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Prevalence of a Polymorphism of the Phosphatidylinositol 3-Kinase p85α Regulatory Subunit (Codon 326$^{Met\rightarrow Ile}$) in Japanese NIDDM Patients

Phosphatidylinositol 3-kinase is a heterodimeric enzyme composed of an 85-kDa regulatory subunit (p85), containing two SH2 and one SH3 domain, and a 110-kDa catalytic subunit (p110) (1,2). This kinase has been shown to be important for insulin-stimulated glucose transport in insulin sensitive cells (3–5).

Recently, Andersen et al. (6) identified a missense mutation at nucleotide 1020 (G→A) changing Met to Ile (codon 326$^{Met\rightarrow Ile}$) in the p85α regulatory subunit of phosphatidylinositol 3-kinase. Thus, we examined the prevalence of a polymorphism of codon 326$^{Met\rightarrow Ile}$ of the p85α subunit of PI 3-kinase, using the double mismatched polymerase chain reaction (PCR)–restriction fragment length polymorphism (RFLP) analysis (Fig. 1) to understand the contribution of this mutation to the development of NIDDM in Japanese patients. The diagnosis of NIDDM and the definition of normal glucose tolerance were established, following a 75-g oral glucose tolerance test, based on the guidelines of the World Health Organization. We examined 260 normal control subjects (mean age, 57.0 ± 10.5 years; BMI, 22.6 ± 2.6 kg/m^2) and 200 Japanese NIDDM patients (mean age, 56.8 ± 13.7 years; BMI, 24.9 ± 5.2 kg/m^2). In agreement with the results of Andersen et al. (6), there was no significant difference between the normal subjects and the NIDDM patients in the distribution of the wild-type, heterozygote, and homozygote genotypes (198, 57, and 5 in normal subjects vs. 150, 43, and 7 in NIDDM patients, respectively) or in the allelic frequency (12.9% in normal subjects vs. 14.3% in NIDDM patients, respectively). We also compared the clinical characteristics of each genotype (wild-type, heterozygote, and homozygote) among the NIDDM patients and found that several parameters, including BMI (25.3 ± 4.7, 23.9 ± 6.8, and 26.2 ± 3.6 kg/m^2), fasting glucose (143.2 ± 39.9, 156.7 ± 53.8, and 157.0 ± 111.7 mg/dl), and age at onset of diabetes (46.1 ± 15.0, 47.1 ± 11.4, and 47.5 ± 10.8 years) were not statistically different among the three genotypes.

In conclusion, our results suggest that the amino acid polymorphism at codon 326$^{Met\rightarrow Ile}$ in the p85α regulatory subunit of phosphatidylinositol 3-kinase is unlikely to be a major contributor to the pathogenesis of NIDDM in Japanese patients. However, further studies are necessary to determine whether the mutations of phosphatidylinositol 3-kinase are involved in the pathogenesis of NIDDM.

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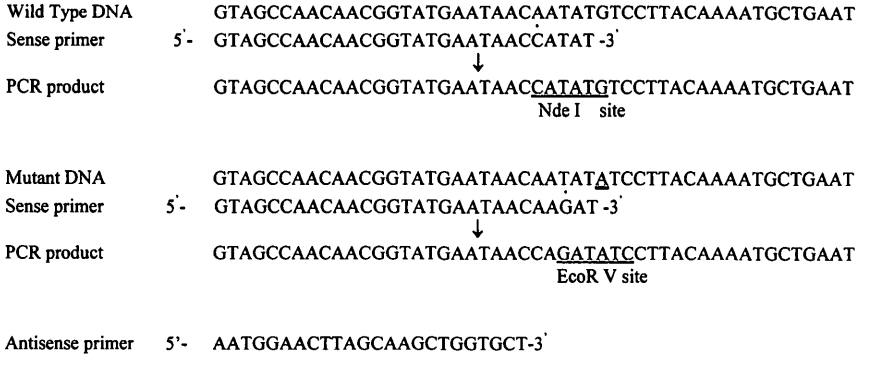

Figure 1—*Oligonucleotide sequences of DNA primers used for the PCR-RFLP analysis. Bases with dotted tops are the mismatched bases for the PCR-RFLP analysis. The products of the PCR fragments amplified from wild-type and mutant DNA create the restriction enzyme sites for NdeI and EcoRV, respectively. The created enzyme sites are underlined. The antisense primer is settled in the intron. The mutated base is double-underlined.*