Disease Markers 31 (2011) 223–229
DOI 10.3233/DMA-2011-0820
IOS Press

Polymorphism in the *KCNA3* gene is associated with susceptibility to autoimmune pancreatitis in the Japanese population

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Abstract. Autoimmune pancreatitis (AIP), characterized by irregular narrowing of the main pancreatic duct, swelling of the pancreas, and histological evidence of lymphoplasmacytic inflammation by high serum immunoglobulin G4, is distinct from ordinary pancreatitis. However, genetic factors involved in the etiology and pathophysiology of AIP remain unclear. Sixty-four patients with autoimmune pancreatitis (53 men, 11 women; mean age, 62.4 years) and 104 healthy Japanese controls were enrolled in this study. We performed an association analysis using 400 microsatellite markers with an average spacing of 10.8 cM in the genome. We also evaluated the association of AIP with seven single nucleotide polymorphisms (SNPs) within the 20-kb region around the potassium voltage-gated channel, shaker-related subfamily, member 3 gene (*KCNA3*). We identified six statistically significant markers (D1S2726, D5S410, D6S460, D10S548, D15S128, and D20S186; $P < 0.05$) related to susceptibility. The surrounding region showing the strong association ($P = 7.4 \times 10^{-7}$, Pc $= 0.0015$) contained the *KCNA3* gene. Further analysis by SNP genotyping in *KCNA3* gene revealed that four SNPs (rs2840381, rs1058184, rs2640480, rs1319782) were significantly associated with the AIP susceptibility ($P < 0.007$). *KCNA3* is known to be involved in immunomodulation of autoreactive effector and memory T cell–mediated autoimmune diseases. Our findings provide the first evidence that *KCNA3* is associated with AIP and suggest that *KCNA3* may influence the risk for AIP.

Keywords: AIP, autoimmune pancreatitis, SNPs, KCNA3, disease susceptibility

Abbreviations

AIP,	autoimmune pancreatitis;
HWE,	Hardy-Weinberg equilibrium;
HWP,	Hardy-Weinberg proportion;
KCNA3,	potassium voltage-gated channel, shaker-related subfamily, member 3;
LD,	linkage disequilibrium;
SNP,	single nucleotide polymorphism;
Pc-value,	corrected P-value.

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1. Introduction

Autoimmune pancreatitis (AIP) is a unique form of chronic pancreatitis characterized by minimal abdominal pain, irregular narrowing of the pancreatic duct, swelling of the pancreatic parenchyma, and predominance in elderly males. It has been referred to by various designations [1–7] and is now generally termed AIP based on clinical features, various serum autoantibodies, hypergammaglobulinemia, histological evidence of lymphoplasmacytic inflammation and fibrosis, and a favorable response to glucocorticoid treatment [3].

Awareness of AIP is a matter of clinical importance because this disease has been frequently misdiagnosed as pancreatic cancer [8]. Furthermore, this disease is

ISSN 0278-0240/11/$27.50

associated with a variety of extra-pancreatic complications such as sclerosing cholangitis [2,5] sialoadenitis [9,10], hypothyroidism [11], hilar lymphadenopathy [10], retroperitoneal fibrosis [7], interstitial pneumonia [12], and tubulointerstitial nephritis [13], and frequently has been designated as primary sclerosing cholangitis, Sjogren's syndrome, Hashimoto's thyroiditis, sarcoidosis, or primary retroperitoneal fibrosis. Because patients with AIP respond to corticosteroid treatment, the correct diagnosis should be made in order that timely and effective treatment can be implemented.

The etiology and pathogenesis of AIP remain unclear. Previous studies have shown that T-lymphocytes infiltrate the pancreatic tissues and that carbonic anhydrase II and lactoferrin are candidate target antigens [14]. However, there have been conflicting reports regarding the role of cellular immunity and effector cells, and anti-carbonic anhydrase II and anti-lactoferrin autoantibodies have not been proven specific to this condition [15]. The most characteristic feature of AIP is a specific augmentation of serum IgG4 concentration, which was found in over 90% of patients and is indicative of disease activity [6]. Histological findings of abundant IgG4-positive plasma cells are a hallmark of this disease [7,9,16]. These results suggest that IgG4 plays a major role in the pathogenesis of AIP.

