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Association of polymorphisms in the insulin-degrading enzyme gene with type 2 diabetes in the Korean population

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ABSTRACT

Insulin-degrading enzyme (IDE) is a metalloproteinase which degrades insulin and terminates its action. Homologous deletion of *IDE* gene resulted in hyperinsulinemia and glucose intolerance in a rat model of type 2 diabetes mellitus. Several genetic association studies examined *IDE* as a susceptibility gene for type 2 diabetes in European descents. Here we investigated the genetic association of *IDE* polymorphisms with the risk of type 2 diabetes and its related phenotypes in the Korean population. Among six single nucleotide polymorphisms analyzed, g.−179T > C (OR = 1.73, $P = 0.04$), and g.IVS18+99G > A (OR = 1.23, $P = 0.02$) revealed borderline association with increased risk of type 2 diabetes. Combining our results with previous data obtained from the European population, g.−179T > C (OR = 1.11, $P = 0.03$), and g.IVS24−64A > T (OR = 1.18, $P = 0.005$) showed significant association with type 2 diabetes. Haplotype consisting of common alleles of the six polymorphisms was associated with decreased risk of type 2 diabetes (OR = 0.82, $P = 0.02$). However, none of the polymorphisms was significantly associated with metabolic phenotypes. We can conclude that variations in *IDE* might contribute to diabetes susceptibility in the Korean population.

1. Introduction

Insulin-degrading enzyme (IDE), a 110 kDa Zn^{2+}-regulated metallopeptidase [1], plays a primary role in insulin degradation and initiating cellular insulin processing [2–5]. It is located at the cell surface, cytosol, peroxisomes, and endosomes of various insulin-responsive tissues. The substrates of IDE include amyloid β-protein, amylin, glucagons, and insulin which are capable of forming β-pleated sheet amyloid. Characterization of mice with homozygous deletions of the *IDE* gene resulted in hyperinsulinemia and glucose intolerance, hallmark of type 2 diabetes [6]. Transferring an ~3.7 cM chromosomal region containing the *IDE* gene from an inbred diabetic Goto-Kakizaki (GK) rat model to a normoglycemic rat showed hyperinsulinemia and postprandial hyperglycemia [7]. The GK allele of *IDE* in this chromosomal region carries two missense mutations that results in 31% reduction in IDE activity [7]. These studies suggest that *IDE* polymorphisms, which result in hypofunction of IDE may be a pathogenic factor in type 2 diabetes. Chromosome 10q23–25, which

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encompasses the *IDE* gene has been pointed as the locus linked to mean fasting plasma glucose over 20 years, and fasting plasma glucose in Caucasian pedigrees by genome-wide scan [8].

These positional and functional candidacy led to several genetic association studies investigating *IDE* polymorphisms related to type 2 diabetes [9–12]. One study revealed that *IDE* polymorphisms were associated with HbA1c, fasting plasma glucose, and mean fasting plasma glucose measured over 20 years in Framingham Heart Study population [9]. *IDE* polymorphisms showed association to plasma insulin levels and correlated traits in a Swedish population [10]. Whereas other study consisting of U.K. population did not show compelling evidence that *IDE* polymorphisms contributed to diabetes susceptibility in humans [11,12]. Recently, study comprising of 4206 Caucasian subjects revealed no significant association between IDE polymorphisms and type 2 diabetes [12]. But there was no study regarding the Asian population. In this study, we examined the potential influence of *IDE* polymorphisms on type 2 diabetes susceptibility and metabolic phenotypes in the Korean population.

