Uteroglobin gene polymorphisms affect the progression of immunoglobulin A nephropathy by modulating the level of uteroglobin expression

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Uteroglobin (UG) is an anti-inflammatory/immunomodulatory protein. Targeted disruption of UG rendered mouse glomerulonephritis resembling immunoglobulin (Ig)A nephropathy (IgAN). Sequence analysis on exon 1 of UG showed several putative binding sites for transcription factors, and polymorphisms in this site might influence the expression level of UG as a competitive protein. We speculated that the single nucleotide polymorphism at the 38th nucleotide (A to G) from the transcription initiation site of UG exon 1 would impact the progression of IgA nephropathy (IgAN). Polymerase chain reaction-restriction fragment length polymorphism and single-strand confirmation polymorphism were instituted to determine the genetic polymorphism. Luciferase assay was performed using the gene constructs containing a region 404-bp long located upstream of UG exon 1 initiation site to analyse whether this polymorphism would affect the expression level. UG polymorphism was distributed no differently in patients with IgAN (n=111) compared to 60 healthy controls. An excess of A genotype was found in one patient having progressive disease (p=0.03) and the risk for the disease progression increased as the number of A alleles increased (p for trend = 0.03) after follow-up for 116 months. The odds ratio for progression with the AA genotype was 4.9 (95% CI = 1.0–23.9) compared to patients having the GG genotype. Significant interactive effects of hypertension and genetic polymorphisms of UG on the disease progression were observed (p for interaction = 0.001). In the luciferase assay, the gene construct with A at 38th site showed a decreased activity of 74±8.4% compared to that showed by G gene construct. Our results suggest that polymorphism at the 5’ UTR region of UG exon 1 is an important marker for the progression of IgAN and may modulate the level of protein expression.

Keywords: IgA nephropathy, uteroglobin, polymorphism, progression of renal disease

Introduction

Immunoglobulin (Ig)A nephropathy (IgAN), the most common glomerulonephritis, is an important cause of end-stage renal disease (D’Amico et al., 1986; Hsu et al., 2000). Although the factors responsible for the progression of renal disease have not been fully elucidated, systemic hypertension and increased urinary protein excretion are suggested to be clinical predictors of poor outcome (D’Amico et al., 1986; Alamartine et al., 1991). The pathological features of IgAN are haematuria, high levels of circulating IgA-fibronectin (FN) complexes, and glomerular deposition of IgA, complement C3, FN and collagen. The identification of risk factors for chronic renal disease might provide a measure for the therapeutic strategy. In this regard, the role of genetic polymorphisms, and whether certain candidate genes might be in-
volved in the progression of the disease, has become an intensely studied field in recent years.

Human uteroglobin (UG) or Clara cell 10-kDa protein is a steroid-dependent, immunomodulatory, and cytokine-like protein. It is secreted by the mucosal epithelial cells of all vertebrates studied to date (Zhang et al., 1997). UG appears to function as an anti-inflammatory agent in both the respiratory and urogenital tracts (Dierynck et al., 1995) and can react with transglutaminase to form a complex capable of suppressing the antigenicity of foreign proteins. Micromolar concentrations of UG could inhibit chemotaxis of both neutrophils and monocytes and prevent the infiltration of inflammatory cells (Vasanthakumar et al., 1988). UG is also a potent inhibitor of phospholipase A2 activity, which limits the metabolism of arachidonic acid and the synthesis of prostaglandin and leukotriene mediators (Hayward, 1995). Zheng et al. (1999) reported that two independent mouse models without UG showed pathologic findings similar to human IgAN, and suggested that exogenous UG would sufficiently prevent glomerular accumulation of exogenous IgA in UG-null mice. Mutation detection methods have identified several polymorphisms in the UG gene. Of several polymorphisms, an adenine to guanine substitution in the UG gene at position 38 (A38G) downstream of the transcription initiation site within the non-coding region of exon 1 is of particular interest. Laing et al. (1998) reported that those homozygous for 38AA and heterozygotes (38AG) had an increased risk of developing asthma. Studies of the exon 1 non-coding region of UG have identified a number of binding sites for the transcription factors involved in the regulation of UG protein expression. Although the significance of an alteration in the non-coding region of the human UG exon 1 is yet to be fully clarified, it may impact significantly upon protein expression levels (Laing et al., 1998).