The development of AIP is likely influenced by multiple interactions between genetic and environmental factors. Our previous report suggested that genetic factors for susceptibility to the disease were premier immune loci, such as the HLA *DRB1*0405-DQB1*0401* haplotype [17], the Fc receptor-like gene 3 (*FCRL3*) [18], and cytotoxic T-lymphocyte antigen 4 gene (*CTLA4*) [19]. However, the genetic factors underlying AIP have not been elucidated conclusively. Moreover, there are numerous candidate genes for AIP susceptibility. Recent progress in molecular genetics has enabled direct approaches for identifying genetic determinants. Here, we aimed to identify potential AIP susceptibility gene regions by performing a genome-wide scan and single nucleotide polymorphism (SNP) genotyping around candidate susceptibility genes.

2. Materials and methods

2.1. Patients

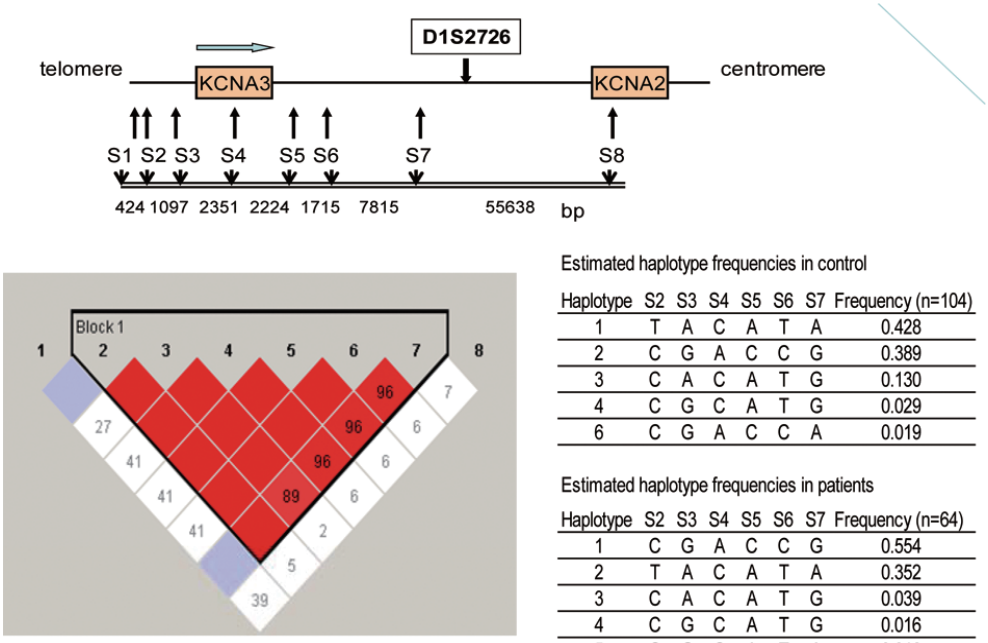
Between September 1994 and October 2004, we treated and followed 64 patients with AIP. The 53 men and 11 women were 38-79 years of age (median age, 62.4 years). Diagnostic criteria for AIP included (1) enlarged pancreas on ultrasonography, computed tomography, or magnetic resonance imaging, and irregular narrowing of the main pancreatic duct on endoscopic retrograde cholangio-pancreatography; (2) increased serum gammaglobulin levels, high serum IgG or IgG4 concentrations, or the presence of autoantibodies; and (3) characteristic histological findings of lymphoplasmacytic infiltration and fibrosis [20]. Thirtynine (61%) had concurrent autoimmune diseases, including hypothyroidism (12 patients; 22%) and sclerosing cholangitis (34 patients; 74%), whose diagnosis was described in our prior study [21]. Eight patients had a pathological diagnosis. In western countries, AIP is classified in type 1 and type 2, in which type 1 corresponds to LPSP (lymphoplasmacytic sclerosing pancreatitis; IgG4-related disease) and type 2 to IDCP or AIP with GEL(granulocyte epithelial lesion). The clinical features of type 2 AIP include the following; on average, patients are a decade or more younger in age than patients with type 1 AIP, there is no gender bias, no association with systemic involvements, no elevation of serum IgG4, no or minimal tissue infiltration of IgG4 bearing plasma cells, and there is an association with inflammatory bowel disease in almost 30% of patients. Clinical findings of Japanese AIP definitely different from type 2. All of our patients showed clinical findings of type 1 AIP or LPSP.

