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ORIGINAL ARTICLE

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SAA1 gene polymorphisms and the risk of AA amyloidosis in Japanese patients with rheumatoid arthritis

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Abstract To investigate the precise modality of association between *SAA1* gene polymorphisms and the development of AA amyloidosis in patients with rheumatoid arthritis (RA), Japanese patients with RA ($n = 153$), among whom 29 were histologically diagnosed as having amyloidosis, were genotyped for three single nucleotide polymorphisms (SNPs), *C-13T*, *C2995T*, and *C3010T*, in the *SAA* gene. Pairwise linkage disequilibrium coefficients between each pair of SNPs were calculated and estimated haplotype frequencies were compared between patients with and without amyloidosis. Possible associations between these SNPs and amyloidosis were analyzed by a case–control study and by the Kaplan–Meier method, in which the endpoint was defined as the time of diagnosis of AA amyloidosis. The *-13T* and *2995C* alleles, which were in a tight linkage disequilibrium, were more frequent in the patients with amyloidosis, and the groups with the *-13TT* and *2995CC* genotype had worse survival curves than patients without these genotypes, whereas *C3010T* was not associated with amyloidosis. Moreover, the haplotype containing *–13C* and *2995T* was found to be protective. Both *C-13T* and *C2995T* were associated with the development of amyloidosis. Examining both polymorphisms may be more useful than examining only one of them for estimating the risk of the development of amyloidosis.

Key words Amyloidosis · Genetic polymorphism · Rheumatoid arthritis (RA) · SAA1 · Single nucleotide polymorphism (SNP)

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Introduction

AA amyloidosis is a major complication of chronic inflammatory diseases, such as rheumatoid arthritis (RA), which is responsible for about 60% of the cases of this severe complication.[1] Although this complication is generally associated with severe, longstanding, and sustained inflammation, the incidence of AA amyloidosis varies among different ethnic groups. In Japan, AA amyloid deposition has been reported to be found in the gastric mucosa in 13.3% of RA patients by endoscopic biopsy[1] and in more than 20% of RA patients in autopsy series,[2] whereas among Caucasians in the United States, RA patients with AA amyloidosis are estimated to comprise less than 3% of RA patients.[3] The difference in the frequency of AA amyloidosis among different races, and the fact that AA amyloidosis is not consistently related to the length and severity of chronic inflammation suggests that AA amyloidosis may be, at least in part, influenced by genetic factors.

AA amyloid deposits are largely made of polypeptides, which constitute about the amino terminal three-fourths of the serum amyloid A (SAA) protein. Among the human SAA family, SAA1 and SAA2 are well known as acute phase proteins, which are synthesized by the hepatocytes in response to inflammatory cytokines, such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF), and transported into the serum by the high-density lipoprotein (HDL) particles.[4–6] The vast majority of the human AA proteins isolated from amyloid deposits are derived from SAA1.[7] Although the relationship between the production of fibril precursor protein, the turnover of amyloid, and amyloidotic organ function is complex, it has been proved that outcome is favorable in AA amyloidosis when the SAA concentration is maintained below 10 mg/l.[8]

There is an increasing body of evidence showing that polymorphisms in *SAA1* gene participate in the development of AA amyloidosis. The presence of two single-nucleotide polymorphisms (SNPs), *C2995T* and *C3010T*, within exon 3 of the *SAA1* gene define three haplotypes that correspond to the *SAA1.1 (2995T-3010C)*, *SAA1.2*

(2995C-3010T), and *SAA1.3 (2995C-3010C)* alleles.[9–11] As indicated in Fig. 1, both SNPs are accompanied by amino acid substitutions. In Japanese RA patients, *SAA1.3* has been reported to be associated with increased risk of AA amyloidosis and *SAA1.1* with decreased risk,[12,13] while *SAA1.1* was shown to be a risk factor for developing AA amyloidosis in a Caucasian population.[14] An adequate explanation of this discrepancy has not been provided.