The aim of this study was to screen exon 1 of the UG gene for sequence variations and determine whether the genetic variation might be associated with the progression of IgAN.

Methods

Study patients and control subject

The study patients were recruited from the Department of Internal Medicine, Seoul National University Hospital. One hundred and eleven patients with primary IgAN who had a minimal follow-up of 5 years and who gave their informed consent, were recruited into this study. The diagnosis of IgAN was based on mesangial proliferation and the presence of typical immunofluorescent changes on renal biopsy. Patients with evidences of systemic diseases such as diabetes, chronic liver disease and systemic lupus erythematosus were excluded. Sixty healthy subjects with normal renal function and normotension were also recruited from the Health Promotion Center of the same hospital as the controls. The research protocol used for this study was approved by the Internal Review Board of our institution. We defined hypertension as systolic blood pressure higher than 140 mmHg or diastolic pressure higher than 90 mmHg. Progression of renal disease was defined to exist when the level of serum creatinine was elevated to twice the basal serum creatinine level during follow-up. The serum creatinine was 1.2 ± 0.55 (mean ± SD) at the time of biopsy and was 2.7 ± 3.50 after 116 ± 44.2 months of follow-up.

Extraction of genomic DNA and genotype determination

Genomic DNA was extracted from peripheral blood lymphocytes by standard methods using a commercially available kit (Wizard Genomic DNA purification kit, Promega, Madison, WI, USA). The A to G polymorphism in the 5' UTR of exon 1 of the uteroglobin gene was determined according to the method of Laing et al. (1998). The nucleotide sequence was obtained from the GenBank (accession number: X59875) and was used to design appropriate primers for the amplification of exon 1 including 5' UTR by polymerase chain reaction (PCR): sense: 5'-CAGTATCCTATGAGAGCCC-3'; antisense: 5'-CCTGAGAGTTCCTAAGTCCAGG-3'. For the PCR amplification of exon 1, 100 ng of genomic DNA was used as template in a 25 μl reaction mixture which contained the following reagents: 3 pmol each primer (Bioneer, Korea), 0.5 U of Pyruvast DNA polymerase (Takara Shuzo Co., Kyoto, Japan), 1 × reaction buffer (67 mmol/l Tris-HCl, pH 8.8, at 25 ºC, 16.6 mmol/l [NH4]2 SO4, 0.45% (v/v) Triton X-100, 0.2 mg/ml gelatin), 1.5 mmol/l MgCl2 and 200 μmol/l of each deoxynucleotide triphosphate (Takara Shujo Co., Japan). Following an initial denaturation at 94 ºC for 5 min, the reactions were cycled 38 times through a temperature profile of 94 ºC for 30 s, 58 ºC for 30 s and 72 ºC for 30 s. A final extension was performed at 72 ºC for 10 min. The products of the reaction were visualized by flat bed agarose gel electrophoresis in a 1.2% agarose gel containing ethidium bromide (1.5 μg/ml). PCR yielded fragments containing exonic sequences of 258 bp. Subjects were genotyped by restriction digestion of the PCR products with Sau96I endonuclease (Promega), resulting in a 128-bp and 130-bp fragment for 38G alleles, whereas the 258-bp 38A alleles, lacking the Sau96I site, were not cut. Digested DNA samples were examined following
electrophoresis on 1.8% agarose gel containing ethidium bromide (1.5 μg/ml). DNA was visualized using a single intensity transilluminator (300 nm) and photographed with the Gel-Doc system (Bio-Rad Laboratories, Hercules, CA, USA) (Fig. 1). Single strand conformational polymorphism analysis was another mutation screening method used to maximize the detection of all potential polymorphisms and to confirm the genotype (Cotton, 1993; Ravnik-Glavac et al., 1994). Approximately 40–100 ng of DNA was mixed with non-denaturing loading dye [30% (v/v) glycerol, 0.05% (w/v) bromophenol blue, 0.05% (w/v) xylene cyanol], boiled for 5 min, and snap chilled on ice. Samples were then loaded onto a 0.5 × MDE (FMC Bioproducts, Rockland, ME, USA) 10% glycerol (Sigma, St Louis, MO, USA) gel. Electrophoresis of the gel was performed using a vertical electrophoresis system at 150 V and 4 °C for 20 h. DNA was visualized by silver staining (Promega) and the gels dried. Single-strand conformation polymorphism (SSCP) analysis also showed three different patterns that coincided with the patterns obtained from the PCR-restriction fragment length polymorphism (RFLP) method (Fig. 2). A 10% random sample of individual PCR products was sent to Macrogen Inc. (Seoul, Korea) to sequence them using an ABI3700 automatic sequencer (Perkin-Elmer, Roche Molecular Systems, Bronchburg, NJ, USA). We verified the sequence by the GeneDoc program (Bio-Rad Laboratories, Hercules, CA, USA).

