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Identification of nonsynonymous polymorphisms in the superantigen-coding region of *IDDMK_{1,2}22* and a pilot study on the association between *IDDMK_{1,2}22* and type 1 diabetes

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Abstract To investigate the possible involvement of *IDDMK_{1,2}22/HERV-K18* in childhood type 1 diabetes mellitus, we identified two nonsynonymous A/G polymorphisms in the superantigen-coding region of *IDDMK_{1,2}22* at the 290- and 461-nucleotide (nt) positions from the initial methionine codon and compared their frequencies in 74 Japanese patients with type 1 diabetes and in 54 nondiabetic controls. Although the G substitution was observed more frequently at either site in the patients than it was in the controls (7% vs. 4% at 290nt, and 29% vs. 20% at 461nt), the differences were not statistically significant. A weak significance of difference in the frequency of 461G was obtained only in an early-onset group of patients manifesting the disease at 5 years of age or less ($n = 24$) when compared with controls (38% vs. 20%; $P = 0.03$). However, in addition to the common absence of a particular allele among the expected four alleles, remarkable differences in allele frequencies were present between Japanese and European populations. This first trial investigating the association of *IDDMK_{1,2}22* with type 1 diabetes presents intriguing suggestions for the role of this region in the etiology of autoimmune and infectious diseases.

Key words Type 1 diabetes mellitus · *IDDMK_{1,2}22/HERV-K18* · Single-nucleotide polymorphism (SNP) · Association · 1q21.2–q22

Introduction

Type 1 diabetes mellitus (insulin-dependent, IDDM) is an autoimmune disease with heterogeneous etiologies that are determined by environmental and genetic factors (Steinman 1995). Conrad et al. (1994, 1997) identified *IDDMK_{1,2}22* as having a superantigen (SAg) activity that is possibly involved in the pathogenesis of the disease. Although other studies following this report have presented conflicting results (Badenhoop et al. 1999; Jaekel et al. 1999; Lan et al. 1998; Lapatschek et al. 2000; Löwer et al. 1998; Murphy et al. 1998), they presented partial or indirect negative data. We have confirmed the expression of the *IDDMK_{1,2}22 env* gene in peripheral blood leukocytes, a prerequisite for its SAg activity, although the expression is at a very low level that is detectable only with polymerase chain reaction (PCR) (Sugimoto et al. 2001). The study of Conrad et al. (1997) is important in that their results suggest that a human endogenous retrovirus (HERV) gene product has SAg activity and that a target was presented. It is implied by the methodological nature of their experiments that either an altered (activated) expression or amino acid substitutions of the SAg-coding region of the gene is required for SAg activity to be exerted at a pathophysiological level. We have previously isolated and identified a nuclear gene, *HERV-K18*, that corresponds to *IDDMK_{1,2}22*, and have assigned its chromosomal location to 1q21.2–q22 (Hasuike et al. 1999). In the present study, we searched for mutations of its SAg-coding region in patients with type 1 diabetes and found two nonsynonymous single-nucleotide polymorphisms (SNPs). Subsequently, we examined whether these SNPs contribute to the susceptibility to type 1 diabetes by comparing their frequencies in patients and in nondiabetic controls.

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Patients, subjects, and methods

Subjects

Blood samples were obtained from 74 patients with typical acute-onset childhood type 1 diabetes and from 54 nondiabetic controls. These 74 patients included 24 patients with particularly early onset of the disease at 5 years of age or less. Consent was obtained from patients or their parents and from control subjects after the nature of the procedure was explained. The Ethics Committees of Kitasato and Ryukyu Universities approved the study protocol. All patients and control subjects were Japanese.

DNA sampling

DNA was extracted from blood leukocytes either by following the standard procedure using proteinase K digestion and phenol extraction, or by using a QIAmp Blood Kit (QIAGEN, Hilden, Germany).

PCR amplification, cloning, and sequencing of the SAg-coding region of IDDMK_{1,2}22