A more recent report evaluated another single nucleotide polymorphism (SNP) in *SAA1*, *T-13C*, and in that study the allele of *SAA–13T* was shown to be a risk factor for AA amyloidosis in both Japanese and Caucasian populations.[15] However, little information has been available regarding the linkage disequilibrium between these polymorphisms of *SAA1*, and their impacts on the onset of AA amyloidosis have not been fully investigated. In addition, previous reports of association analysis between *SAA1* polymorphism and the prevalence of AA amyloidosis in RA patients have been largely reports of case control studies, which did not take chronological factors into account in the analysis.

In this study, we examined the three SNPs described above, a SNP upstream of exon 1 and two SNPs of exon 3, regarding their impact on the onset of AA amyloidosis using a case–control and time–to-event analysis. Furthermore, we evaluated the linkage disequilibrium between each pair of polymorphisms in Japanese patients with RA.

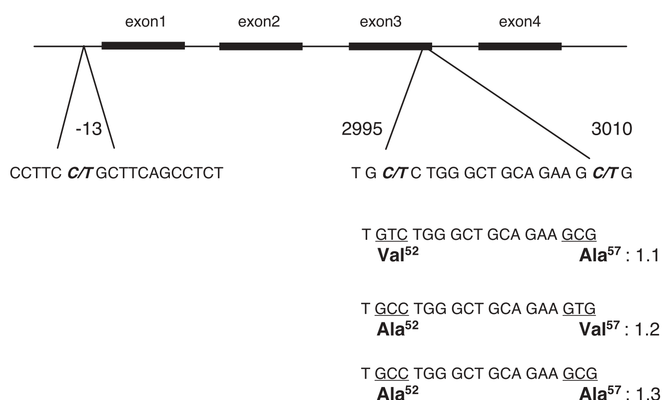

Fig. 1. Partial genomic structure and location of single nucleotide polymorphisms (SNPs) in the *SAA1* gene

Patients and methods

Study subjects

The ethics committee of the Niigata University Graduate School of Medical and Dental Sciences approved the protocol for the genetic study. Written informed consent was obtained from all DNA donors. The study included 153 Japanese patients with RA. All patients fulfilled the 1987 revised criteria for the classification of RA by the American College of Rheumatology.[16] In each patient, vigorous efforts were made to suppress the inflammatory activity as completely as possible: corticosteroids and/or other disease-modifying drugs were given at the discretion of each patient's physician based on the standard protocol.

Among 153 patients, 29 were diagnosed as having AA amyloidosis (Table 1). All patients with AA amyloidosis were identified by examining biopsy specimens, including gastro-duodenal ($n = 24$), rectal ($n = 1$) endoscopic biopsy, renal biopsy ($n = 3$), and abdominal fat biopsy ($n = 1$) specimens, and the sections were subjected to Congo red and immunohistochemical staining. In most cases, a work-up for amyloidosis was conducted because of renal injury manifested by either proteinuria, elevation of serum creatinine, or hematuria. Gastrointestinal symptoms such as diarrhea lasting more than 7 days that failed to respond to standard therapy were another reason to investigate for amyloidosis in some other cases. The mean age of the patients with AA amyloidosis was 65.5 years and their duration of RA ranged from 9.0 to 43.2 years with a mean of 20.4 years. The patients without amyloidosis ($n = 124$, 24 male), had a mean age of 61.8 years and their duration of RA ranged from 1.8 to 59.6 years with a mean of 12.3 years, and did not have any clinical symptoms associated with amyloidosis, such as refractory diarrhea, proteinuria, renal dysfunction, or nephrotic syndrome.