Construction of luciferase reporter plasmid and luciferase assay

The 5′ UTR of UG exon 1 was amplified by 35 cycles of PCR using the sense primer 5′-AAGCT TAGGTGGCCTCCACAATTGC-3′ and the antisense primer 5′-GCCATGGTGAGGAGGGATG-3′ under the conditions of denaturing at 94 °C for 1 min, annealing at 65 °C for 1 min, and elongation at 72 °C for 1 min. The templates for PCR were DNA from the patients having either A or G genotype. The PCR products had 404 bp long and was cloned into PGL3 (Promega). The sequence was confirmed by automatic sequencing at Macrogen Inc (Seoul, Korea). We transfected A549 cell line with 1 μg of each DNA construct using Lipofectamine Plus reagent (GibcoBRL, Life Technologies, Rockland, MD, USA). PSV-β-galactosidase control vector was cotransfected to A549 cell lines for the normalization of transfection. After 72 h, we harvested cell lines and measured luciferase activity according to the methods supplied by the company. In brief, cells were lysed with 100–150 μl reporter lysis buffer. After transfer of cells and liquid to a microcentrifuge tube, we vortexed the tube for 10 s. We stored the samples at −70 °C until they were examined after centrifuging the tube at 12000 g for 15 s. A mixture of 4 μl of cell extract and 20 μl of luciferase assay reagent (Promega) was used for measuring luciferase activity by the scintillation counter (Packard Instrument Company Inc., Meriden, CT, USA). All the activities were normalized according to the activities of β-galactosidase.

Statistical analysis

The Mantel–Haenszel chi-squared method (Stokes et al., 1995) was used for detecting differences in the genotype distributions of patients and controls, and univariate logistic regression analysis was performed to determine the effect of each variable on renal outcome. Odds ratios were used to estimate the risk of an association between the renal outcome and each variable. To further delineate the relationships between the above gene polymorphisms, hypertension and the degree of proteinuria, stepwise multiple logistic regression analysis was performed. The multiplicative interaction parameter is defined as the ration of the joint odds ratio and the product of the odds ratios for each factor at the reference level of the other factor. In the absence of a multiplicative interaction, the parameter is 1.0 (Garcia-Closas et al., 1999). The Kruskal–Wallis test was used to calculate the statistical significance of the data that was not
normally distributed. All of the statistical analyses were performed using SAS version 6.12 (Cary, NC, USA).

Results

The frequencies of UG polymorphism were similar between patients and controls

Twenty-three patients with IgA nephropathy (21%) were homozygous for adenine at position 38 (38AA), 56 (50%) were heterozygous and 32 (29%) were homozygous for guanine (38GG). These genetic frequencies were statistically no different from those of normal controls; 13 (22%) of 60 controls for 38AA, 35 (58%) for 38AG, 12 (20%) for 38GG ($p = 0.37$; Mantel–Haenszel test). Hardy–Weinberg equilibrium was attained for these analyses. The average (±SD) period of follow-up was 116 ± 44.2 months. Patients were segregated into two subgroups on the basis of progression of underlying disease. Thirty patients had progressive renal disease (PD) and the other 81 patients had stable renal disease (SD). The patients with PD were older at the time of biopsy and had higher basal serum creatinine value than patients with SD (Table 1). In addition, the presence of hypertension was more prevalent in PD group. The average serum creatinine level (± SD) at the time of kidney biopsy was no different among three UG genotypes (1.3 ± 0.46:1.3 ± 0.29:1.1 ± 0.20 mg/dl; AA : AG : GG, respectively; $p > 0.05$). The amount of daily proteinuria, and the level of IgA were not different by genotype (data not shown).