One hundred and four individuals (56 men and 48 women, median age, 54.5 years) for controls were enrolled in this study. The control subjects are all healthy volunteers having regular medical check-ups and they reside in Nagano prefecture.

The institutional ethics committee granted permission for this study; all patients and control subjects provided written performed consent to participate in this study.

2.2. Microsatellite genotyping

The genome scan was carried out using 400 microsatellite markers (ABI Linkage Mapping Set v.2.5 – MD10; Applied Biosystems, Foster City, CA) with an average heterozygosity of 79% and an intermarker distance of 9.4 $\pm$ 2.9 cM (mean $\pm$ SD). The entire marker set consisted of 28 panels, each containing markers pooled together according to size and fluorescent tag (6-FAM, VIC, NED). The markers were amplified by polymerase chain reaction (PCR) in 10-μl reactions each containing 40 ng of genomic DNA, according to the manufacturer's protocol. After PCR, the pooled



Estimated haplotype frequencies in control

Haplotype	S2	S3	S4	S5	S6	S7	Frequency (n=104)
1	T	A	C	A	T	A	0.428
2	C	G	A	C	C	G	0.389
3	C	A	C	A	T	G	0.130
4	C	G	C	A	T	G	0.029
6	C	G	A	C	C	A	0.019

Estimated haplotype frequencies in patients

Haplotype	S2	S3	S4	S5	S6	S7	Frequency (n=64)
1	C	G	A	C	C	G	0.554
2	T	A	C	A	T	A	0.352
3	C	A	C	A	T	G	0.039
4	C	G	C	A	T	G	0.016
5	C	G	C	A	T	A	0.016
6	C	A	C	A	T	A	0.015

Fig. 1. Structures of linkage disequilibrium (LD) and the haplotype block from rs3762379 to rs3887820 on chromosome 1p13.3. The pairwise LD (D') diagram was delineated using the solid spine method with D' $>$ 0.8 for the 104 Japanese control samples. Haplotype frequencies were estimated by the maximum-likelihood method, with an expectation-maximization algorithm. S1: rs3762379, S2: rs2821557, S3: rs2840381; S4: rs1058184, S5: rs2640480, S6: rs1319782, S7:rs2821548, S8: rs3887820.

panels were electrophoresed on an ABI 3130 DNA Analyzer. Semi-automated genotyping was performed using GeneMapper v 3.5 (Applied Biosystems). DNA samples from all patients were collected before steroid therapy.

2.3. Singlel nucleotide polymorphism genotyping

We identified one locus located on chromosome 1p13.3 (microsatellite marker D1S2726) as potentially associated with AIP. The gene encoding potassium voltage-gated channel, shaker-related subfamily, member 3 (*KCNA3*) lies 31 kb telomeric of the D1S2726 microsatellite marker and was therefore targeted as a candidate susceptibility gene.

Eight SNPs distributed around *KCNA3* were selected from the National Center for Biotechnology Information (NCBI) dbSNP database (build 36), the JSNP database, and the SNP database of Applied Biosystems (Fig. 1) based on the following criteria: (a) location within the 20-kb region around the candidate microsatellite marker; (b) greater than 10% minor allele frequency in the Japanese population; (c) 0.3 average heterozygosity; (d) marker density of at least one SNP per 8 kb; and (e) availability for validation assays. SNP genotyping was performed using TaqMan® SNP Genotyping Assays, according to manufacturer's instructions.