A 2.9-kb DNA fragment that included the SAg-coding and 3' long terminal repeat (LTR) sequences of IDDMK_{1,2}22 was amplified by nested PCR using an Expanded Long Template PCR system (Boehringer Mannheim, Mannheim, Germany). In the first PCR, 200 ng of genomic DNA was subjected to 32 thermal cycles of 94°C for 40 s, 55°C for 30 s, and 68°C for 120 s in 20 µl of reaction mixture containing primers K18A and K18B (1 µM in each), 350 µM each of dNTP and 1.75 mM MgCl₂, and 0.6 µl of enzyme mix (Taq and Pwo DNA polymerases). Using 4 µl of the 10-fold diluted first PCR, the nested PCR was performed with primers K18a and K18b for 30 cycles of 94°C for 40 s, 53°C for 30 s, and 68°C for 120 s in 50 µl of the same buffer conditions as in the first PCR. Primer sequences were as follows: K18A, 5'-CAGTAAGGAGTGTACCACTC; K18B, 5'-GGCTTGGTGCAGAATACTTC; K18a, 5'-TGAAGATCTACAATGAACCCATCAG; and K18b, 5'-GCTATGTAAGTCCTACAGACA. A Bgl II recognition site was introduced into primer K18a by substituting A for T (underlined in the sequence of K18a).

After specific amplification of the expected 2.9-kb fragment was confirmed by electrophoresis in 0.8% agarose gel, the remaining PCR product was digested with Bgl II and Xba I. After completion of the restriction enzyme digestion, the primers and short Bgl II-end fragments were removed using a QIAquick PCR purification kit. Subsequently, the purified Bgl II/Xba I fragments were cloned to pBluescript II (Stratagene, La Jolla, CA, USA). Ten to 15 colonies were cultured together overnight at 37°C in a tube, and plasmid DNA was extracted for use in the sequence analysis. Sequencing reactions were carried out using a Thermo Sequenase Fluorescent Labelled Primer Cycle Sequencing kit (Amersham Pharmacia Biotech, Buckinghamshire,

UK), and the sequence of both strands was determined using an automated sequencer 4200L-2 (LI-COR, Lincoln, NE, USA).

Mutation search and their association analysis

Mutation search was performed by sequencing the PCR-amplified and cloned SAg-coding region in the 74 patients described above. To examine their relevance to the disease, we carried out the same sequencing analysis in 54 control subjects and compared their frequencies in the patients and control group. Significant differences in genotype and allele frequencies between the patients and control group were evaluated using the χ^2 test with Yate's correction or Fisher's exact probability test with the significance level of 0.05.

Results

Amplification of IDDMK_{1,2}22 and identification of SNPs in the SAg-coding region

IDDMK_{1,2}22 is most likely to be a product derived from the *HERV-K18* locus (Hasuike et al. 1999). The *HERV-K* family is biologically the most active family among *HERVs*, and some members of the family appear to have entered the human genome after the divergence of humans and chimpanzees (Barbulescu et al. 1999; Löwer et al. 1996). Thus, it is critical to amplify and discriminate the sequence of IDDMK_{1,2}22/*HERV-K18* specifically from those of other members. Among the numerous highly homologous *HERV-K* family members, we achieved specific amplification of an *env*-containing DNA fragment from the IDDMK_{1,2}22/*HERV-K18* locus by nested PCR using primers designed from sequences just upstream from the SAg-coding region and downstream from 3' LTR (Fig. 1A). The nested PCR amplification yielded a clear single band 2.9 kb in size. The amplified DNA was digested with Bgl II and Xba I. The Xba I site was found only in two loci, including *HERV-K18*, among 30 GenBank sequences that seemed to derive from at least 18 distinct loci and possessed 95% or more homologies with the *HERV-K18 env* sequence. Thus, the Xba I site helped to increase the cloning specificity further (Fig. 1B). A 610-bp Bgl II/Xba I fragment was directionally cloned to pBluescript II (Stratagene), and 10–15 colonies were cultured and sequenced concurrently. Two nonsynonymous substitutions of G for A were identified at the 290- and 461-nt positions from the initial methionine codon within the region. These substitutions of 290G and 461G are predicted to change Tyr to Cys at codon 97 and the stop codon to Trp, resulting in an extension of 407 more amino acids to the C terminus, respectively. We later confirmed that an allele having the two substitutions (290G and 461G) is identical to an *HERV-K18* sequence previously reported in a database (GenBank accession no. Y18890). No other substitution could be found within the SAg-coding region in 74 patients with type 1 diabetes.