The presence of adenine at position 38 (38A) was associated with the renal disease of poor clinical outcome

We examined whether the distribution of the genotypes of UG differed in the two subgroups. Ten of 30 patients (33%) with PD had the 38AA genotype, 16 of 30 (53%) were 38AG, and four patients (14%) were of the 38GG genotype, whereas 28 out of 81 patients (35%) with stable disease were of the 38GG genotype. An excess of A genotype was found in the progressive disease group ($p = 0.03$). The risk for developing the progressive disease increased as the number of A allele increased ($p$ for trend $= 0.03$) (Table 2). The mean duration of follow-up was similar for the PD and SD patients, 109 ± 37.7 and 118 ± 46.4 months, respectively. Univariate regression analysis revealed that the amount of daily proteinuria, the serum creatinine value at the time of biopsy, the presence of hypertension, the age of the patients, and the genotypes of UG were significantly associated with the progression of renal disease (data not shown). Multiple logistic regression analysis identified the genotypes of UG, the presence of hypertension and elevated serum creatinine at the time of biopsy as significant predictive variables for the progression of the disease. The odds ratio for the progression of renal disease in patients with the AA genotype was 4.9 ($p = 0.0495$) and 1.8 ($p = 0.3834$) in patients with the AG genotypes compared to patients having the GG genotype (Table 3). Presence of hypertension had an odds ratio of 4.4 ($p = 0.0118$) for the progressive renal disease. No association was found between the presence of hypertension and the genotypes of UG (chi-squared test,

<table>
<thead>
<tr>
<th></th>
<th>Stable disease ($n = 81$)</th>
<th>Progressive disease ($n = 30$)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>32.8 ± 13.9</td>
<td>39.5 ± 12.8</td>
<td>0.023*</td>
</tr>
<tr>
<td>Baseline creatinine (mg/dl)</td>
<td>1.07 ± 0.378</td>
<td>1.69 ± 0.698</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Daily proteinuria (mg)</td>
<td>1780 ± 2101</td>
<td>2381 ± 1927</td>
<td>0.2063*</td>
</tr>
<tr>
<td>Serum IgA (mg/dl)</td>
<td>353 ± 163</td>
<td>318 ± 104</td>
<td>0.3182*</td>
</tr>
<tr>
<td>Presence of hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td>67 (83)</td>
<td>10 (33)</td>
<td></td>
</tr>
<tr>
<td>Hypertensive</td>
<td>12 (15)</td>
<td>17 (57)</td>
<td>0.001**</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (2)</td>
<td>3 (10)</td>
<td></td>
</tr>
</tbody>
</table>

*t-test, **chi-squared test.
We further investigated the interactive effects of hypertension and genetic polymorphisms of UG on the progression of IgAN. The data in Table 4 indicate that patients with hypertension and AA genotype had more than a multiplicative interactive effect on the risk for developing the progressive disease (p for interaction \( \hat{p} = 0.001 \)).

