS2). The human liver glycogen synthase isozyme gene is located on the short arm of chromosome 12.[3] Affected-sibling pair studies using a simple sequence-repeat DNA polymorphism physically linked to the islet amyloid polypeptide and liver glycogen synthase genes showed no evidence for linkage with NIDDM, indicating that they are not the major genes contributing to NIDDM susceptibility.[4] Skeletal muscle glycogen synthase on chromosome 19q13.3 is the rate-limiting enzyme in insulin-mediated nonoxidative glucose disposal. Independent studies showed an association of the skeletal muscle glycogen synthase gene with NIDDM in Finnish[5] and Japanese[6] populations and in Pima Indians.[7] Recently, Groop et al[5] reported that a *Xba*I polymorphism of GYS1 is associated with a higher risk for the development of insulin resistance and NIDDM in the Finnish population. This DNA polymorphism (A2 allele) appeared to identify a subgroup of patients with NIDDM characterized by a strong family history of NIDDM, high prevalence of hypertension, and marked insulin resistance. However, in contrast to the results obtained in Finland, the A2 allele was not associated with NIDDM in the French and Japanese populations.[8,9]

The aim of this study was to investigate whether the *Xba*I polymorphism of GYS1 is a useful marker for NIDDM in the Russian population.

SUBJECTS AND METHODS

We studied 150 patients with NIDDM (75 had at least two family members with NIDDM, and 75 had no family history) and 109 healthy controls. Diabetes was documented according to World Health Organization criteria. All subjects were unrelated Russians and residents of the Moscow area. Patients were aged 20 to 68 years, with an age of onset of 48.5 ± 8.2 and body mass index 27.3 ± 2.1 kg/m^2. Controls had a mean age of 36.1 ± 13.9 years, 25.6 ± 3.8 kg/m^2, and normal glucose

From the Schwerpunkt Endokrinologie, Medizinische Universitätsklinik Würzburg, Germany; and the Department of Internal Medicine, Moscow State Medical University, Moscow, Russia.
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Address reprint requests to Martin Reincke, MD, Schwerpunkt Endokrinologie, Medizinische Universitätsklinik Würzburg, Josef-Schneider-Strasse 2, D-97080 Würzburg, Germany.

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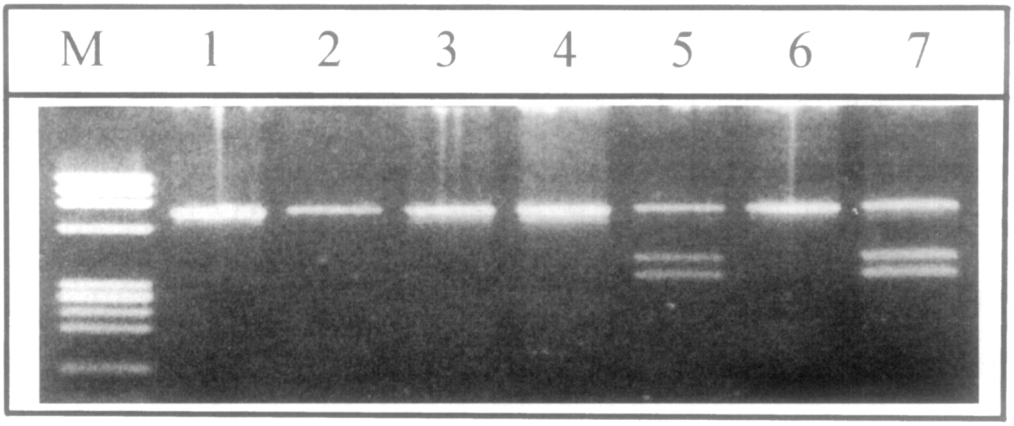

Fig 1. Agarose gel electrophoresis of polymerase chain reaction–amplified DNA digested with the restriction enzyme *Xba*I. M, molecular size marker ϕX174 RF. Lanes 1 to 4 and 6, homozygous for the A1 allele. Lanes 5 and 7, 3 fragments representing the undigested A1 allele and 2 fragments representing the digested A2 allele.

tolerance. All patients were treated with diet and/or oral hypoglycemic agents without insulin therapy.

Genomic DNA was extracted from peripheral blood leukocytes, photometrically measured, used for detection of the *Xba*I polymorphism by polymerase chain reaction–restriction fragment length polymorphism analysis as previously reported,[5] and assayed on a 2% agarose gel. The A1 and A2 allele were defined as follows: the A1 allele lacked the *Xba*I site, whereas the A2 allele contained the *Xba*I site (Fig 1).

Chi-square analysis was used to determine the significance of differences in frequency.

RESULTS AND DISCUSSION

The *Xba*I polymorphism of GYS1 representing the A2 allele was identified in 16 (six with a family history and 10 without) of 150 NIDDM patients (10.7%) and 17 of 109 controls (15.6%). All NIDDM patients with the A2 allele had a significantly later age of onset of NIDDM ($P = .001$). The young age of the controls cannot substantially affect the results, since the cumulative morbidity risk (population risk of development of diabetes for each individual born) of NIDDM by the age of 40 years is 0.1% for men and 0.15% for women in the Moscow area population.[10]

Therefore, contrary to the results obtained in the Finnish population,[5] where the A2 allele was identified in 30% of NIDDM patients and 8% of controls, and in accordance with the results obtained in the Japanese[9] (9% of NIDDM patients and 9% of controls) and French[8] (4% of NIDDM patients and 12% of controls) populations, no association between the A2 allele and NIDDM was found in the Russian population. Thus, the *Xba*I polymorphism of the glycogen synthase gene cannot be considered a marker for NIDDM in the Russian population.

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