Fig. 1a,b. Specific amplification of the SAg-coding region of the IDDMK_{1,22}/HERV-K18 locus. **a** Schema of the 3' portion of the IDDMK_{1,22} gene and downstream sequence. The SAg-coding region is depicted by a *hatched box*, and the cloned and sequenced fragment is denoted by a *thick line* beneath the gene. Primer locations are indicated by *filled* (first polymerase chain reaction [PCR]) and *open* (nested PCR) *arrowheads*. *X* and *B* denote the *Xba* I and *Bgl* II sites,

respectively. The *Bgl* II site was introduced in the primer of the nested PCR. **b** Electrophoresis of the PCR products and their restriction digests on a 0.8% agarose gel. *Lanes 2 and 3* are the products of first PCR; *lanes 4 and 5* are nested PCR products; *lanes 6 and 7* are *Xba* I and *Bgl* II digests of the nested PCR products. *Lanes 1 and 8* are size marker DNA. The SAG-containing fragment is indicated by an *arrow*

Table 1. Observed genotypes in the SAg-coding region and their frequencies in patients and controls

Genotype (290–461)	Controls (<i>n</i> = 54) No. (%)	All patients (<i>n</i> = 74) No. (%)	Patients with early onset (<i>n</i> = 24) No. (%)
AA–AA	36 (66)	45 (61)	14 (59)
AA–AG	13 (24)	12 (16)	2 (8)
AA–GG	2 (4)	10 (14)	7 (29)
AG–AG	1 (2)	3 (4)	0 (0)
AG–GG	1 (2)	0 (0)	0 (0)
GG–GG	1 (2)	4 (5)	1 (4)

Population frequency and association analysis of the two SNPs

To evaluate the significance of the two SNPs in the etiology of type 1 diabetes, we sequenced the SAg-coding region of 54 nondiabetic controls in the same protocol as used in the sequence analysis of the patients. As summarized in Table 1, genotype analysis revealed the presence of six distinct genotypes among the expected nine genotypes in the patient and control groups. However, three expected genotype combinations, GG–AA (290–461), GG–AG, and AG–AA, were not found in either group in a total of 128 individuals. These results are best explained by the absence of the G–A allele in the Japanese population analyzed. Consistent with these results, a sequence reevaluation of a patient with the AG–AG genotype combination revealed heterozygous A–A and G–G alleles in a clone-by-clone analysis. Furthermore, the same finding was reported in a

Table 2. Haplotype frequencies in patients and controls

Allele	Nucleotide at 290 and 461	Patients (<i>n</i> = 74 × 2) No. (%)	Controls (<i>n</i> = 54 × 2) No. (%)	European population ^a (<i>n</i> = 60 × 2) No. (%)
1	A–A	105 (71)	86 (79)	56 (47)
2	A–G	32 (22)	18 (17)	13 (11)
3	G–G	11 (7)	4 (4)	51 (42)

^a Results of Stauffer et al. 2001

European population (Stauffer et al. 2001) during the manuscript preparation. Frequencies of the three alleles calculated from the observed genotypes are shown in Table 2, referenced with the data of Stauffer et al. In contrast to the common absence of the G–A allele in the Japanese and European populations, there was a remarkable reduction in the G–G allele frequency in the Japanese population examined, which presents a steep contrast to its 10-fold more frequent presence in the European population (Table 2). This difference in frequency is reminiscent of the relationship between the non-Asp57 frequency of HLA-DQβ and the prevalence of type 1 diabetes in Asian and Caucasian populations (Matsuura et al. 1996). Although the G substitution was more frequently observed at either site in the patients (*n* = 74 × 2) than in the control subjects (*n* = 54 × 2) (7% vs. 4% at 290nt and 29% vs. 20% at 461nt), the differences were not statistically significant (Table 3). When the patients were divided into subgroups on the basis of their clinical features to compare them to controls, a weak

Table 3. Allele frequencies in patients and controls

Allele	Controls (<i>n</i> = 54 × 2)	All patients (<i>n</i> = 74 × 2)		Patients with early onset (<i>n</i> = 24 × 2)	
	No. (%)	No. (%)	<i>P</i> value*	No. (%)	<i>P</i> value*
Position 290					
A	104 (96)	137 (93)	0.28	46 (96)	>0.99
G	4 (4)	11 (7)		2 (4)	
Position 461					
A	86 (80)	105 (71)	0.15	30 (62)	0.03
G	22 (20)	43 (29)		18 (38)	

* Fisher's exact test between controls and patients

significance of difference in the frequency of 461G was obtained in patients who had a particularly early onset at 5 years of age or less (*n* = 24 × 2) (18/48 vs. 22/108 or 38% vs. 20%; *P* = 0.03).