### Effect of the gene polymorphism in the 5' UTR of UG gene transcript

To assess the functional significance of the polymorphisms in the 5' UTR of UG exon 1, we made two different genetic constructs using a PGL3-control vector. One had adenine homozygote and the other had guanine homozygote at the 38th nucleotide of UG exon 1 (Fig. 3a). The sequence of insert was confirmed by the automatic sequencer. Thereafter, the plasmid was transfected transiently into UG producing lung cancer cell line, A549. The cells were cultured for 72 h, and the activities of luciferase were measured using a scintillation counter. As shown in Fig. 3(b), A gene construct showed weaker effects on the induction of luciferase activities than those by G

### Table 2. Association of genetic polymorphisms of UG and progression of IgAN

<table>
<thead>
<tr>
<th>State of renal disease</th>
<th>Stable disease</th>
<th>Progressive disease</th>
<th>OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>GG</td>
<td>28 (35)</td>
<td>4 (14)</td>
<td>1.0 (reference)</td>
</tr>
<tr>
<td>AG</td>
<td>40 (49)</td>
<td>16 (53)</td>
<td>2.8 (0.8–9.3)</td>
</tr>
<tr>
<td>AA</td>
<td>13 (16)</td>
<td>10 (33)</td>
<td>5.4 (1.4–20.4)</td>
</tr>
<tr>
<td>Total</td>
<td>81 (100)</td>
<td>30 (100)</td>
<td></td>
</tr>
</tbody>
</table>

AA, 38AA genotype; AG, 38AG genotype; GG, 38GG genotype. *p for trend = 0.03 by Mantel-Haenszel chi-square.

### Table 3. Predictors for the progression of renal disease by the logistic regression analysis*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline creatinine (per 1 mg/dl)</td>
<td>5.1</td>
<td>1.5–17.2</td>
</tr>
<tr>
<td>Presence of hypertension</td>
<td>4.4</td>
<td>1.4–14.1</td>
</tr>
<tr>
<td>UG genotype** AG</td>
<td>1.8</td>
<td>0.5–7.6</td>
</tr>
<tr>
<td>AA</td>
<td>4.9</td>
<td>1.0–23.9</td>
</tr>
</tbody>
</table>

*Adjusted for age and sex. **Compared with GG genotype.

\( p = 0.23 \). We further investigated the interactive effects of hypertension and genetic polymorphisms of UG on the progression of IgAN. The data in Table 4 indicate that patients with hypertension and AA genotype had more than a multiplicative interactive effect on the risk for developing the progressive disease (p for interaction = 0.001).

### Fig. 3. (a) Location of the 404-bp-long insert and structure of the reported plasmid used in the luciferase assay. The sequences of two oligos are depicted in the complementary positions of the insert. (b) Plasmid that had the A 5' UTR sequence showed decreased luciferase activity compared to the G sequence. Pr, SV-40 promoter; LUC, luciferase gene.
gene construct (74 ± 8.4% of activities by G; p = 0.0044).

Discussion

A new aspect of research in human genetics involves associating sequence variations with specific human diseases. The single nucleotide polymorphisms (SNPs) is probably the common of these variations (Collins et al., 1997). Mathematically, we can expect any SNP to occur approximately once in every 100–300 bp. However, the frequent appearance of a polymorphism can be admitted as a marker for different individuals or families. Studies on the nucleotide polymorphisms might provide insights into the pathogenesis of human diseases. Genome-wide association studies for SNPs have been made in an effort to identify complex disease genes and/or pharmacogenomic applications. In this regard, we propose that the polymorphic nucleotide in the 5' UTR of UG be identified as a marker for the progression of IgAN.

UG is a steroid-dependent protein that has been called a uterine marker for progesterone action (Mukherjee et al., 1999). However, investigations during the past two decades have shown that expression of this protein is not restricted to the uterus, but that it is present in almost all epithelial cells, including those of the respiratory, gastrointestinal, and genitourinary systems of both sexes (Miele et al., 1994). UG has many biological properties, and one of the first of these to be discovered was its ability to bind progesterone (Beato, 1976). Subsequently, in a series of experiments, it was demonstrated that UG has potent anti-inflammatory and immunomodulatory properties (Mukherjee et al., 1999). One of the most important properties of UG is its ability to dramatically inhibit both the chemotaxis and phagocytosis of monocytes and neutrophils (Vasanthakumar et al., 1988). In our patients, the prevalence of 5' UTR gene polymorphism was similar to that of the normal controls, and this genetic prevalence was quite different from that of the Caucasian population (Laing et al., 1998).