Determination of SAA genotypes

Genomic DNA from the peripheral blood cells was isolated with an automatic DNA isolation system (NA-1000; Kurabo, Osaka, Japan). The genotype of the *SAA1 C-13T* in the 5′-region of exon 1 was determined by the polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) method. The primers used for the PCR reaction were 5′-ACA TCT TGT TCC CTC AGG TTG-3′ (sense) and 5′-GCT GTA GCT GAG CTG CGG-3′

Table 1. Patients analyzed in this study

	With amyloidosis	Without amyloidosis
No. of patients (male)	29 (1)	124 (24)
Age (years)	65.5 ± 9.5	61.8 ± 13.8
Age at diagnosis of RA (years)	45.1 ± 9.8	47.2 ± 14.7
Duration of RA (years)	20.4 (9.0–43.2)	12.3 (1.8–59.6)

Values are mean ± SD. or mean (range)
RA, rheumatoid arthritis

(antisense). The reaction mixture contained 1× PCR buffer, 1.5 mmol/l $MgCl_2$, 200 mmol/l deoxynucleoside triphosphates (dNTPs), 1 unit *Taq* DNA polymerase (Takara, Kyoto, Japan), 10 pmol of each primer, and 50–100 ng genomic DNA. The PCR amplification reaction consisted of an incubation at 95°C for 5 min, followed by 35 cycles of denaturation at 95°C for 45 s, annealing at 60°C for 60 s, and extension at 72°C for 60 s. A final extension was performed at 72°C for 7 min. The 229-bp PCR products were digested with restriction endonuclease *Aci*I (BioLabs, Beverly, MA, USA) and electrophoresed on a 12.5% polyacrylamide gel (GeneGel Excel 12.5/24 Kit, Amersham Biosciences, Tokyo, Japan).

The *SAA1.1*, *1.2*, and *1.3* alleles, corresponding to the *T-C*, *C-T*, and *C-C* haplotypes of the *C2995T* and *C3010T* polymorphisms, respectively (Fig. 1), were also determined by the PCR-RFLP. The primers used for the PCR reaction were 5′-GCC AAT TAC ATC GGC CTC AG-3′ (sense) and 5′-TGG CCA AAG AAT CTC TGG AT-3′ (antisense). The PCR amplification reaction consisted of an initial incubation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 60 s, annealing at 62°C for 60 s, and extension at 72°C for 60 s. A final extension was performed at 72°C for 7 min. The 518-bp PCR products were digested with restriction endonucleases *Bcl*I (Promega, San Luis Obispo, CA, USA) and *Ban*I (Promega) and electrophoresed on a 2.5% agarose gel. The genotypes of both the *C2995T* and *C3010T* polymorphisms were determined for all individuals according to previously reported procedures.[13]

Statistical analysis

We used Fisher's exact test and the χ^2 test to compare allele frequencies and categorical variables between the groups. The Kaplan–Meier method with the log rank test was used to compare the duration from the diagnosis of RA to the occurrence of AA amyloidosis between the groups with and without a given gene allele or genotype. When overall survival was significantly different in the Kaplan–Meier method, Greenwood's estimation was performed at every 12 months of observation to test at what time point the difference between groups became significant. Values of $P < 0.05$ were considered significant. Haplotype analysis, which was based on the maximum likelihood method, was performed with SNPAlyze™ software (Version 3.1; Dynacom, Shigehara, Japan). Pairwise linkage disequilibrium coefficients were calculated and expressed as $D' = D/D_{max}$ or D/D_{min}, according to Thompson et al.[17]

Results

Genotype, allele, estimated haplotype frequency of *SAA1* gene polymorphisms

Table 2 lists the genotype distributions and allele frequencies of the *SAA1 C-13T*, *C2995T*, and *C3010T* polymorphisms in RA patients with and without AA amyloidosis. The expected frequency of the genotypes, under the assumption of the Hardy–Weinberg equilibrium, did not

Table 2. Genotype distributions and allele frequencies of 3 SNPs of *SAA1* in patients with and without AA amyloidosis