2.4. Statistical analysis

Frequencies of alleles in each microsatellite marker were estimated by direct counting. To estimate the statistical significance of comparisons between patients with AIP and healthy control subjects, we used the χ^2-test and Fisher's exact probability test for 2×2 contingency tables. We defined a P-value of less than 0.05 as statistically significant. The P-values were corrected by multiplying by the number of different alleles observed in each locus (Pc), and also by multiplying the 400 markers typed in the study. The pairwise relationships between microsatellites, SNPs, and haplotypes were estimated by calculating odds ratios (ORs) and 95% confidence intervals (CIs). The Hardy-Weinberg proportion (HWP) for multiple alleles was calculated by the Markov chain method within the GENEPOP software package (http://wbiomed.curtin.edu.au/genepop/index.html). The linkage disequilibri-

Table 1
Statistically significant STR markers by association for AIP

Chromosome	locus	allele	patient (%) $n = 64$	control (%) $n = 104$	OR	95%CI	c2	P	Pc	Pc*
1	D1S2726	280	27 (42.2)	9 (8.7)	7.70	3.31–17.92	24.507	0.00000074	0.0000037	0.00030
		292	6 (9.4)	27 (26.0)	0.30	0.11–0.76	5.895	0.015	0.076	
	D1S0655i	266	47 (73.4)	47 (45.2)	3.35	1.71–6.59	12.825	0.00034	0.0014	
5	D5S410	331	38 (59.4)	32 (30.8)	3.29	1.72–6.30	13.340	0.00026	0.0067	
6	D6S460	289	23 (35.9)	17 (16.3)	2.87	1.39–5.95	8.383	0.0038	0.0010	
10	D10S548	188	60 (93.8)	69 (66.3)	7.61	2.56–22.65	16.691	0.000097	0.00039	0.039
15	D15S128	203	37 (57.8)	33 (31.7)	2.95	1.55–5.62	11.089	0.00087	0.0070	
20	D20S186	127	35 (54.7)	32 (30.8)	2.72	1.43–5.17	9.450	0.0021	0.021	

Pc was calculated by multiplying the numbers of alleles in the locus.
Pc* was calculated by multiplying the 400 markers typed in the study.

um (LD) patterns, haplotype block structure, and haplotype frequency analysis for SNPs were identified using the block definition of Gabriel et al. [22] and were based on the 95% CI of pairwise LD (D'), as determined with Haploview software [23].

3. Results

Genome-wide linkage association analysis using 400 microsatellite markers identified seven markers as new candidate loci for AIP (Table 1). Strong evidence of positive association was detected for the marker D1S2726 (42.2% vs. 8.7%, $Pc = 0.0000037$) on chromosome (chr) 1p13.1, D5S410 (59.4% vs. 30.8%, $Pc = 0.0067$) on chr 5q31-33, D6S460 (35.9% vs. 16.3%, $Pc = 0.0010$) on chr 6q14, D10S548 (93.8% vs. 66.3%, $Pc = 0.00039$) on chr 10p12, D15S128 (57.8% vs. 31.7%, $Pc = 0.007$) on chr 15q15, and D20S186 (54.7% vs. 30.8%, $Pc = 0.021$) on chr 20p12.2. The observed and expected frequencies of each genotype for the seven markers in both case and control subjects were within Hardy-Weinberg equilibrium (HWE; data not shown).

D1S2726 was identified as a marker of interest for further analysis. To further validate the association of the D1S2726 marker with AIP, we examined the association of AIP with an additional marker located 30.7 kb centromeric of D1S2726, D1S0655i. Allele 266 of D1S0655i was also indicated a positive association with AIP (73.4% vs. 45.2% OR = 3.35, $Pc = 0.0014$, Table 1).