Discussion

In the present study, we identified two nonsynonymous SNPs in the SAg-coding region of *IDDMK_{1,2}22/HERV-K18* and examined their frequencies in 74 patients with type 1 diabetes and in 54 nondiabetic controls. Although the two SNPs have already been reported as the *HERV-K18* sequence in GenBank and their frequencies in European healthy individuals will soon be published (Stauffer et al. 2001), the present study is the first to report the association of *IDDMK_{1,2}22/HERV-K18* with type 1 diabetes and compare their frequencies between Japanese and European populations. These results include A/G substitutions at the 290- and 461-nt positions, slight but not significant increases in 290G and 461G in patients with type 1 diabetes, a weak significance of difference of 461G frequency in the patients with early onset of the disease (5 years of age or less), and a remarkable deviation of allele frequencies between Japanese and European populations with the common absence of a particular allele.

Although the increase in G substitution frequencies in the patients was not statistically significant, when the patients were divided into subgroups on the basis of their clinical features for comparison with controls, a weak significance of difference in the 461G frequency was obtained in the patients with very early onset of the disease at 5 years of age or less. Although this weak association may likely be due to spurious association, it is possible to interpret it as a reflection of a true association between *IDDMK_{1,2}22* and type 1 diabetes, especially the very early abrupt-onset type of the disease, considering the effect of viral infection on the pathogenesis of the disease and on the expression of *IDDMK_{1,2}22* (Singh et al. 1998; Stauffer et al. 2001). There is a deviation from Hardy–Weinberg equilibrium in genotype frequencies in patients in the early-onset group (Table 1). Deviation mainly results from an excess of homozygotes with allele 2 (290A–461G) (expected vs. observed values: 3 vs. 7) and deficiency of heterozygotes with allele 2 and allele

1 (290A–461A) (expected vs. observed values: 10 vs. 2). Hardy–Weinberg disequilibrium has been successfully used to refine the location of the hereditary hemochromatosis-susceptible locus (Feder et al. 1996). Therefore, it is important to determine whether the observed deviation in the present study is a characteristic feature inherent to early-onset diabetes or whether it is due to typing errors. The origin of the deviation can be determined using proper methods and SNPs in other loci surrounding the *IDDMK_{1,2}22/HERV-K18* gene and by increasing the number of samples (Mizuki et al. 2001). Comparison of allele frequencies in Japanese and European populations revealed a remarkable difference between the two populations, along with evidence of a consistent lack of one of four alleles in the *IDDMK_{1,2}22* locus. Deviation of population frequencies between different ethnic groups may occur frequently, and the lack of a particular allele may not simply reflect selection against that allele. However, natural selection is the most likely explanation for the deviation, especially when analyzed regions contain genes that interact with environmental factors such as viruses. Such genes are found in the *IDDMK_{1,2}22/HERV-K18* locus region.

The *IDDMK_{1,2}22/HERV-K18* gene is located in the first intron of the *CD48* gene that codes for a ligand of 2B4, and the expression of *CD48* is at least 10-fold greater on Epstein Barr virus (EBV)-transformed cells than on EBV-negative cells (OMIM, #109530). The signaling lymphocyte activation molecule (SLAM), which shows a strong homology with 2B4 and is a receptor for the measles virus (Tatsuo et al. 2000), is also located 32kb downstream from the *CD48* gene. Mutations of SLAM-associated protein (SAP/SH2D1A) have been shown to cause an X-linked lymphoproliferative syndrome that is characterized by fatal infectious mononucleosis, aplastic anemia, hypogammaglobulinemia, and malignant B-cell lymphoma (Coffey et al. 1998; Sayos et al. 1998). Two other genes belonging to the immunoglobulin superfamily are located within the 226-kb region surrounding the *CD48* gene (Boles and Mathew 2001). The *2B4* and *CD84* genes are also found in a 1256-kb draft sequence (GenBank accession no. NT_004406). The absence of the G–A allele of *IDDMK_{1,2}22* in the Japanese and European populations examined might be due to the lethal effect of mutations of either gene in this region, which is in linkage disequilibrium with *IDDMK_{1,2}22*. The susceptible locus/loci have been detected in the region encompass-

ing the *IDDMK_{1,2}/HERV-K18* locus (Mein et al. 1998). Together, these findings suggest the involvement of this region in the pathogenesis of type 1 diabetes and other autoimmune diseases and/or infectious diseases.

The proximity of candidate genes may complicate genetic studies designed to examine this issue and the interpretation of their results, but identifying the responsible susceptible loci may be possible, as exemplified in the case of *IDDM2* (Bennett and Todd 1996). Although our preliminary study does not necessarily provide direct support for the involvement of *IDDMK_{1,2}* in type 1 diabetes, our findings present a basis for more intensive genetic analyses of the *IDDMK_{1,2}* locus region in childhood type 1 diabetes.

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