2. Patients and methods

2.1. Subjects

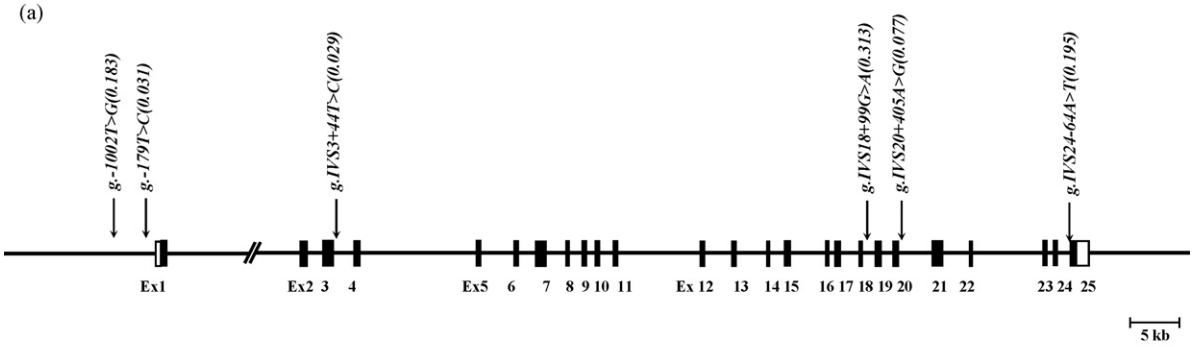
We studied 776 unrelated patients with type 2 diabetes and 637 non-diabetic control subjects. Type 2 diabetes was diagnosed according to the World Health Organization criteria. To select the non-diabetic control subjects, the following criteria were used: 60 or more years of age, no past history of diabetes, no diabetes in their first-degree relatives, a fasting plasma glucose level <6.1 mmol/L, and a HbA1c level <5.8%. Institutional Review Board of Clinical Research Institute in Seoul National University Hospital approved the study protocol and informed consent for genetic analysis was obtained from each subject.

2.2. Selection of polymorphisms

As we were interested in replicating the result of Groves et al. we adopted the same SNPs from their study [11]. Six previously reported polymorphisms of IDE gene [11] were genotyped in *IDE*: four in intron and two in 5′ UTR: g.−1002T > G (position in NCBI: 94324758, dbSNP ID; rs3758505), g.−179T > C (position in NCBI: 94323935, dbSNP ID; rs4646953), g.IVS3+44T > C (position in NCBI: 94284270, dbSNP ID; rs4646955), g.IVS18+99G > A (position in NCBI: 94219892, dbSNP ID; rs4646957), g.IVS20+405A > G (position in NCBI: 94214145, dbSNP ID; rs1887922), and g.IVS24−64A > T (position in NCBI: 94204339, dbSNP ID; rs4646958). The locations and allele frequencies of identified polymorphic sites are shown in Fig. 1.

2.3. Genotyping of polymorphisms

Genomic DNA was isolated with a commercial kit (Gentra Systems, Minneapolis, MN). For genotyping of polymorphic



(b)

Hap.	g.-1002T>G	g.-179T>C	g.IVS3+44T>C	g.IVS18+99G>A	g.IVS20+405A>G	g.IVS24-64A>T	Freq.
ht1	T	T	T	G	A	A	0.609
ht2	G	T	T	A	A	T	0.182
ht3	T	T	T	A	A	A	0.096
ht4	T	T	T	G	G	A	0.068
ht5	T	C	C	A	A	A	0.029
ht6	T	T	T	G	G	T	0.010
ht7	T	T	T	A	A	T	0.002
ht8	G	T	T	A	A	A	0.001
ht9	G	T	T	G	A	A	0.001
ht10	T	C	T	G	A	A	0.0005

(c)

r^2 \ |D'|	g.-1002T>G	g.-179T>C	g.IVS3+44T>C	g.IVS18+99G>A	g.IVS20+405A>G	g.IVS24-64A>T
g.-1002T>G	-	1.000	1.000	0.993	1.000	0.984
g.-179T>C	0.007	-	1.000	0.977	1.000	1.000
g.IVS3+44T>C	0.007	0.984	-	1.000	1.000	1.000
g.IVS18+99G>A	0.492	0.065	0.067	-	1.000	0.923
g.IVS20+405A>G	0.019	0.003	0.003	0.038	-	0.322
g.IVS24-64A>T	0.906	0.007	0.007	0.455	0.002	-

Fig. 1 – Gene map and haplotypes of the *IDE* gene (NM_004969). (a) Map of *IDE* (insulin-degrading enzyme) on chromosome 10q23–25: 120kb. Polymorphisms identified in *IDE*. Coding exons are marked by shaded blocks and 5′ and 3′ UTR by white blocks. First base of transcription start site is denoted as nucleotide +1. (b) Haplotypes of *IDE* in Korean. (c) LD coefficients (|D′| and r^2) among SNPs in *IDE*.