To predict novel susceptibility genes within 100-kb of significant markers, we used the NCBI Map Viewer (http://www.ncbi.nlm.nih.gov/mapview/; Table 2). Two genes, *KCNA3 and KCNA2,* were identified within the candidate region around D1S2726. We characterized *KCNA3* as a candidate gene by performing an association analysis using seven SNPs (Fig. 1). Four SNPs (rs2840381: allele G, rs1058184: allele A, rs2640480: allele C, rs1319782: allele C) showed statistically significant association (Table 2). All SNPs were screened in all AIP cases and control subjects. The frequencies of the SNPs for both patients and controls were within HWE. Pairwise LD mapping confirmed that the haplotype structure including*KCNA3* was divided into three blocks (rs3762379, major block; rs2821557 to rs2821548, and rs3887820, Fig. 1). The CGACCG haplotype of the major block was significantly more prevalent in the patient group than in the control group ($P = 0.04$, OR = 1.93).

4. Discussion

Despite recent progress in its clinical, immunological, radiological, and morphological characterization [24], the etiology of AIP still remains unclear. Genetic factors including the HLA DRB1*0405-DQB1*0401 haplotype [17] and polymorphisms of the *FCRL3* and *CTLA4* genes [18,19] have been implicated in the etiology of AIP. However these risk factors are identified during analyses performed in a limited region of the genome. A more comprehensive understanding of how the genetic background influences the outcome of AIP requires genome-wide association analyses [25].

This is the first case-control genome-wide association study aimed at identifying candidate genes for AIP pathogenesis, even though the number of enrolled subjects was too small to overcome type I error. Four hundred microsatellite markers were used for this study, providing 10.8-cM genome-wide resolution. This approach is not as efficient as using tens of thousands of microsatellite markers at 100 kb intervals across the human genome [26]; therefore, there are likely to be many undetected genes involved in susceptibility to

Table 2

Association of 8 SNPs around KCNA3 gene with AIP

SNP rs	Observed Allele (1/2)	Frequency		Genotype distribution						P value (1/2)	OR 95% CI (1/2)	P value (11/12+22)	P value (11+12/22)	HWE	
		Allele 1		Allele 1/1		Allele 1/2		Allele 2/2							
		Patients	Controls	Patients	Controls	Patients	Controls	Patients	Controls					Patients	Controls
rs3762379	C/T	0.922	0.856	55	75	8	28	1	1	0.0692	1.99 (0.94–4.22)	0.038	0.727	0.290	0.355
rs2821557	C/T	0.648	0.567	27	39	29	40	8	25	0.1407	1.14 (0.89–2.22)	0.546	0.068	0.961	0.027
rs2840381	G/A	0.594	0.438	22	24	32	43	10	37	0.0054	1.88 (1.20–2.94)	0.111	0.005	0.771	0.103
rs1058184	A/C	0.563	0.409	21	22	30	41	13	41	0.0061	1.86 (1.19–2.90)	0.093	0.010	0.703	0.060
rs2640480	C/A	0.563	0.409	21	22	30	41	13	41	0.0061	1.86 (1.19–2.90)	0.093	0.010	0.703	0.060
rs1319782	C/T	0.563	0.409	21	22	30	41	13	41	0.0061	1.86 (1.19–2.90)	0.093	0.010	0.703	0.060
rs2821548	G/A	0.609	0.553	24	37	30	41	10	26	0.3091	1.26 (0.81–1.97)	0.801	0.150	0.902	0.039
rs3887820	C/A	0.586	0.457	25	22	25	51	14	31	0.0214	1.68 (1.08–2.63)	0.012	0.260	0.119	0.904

SNPrs: public reference SNP number from the dbSNP database.
95% CI: 95% confidence interval; OR: odds ratio.
P value was calculated by c2 test 2×2 contingency table.
HWE: Hardy-Weinberg Equilibrium.

