T-Cell Receptor Beta-Chain Gene Polymorphism and the Prognosis of IgA Nephropathy in Japanese Patients

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Dear Sir,

IgA nephropathy (IgAN), which is characterized by predominant IgA deposition in the glomerular mesangial area, is now recognized as the most common form of chronic glomerulonephritis worldwide [1]. The course of IgAN was first considered to be benign, but it has now become apparent that approximately 20-30% of these patients gradually lose their renal function and eventually progress to renal failure over a period of 20 years. At present, no therapy exists to halt this progression.

Several clinical factors predict a poor prognosis for patients with IgAN. These factors are advanced age at the onset of disease, heavy proteinuria, hypertension, and severe histological renal damage [2]. However, not all patients with more than one such factor progress to end-stage renal failure, and, conversely, some without any of these factors undergo renal failure. Although the exact mechanism(s) governing the fate of renal function in IgAN is unclear, genetic factors are presumed to participate in its initiation and progression [3,4].

Clinically, a high level of serum IgA is the prominent immunological abnormality in patients with IgAN, in association with autoantibodies, hyperactivity of helper T cells, high serum levels of T-cell-derived cytokines, etc. [5]. Such associated features are commonly observed in patients with systemic lupus erythematosus. Because the T cell receptor beta chain constant region (TCRC- β) gene has been linked with autoantibody production in patients with systemic lupus erythematosus [6], we analyzed the restriction fragment length polymorphism (RFLP) of the TCRC- β locus to seek the probable genetic contribution of T cells to IgAN.

Thirty-four Japanese patients with biopsy-proven IgAN were investigated. High-molecular-weight DNA was extracted from their peripheral blood leukocytes and digested with the restriction enzyme BglIII. After gel electrophoresis, DNA was hybridized to a cDNA probe from the constant region of the TCRC- β locus. The results of RFLP analysis identified three allelic fragment lengths (type A: 10.0/10.0/0.8 kb; type B: 10.0/9.2/ 0.8 kb; type C: 9.2/9.2/0.8 kb). Four patients belonged to type A (12%), 16 to type B (47%), and 14 belonged to type C, (41%).

The chi-square test showed that the genotype frequency of TCRC- β RFLP was not significantly different between healthy (type A: 11%, type B: 50%, and type C: 39%) [7] and IgAN patients. Next, we compared these patients' renal function as assessed by creatinine clearance (Ccr) at the final observation. Fifty percent of type A and 25% of type B patients exhibited a Ccr < 65 ml/min. On the other hand, all type C patients showed a Ccr > 65 ml/min. Therefore, it seemed that in type A and B patients renal function could deteriorate. Indeed, as table 1 shows, when testing begun, the difference in Ccr between type A and B and type C patients was not significant (Mann-Whitney test). Subse-

quently, at the final observation, only the type C patients remained stable in Ccr (initial 88.0, final 92.6 ml/min; paired Student t test: not significant). Comparatively, the type A and B group had a significant decrease (the mean Ccr dropped from initial 83.7 to final 72.2 ml/min; paired Student t test: $p < 0.002$). In addition, the mean Ccr in type A and B patients at the final observation was significantly lower than in type C patients ($p < 0.05$). No differences were apparent during the follow-up period between two groups (table 1). Therefore, the type A and B patients with the 10.0-kb allele seemed to sustain a decrease in renal function, whereas type C patients with the 9.2/9.2-kb allele preserved their function in terms of Ccr.

Next, we compared four other clinical factors of the two patient groups (table 1): (1) the age at onset of disease did not differ statistically among the groups; (2) the maximum proteinuria during the test varied significantly; (3) the chi-square test revealed that the number of patients who exhibited hypertension during the follow-up period was not significant between two groups, and (4) the renal damage was more severe in type A and B than in type C patients according to histological analysis. Thus, some of these clinical factors contradicted the results of RFLP analysis, but proteinuria and histological examination did not.

The reason why the TCRC- β RFLP correlated with the progression of IgAN is un-

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Table 1. Comparison of clinical data for IgAN according to RFLP type (mean $\pm$ SD)

clear. Of several possible explanations, one is that the specific variable region may undergo rearrangement to some constant region. The resulting change in T cell receptors could evoke immunological abnormalities that lead to the progression of IgAN. Alternatively, one or more genes closely linked to the constant region may affect the progression of IgAN.

Because the number of patients in this study is relatively small and most of them live within 20 km of our hospital, we might have observed a skewed population. Therefore, we are currently broadening this study by investigating whether RFLP analysis of the TCRC- β correlates with the outcome of IgAN in patients elsewhere in Japan and also abroad.

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