	RA patients		χ^2	*P* value
	With amyloidosis ($n = 29$)	Without amyloidosis ($n = 124$)		
Locus –13				
Genotype				
CC	0.172	0.290		
CT	0.448	0.532		
TT	0.379	0.177	6.100	0.047
Allele				
C	0.411	0.558		
T	0.589	0.442	4.910	0.029
Locus 2995				
Genotype				
CC	0.793	0.500		
CT	0.207	0.411		
TT	0.000	0.089	8.408	0.015
Allele				
C	0.893	0.702		
T	0.107	0.298	8.571	0.003
Locus 3010				
Genotype				
CC	0.380	0.452		
CT	0.448	0.452		
TT	0.172	0.089	2.556	0.279
Allele				
C	0.589	0.689		
T	0.411	0.311	2.042	0.153

Table 3. Estimated frequencies of haplotypes of polymorphisms in *SAA1*

Locus −13	2995	3010	Haplotype	With amyloidosis	Without amyloidosis	χ^2	*P* value
C	C	C	C-3	0.020	0.023		
T	C	C	T-3	0.462	0.370		
C	T	C	C-1	0.107	0.280	7.761	0.005
T	T	C	T-1	0.000	0.019		
C	C	T	C-2	0.284	0.261		
T	C	T	T-2	0.127	0.047		

differ from the observed genotype frequencies (data not shown). These genotype and allele frequencies were compatible with data previously reported in Japanese RA patients.[18] Table 3 shows the estimated haplotype frequencies. The three most frequent haplotypes, *T-C-C*, *C-T-C*, and *C-C-T* accounted for 89.8 % of the total. The linkage between *C2995T* and *C3010T* was complete (D' = 1.0000, P < 0.0001), whereas *C-13T* was in tight, but incomplete, linkage disequilibrium with *C2995T* (D' = 0.8850, P < 0.0001), and with *C3010T* (D' = 0.5944, P < 0.0001).

Table 4. Odds ratios and 95% confidence intervals of genotypes and haplotypes significantly associated with the development AA-amyloidosis

Genotypes or haplotypes	OR	95% CI	χ^2	*P* value
−13TT	2.83	1.17, 6.83	5.90	0.029
2995CC	3.00	1.51, 10.39	9.19	0.003
T-3+T-2	2.01	1.13, 3.60	5.55	0.018
C-1	0.29	0.12, 0.73	7.76	0.005

OR, odds ratio; CI, confidence interval

Association between SAA1 polymorphisms and AA amyloidosis

As shown in Table 2, the frequency of the *TT* genotype of the *C-13T* polymorphism was significantly higher in the patients with AA amyloidosis than in those without amyloidosis (χ^2 = 6.100, P = 0.047), and the *-13T* allele was associated with the development of AA amyloidosis (χ^2 = 4.910, P = 0.029). The odds ratio (OR) for the patients with the *-13TT* genotype was 2.83 (95% confidence interval (CI), 1.17–6.83; χ^2 = 5.90, P = 0.029). Similarly, the frequencies of the CC genotype and the C allele of *C2995T* were significantly higher in patients with AA amyloidosis (χ^2 = 8.408, P = 0.015 and χ^2 = 8.571, P = 0.003, respectively). There were no cases of the *SAA 2995TT* genotype in patients with AA amyloidosis. The OR for the CC genotype of *C2995T* was 3.00 (95%CI, 1.51–10.39; χ^2 = 9.19, P = 0.003). In contrast, no significant difference was observed in the genotype and allele frequencies of *C3010T* between patients with and without AA amyloidosis. In terms of haplotypes, the estimated frequencies of haplotypes of these SNPs were significantly different between the two groups. The frequency of haplotype T-3 plus T-2, which involved *-13T* and *2995C*, was higher in patients with amyloidosis (0.59 vs. 0.42, χ^2 = 5.55, P = 0.018, OR = 2.01, 95% CI, 1.13–3.60). On the other hand, among the three major haplotypes, *C-T-C* (C-1) was found to be protective against the development of amyloidosis (χ^2 = 7.76, P = 0.005, OR = 0.29, 95%CI, 0.12–0.73). The ORs and 95%CIs of genotypes and haplotypes, which significantly associated with the development of AA-amyloidosis, are summarized in Table 4.