Table 3
Estimated haplotype frequencies from 3 SNPs in four different populations

SNP	rs1058184	rs2640480	rs1319782	Frequency
Pop				
CEU	C	A	T	0.70
	A	C	C	0.30
CHB	C	A	T	0.56
	A	C	C	0.44
YRI	C	A	T	0.65
	A	C	C	0.34
	C	A	C	0.01
JPA (Cont)	C	A	T	0.59
	A	C	C	0.41
JPA(AIP)	C	A	T	0.44
	A	C	C	0.56

Haplotye frequencies in CEU, CHB, and YRI populations were calculated by HapMap database data.
CEU: Utah residents with ancestry from northern and western Europe.
CHB: Han Chinese in Beijine, China.
YRI: Yoruba in Ibadan, Nigeria.
JAP (Cont): Control group in this study, Japanese.
JAP (AIP): Patients group in this study, Japanese.

AIP. Nonetheless, this approach identified seven statistically significant makers (Table 1). In the regions surrounding these markers, we noted interesting genes that might be linked to AIP susceptibility, including *KCNA3*.

KCNA3 is located 30 kb telomeric of D1S2726 and encodes the voltage-gated potassium channel Kv1.3 [27]. Kv1.3 regulates membrane potential and Ca^{2+}-signaling in human T cells and plays an essential role in T-cell proliferation and activation [28–30]. This molecule is expressed in a variety of tissues and hematopoietic cells, particularly in effector memory T cells (T_{EM}). Terminally differentiated T_{EM} cells enter inflamed tissues rapidly and produce copious amount of IFN-γgnd IL-4 [31]. Therefore, suppressing the function of these cells by selectively blocking the Kv1.3 channel offers a potential therapeutic strategy for T cell-mediated autoimmune diseases [32]. Interestingly, Kv1.3 blockers preferentially suppress the proliferation of late memory B cells (CD27+IgG+IgD-) [33], which play an important role in production of IgG antibodies. Consequently, Kv1.3 serves a critical function in modulating immune responses. Thus, the high level production of IgG4 in patients with AIP could be caused by the proliferation of late memory B cells and the elevated expression of Kv1.3 molecules.

Association analysis using eight SNPs in the region of *KCNA3* identified four SNPs (rs2840381, rs1058184, rs2640480, rs1319782) significantly associated with susceptibility to AIP ($P < 0.007$). SNPs in the promoter region of the Kv1.3 gene were examined whether they were associated with impaired glucose tolerance and reduced insulin sensitivity in patients with diabetes mellitus [34]. One of these, rs2821557 (T-1645C) was shown to exhibit differential transcription activity. However, rs2821557 SNP in our analysis was not associated with disease susceptibility to AIP. The haplotype (GACC) frequency of these four SNPs involved in the one haplotype block (rs2821557 to rs2821548: CGACCG) was significantly higher in the patient group than in the control group ($P = 0.014$, OR $= 2.45$). This haplotype locates at 6.29 kb upstream of the promoter/5'-untranslated region (UTR) to downstream of the 3'-UTR in *KCNA3* and includes the full length of the *KCNA3* coding region. This result highlights the need to investigate haplotype frequencies in different populations. When comparing the distribution of haplotype frequencies constructed by three of these SNPs (rs1058184, rs2640480, rs1319782) using HapMap data (http://www/hapmap.org/) in three different populations (northern and western Europe, Han Chinese, Yoruba in Ibadan, Nigeria) and in our control group, the CAT haplotype was the most frequent (Table 3). These results provide further support that *KCNA3* is a general susceptibility gene for AIP.

Currently, we are searching for candidate susceptibility genes by performing high-resolution microsatellite analysis around the positive markers identified in this study. Future studies also need to focus in the identification of therapy-effectiveness- or disease-severity-related genes. These types of studies could aid in the identification and development of specific therapies for patients with AIP.

Acknowledgements

This work was supported in part by Grants-in-aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan (15659167 and 16390205), a grant from the Japan Health Sciences Foundation (KH21022), a Research of Specific Diseases, Health, and Labor Sciences Research Grant, and the Pancreas Research Foundation of Japan.

Competing interests

The authors declare that they have no competing interests.

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