We found that the patients with 38AA and 38AG polymorphisms had an increased risk of IgAN progression. Moreover, the homozygocity of AA seemed to have a profound deleterious effect on the progression of renal disease. This result gives some indication of a significant linear trend across the three genotypes. These associations are independent of age, gender and other clinical manifestations, such as the amount of proteinuria or the presence of hypertension (Tables 2 and 3). However, the presence of hypertension was found to be an independent risk factor for the progression of disease in our patients, which is in agreement with other reports (D'Amico et al., 1986; Alamartine et al., 1991). Risk factors for the progression of IgAN, such as the age of patients, amount of proteinuria and creatinine levels, affected the fate of renal disease in our study as others have also previously stated (D’Amico et al. 1986; Alamartine et al., 1991). The clinical presentation was no different in patient groups according to UG genotypes. Thus, we propose that SNP of UG exon 1 does not influence the development of IgA nephropathy but does affect the progression of disease, which would fit the anti-inflammatory property of UG (Vasanthakumar et al., 1988; Hayward, 1995). We also found interactive effects of hypertension and genetic polymorphisms on the progression of IgAN (Table 4). A more than multiplicative interactive effect of these variables would be very informative for clinicians to screen high-risk individuals, thus helping in the development of a practical application of the molecular findings in clinical practice. However, the small sample size and potential misclassification in this study needs be further addressed in larger study with longer follow-up periods of patients. Garcia-Closas et al. (1999) reported that the effect of gene prevalence and misclassification on the sample size are important issues in the study of the gene–environment interaction.

**Table 4.** Interactive effects of hypertension and genetic polymorphisms of UG on the progression of the IgAN (OR and 95% confidence interval)

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>AG and GG (no. of PD/no. of SD)</th>
<th>AA (no. of PD/no. of SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>1.0 (reference) (7/55)</td>
<td>2.0 (0.4–10.0) (3/12)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>4.4 (0.5–39.2) (10/11)</td>
<td>23.6 (4.3–129.4)* (7/1)</td>
</tr>
</tbody>
</table>

PD, progressive disease; SD, stable disease. *p for interaction = 0.001.
Uteroglobin polymorphism in IgA nephropathy

The tissue and organ-specific expression of the UG gene is due to the presence of hormone-responsive elements in its 5′ promoter region (Jantzen et al., 1987). Studies of the rat UG promoter and exon 1 non-coding region have identified a number of important transcription factors involved in the regulation of UG protein expression (Sawaya et al., 1994; Whitsett et al., 1996). UG promoter contains at least three transcription factor binding sites. These include an upstream hepatocyte nuclear factor-3 (HNF-3) and, downstream, an activator protein-1 (AP-1) and HNF-3 site which overlap. Downstream of the TATA box, a minimal promoter was identified within a −50 to +58 segment and was shown to be important in the transcriptional regulation of the UG promoter. The A38G polymorphism is located within a region that corresponds to the rat minimal promoter. Therefore, although the significance of an alteration to UG exon 1 non-coding region in human is yet to be fully clarified, it may impact significantly upon protein expression levels. Laing et al. (1998) reported that the presence of adenine instead of guanine at this site was associated with an increased risk of the development of asthma. This and the study of Zheng’s et al. (1999) suggested that the absence or decreased amount of UG predisposed robust inflammatory reactions in the host. Although we did not check the levels of uteroglobin protein in each group, there is a possibility that the 5′ UTR of UG might regulate translation efficiency. To examine this hypothesis, we undertook in-vitro work on the translational regulation of UG by 5′ UTR. As shown in Fig. 3, the presence of adenine instead of guanine decreased the translational efficiency in the luciferase system. Although the system we used does not represent the exact serum levels of protein, we propose that translational inefficiency of UG is associated with the progression of IgAN, thus supporting the fact that AA genotype is an independent risk factor.

In conclusion, this study identified a significant relationship between genotype differences at position 38 of exon 1 of the UG gene and the risk of IgA nephropathy progression. The polymorphism may alter UG protein expression, and therefore alter glomerular inflammation. One of the prospects of the present study is the potential for screening high-risk individuals, thus helping in the development of a practical application of the molecular findings in clinical practice.

Acknowledgements

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