Survival analysis

Because it was not possible to assign the haplotype of the three SNPs for each individual, the survival analysis was performed according to the genotypes of each SNP. Fig. 2A and B show the survival curves of patients with each SAA1 genotype, in which the end point was defined as the time of diagnosis of AA amyloidosis and analyzed by the Kaplan–Meier method. The survival rates without amyloidosis in patients without the *-13TT* genotype and those without the *2995CC* genotype were significantly better than those of other genotypes (Kaplan–Meier, log rank test χ^2 = 4.496 and 5.293, P = 0.0340 and 0.0214, respectively). However, no significant effect of the *C3010T* polymorphism was detected.

In Greenwood's estimation, the difference in survival rate between patients with and without the *2995CC* genotype became significant after 180 months of observation, whereas no significant effect of the *C-13T* polymorphism was detected during the observation period. The survival rates of patients with and without the *2995CC* genotype at 180 months were 0.796 ± 0.081 and 0.561 ± 0.083, respectively (P = 0.043) by Greenwood's estimation.

Discussion

The serum concentration of SAA closely reflects the activity of chronic inflammation, and a persistently high concentration is a prerequisite for the development of AA amyloidosis.[8,19] The biological function of SAA is not fully understood, although a number of biological activities of SAA have been described.[20–22] Although genetic predisposition to AA amyloidosis in patients with chronic inflammatory diseases has already been reported, the precise modality of the role of genetic polymorphisms in *SAA1* remains controversial. In the present study, we investigated possible associations between three SNPs, *C-13T*, *C2995T*, and *C3010T*, in the *SAA1* gene and AA amyloidosis in

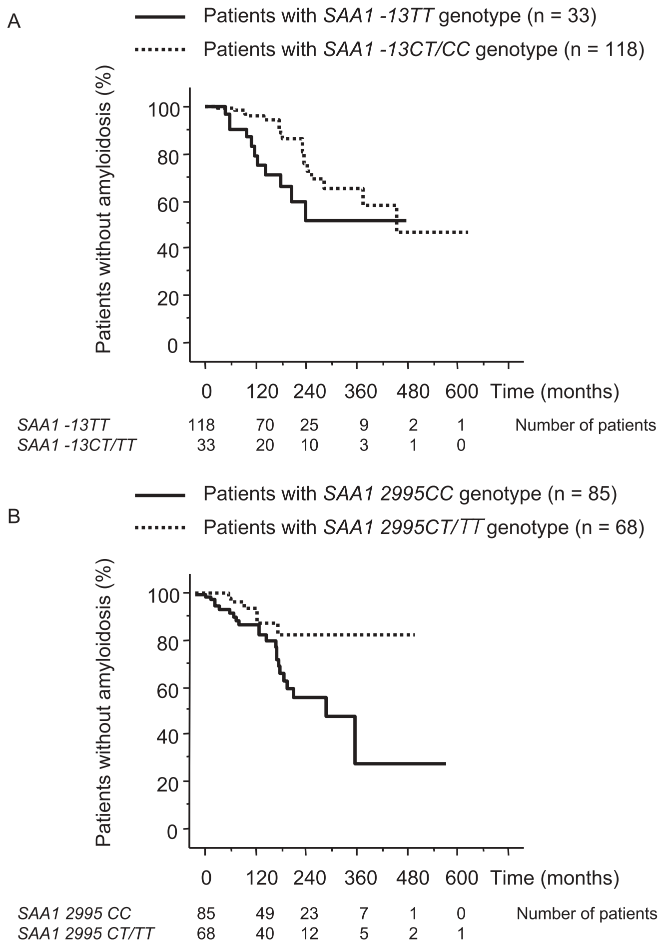

Fig. 2. Survival rates of RA patients with and without *-13TT* (**A**) or *2995CC* (**B**) genotype of *SAA1* polymorphism. **A** The survival of patients with the *-13TT* genotype (solid line; $n = 33$) was significantly worse than that of those with other genotypes (dotted line; $n = 118$; Kaplan–Meier, log rank test, $\chi^2 = 4.496$, $P = 0.0340$). **B** The survival of patients with the *2995CC* genotype (solid line; $n = 85$) was significantly worse that of those with other genotypes (dotted line; $n = 68$; Kaplan–Meier, log rank test, $\chi^2 = 5.293$, $P = 0.0214$). The numbers of available observations per genotype are indicated. The primary endpoint was defined as the time of the diagnosis of amyloidosis

Japanese patients with RA by using a case-control study and the Kaplan–Meier method. In addition, we analyzed pairwise linkage disequilibrium coefficients among these SNPs by the maximum likelihood method. The results were in good agreement with previous studies in Japanese patients. In our patients, both the *SAA1 -13T* and *2995C* alleles, which are parts of the *SAA1*.3 allele, were significantly associated with amyloidosis, whereas the *C3010T* allele was not. According to the haplotype analysis, the two SNPs, C*-13T* and *C2995T*, were in tight linkage disequilibrium and *-13T* and *2995C* were components of two major haplotypes, T-3 and T-2, which showed higher prevalence in patients with amyloidosis than in those without. Moreover, the opposite haplotype, *–13C* and *2995T*, was significantly more frequent in patients without amyloidosis. Recently, the association between *SAA1 -13T* and amyloidosis in Japanese RA patients has been suggested to be the result of an increased transcriptional activity of the gene.[23] Therefore, our data strongly support the notion that the previously reported associations between the *SAA1.3* allele and amyloidosis may be accounted for by a strong linkage between *-13T* and *2995C* in the *SAA1* gene in Japanese[23,24] Our data also indicate that examining both of the polymorphisms may be more useful than examining just one of them for estimating the risk of the development of amyloidosis.

However, because pairwise linkage disequilibrium between polymorphic loci in this gene and the magnitude of the association between these markers and SAA levels have been reported to vary depending on ethnicity, it remains to be seen if the effect of the genetic variant investigated in this study is observed in other ethnic groups to confirm the results of the present study.

The high SD values of the duration of RA and the wide range of observation times indicate that substantial numbers of patients in this study were censored from being followed-up, mainly due to the varying times of enrollment. Moreover, the longer duration of RA in the group with amyloidosis explicitly indicates that a temporal factor should be included in the statistical analysis. Therefore, we used Kaplan–Meier analysis to compare the time course of RA patients with each genotype, because censored observations cannot be used in multiple logistic regression analysis.[25]

In the present study, the significant association of both *C-13T* and *C2995T* polymorphisms with the development of AA amyloidosis was detected both in the case-control study and log rank test in Kaplan–Meier method, whereas only *2995CC* genotype was found to be significant after 180 months in the Greenwood estimation. We could not provide a plausible explanation for this inconsistency. However, there is a possibility that the impact of the two polymorphisms may vary according to the different stages of the disease. Further larger-scale and longer-term study is needed to solve this issue.

A major drawback of this study was that the clinical factors, such as serum levels of inflammatory proteins and methods of therapy, were not included in the analysis. Because the patients were analyzed retrospectively, the modality of treatment was not selected according to the genotype, and the pretreatment levels of SAA and CRP were not available in this study. Moreover, the histological diagnosis of amyloidosis was made at different stages depending on the nature and timing of the symptoms. To confirm the results of the present study, a randomized controlled prospective study with a large-scale population of patients using a fixed medication protocol is necessary. However, drawing conclusions about the long-term outcome of RA in a prospective study is difficult, because the actual prognosis in each case can only be determined after a sufficiently long observation period.

Intriguingly, it was reported recently that SAA was an independent and significant predictor of coronary artery disease and cardiovascular outcome in Caucasian women without RA.[26] This suggests that, in addition to being a marker for high risk of AA amyloidosis, *SAA1* polymorphism may also be useful as a risk factor for cardiovascular

diseases even in a population without chronic inflammatory diseases. Further studies need to be performed to determine the impact of *SAA1* polymorphisms on other inflammatory and non-inflammatory diseases in Japanese.

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