Contribution of *LOC105371267* and *MRPS30-DT* Genetic Polymorphisms in IgA Nephropathy Among Chinese Han Population

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Research

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Abstract

Background: IgA nephropathy (IgAN) is the common primary glomerulonephritis worldwide. Genetic factors have been reported to take essential part in IgAN progression. This study was designed to investigate the association between LOC105371267 and MRPS30-DT with IgAN risk among Chinese.

Methods: 6 SNPs were genotyped. A logistic recession model was used to calculate the effects of candidate SNPs on IgAN. The SNP-SNP interaction was analyzed by MDR.

Results: We observed only LOC105371267 had relationships with IgAN. The results indicated an association between the genotype “CC” and the decreased IgAN risk (OR = 0.44, p = 0.014). The stratification analysis at age ≥ 35 showed that rs3931698 contributed to the IgAN susceptibility in “GT” (OR = 1.78, p = 0.038), while rs8044565 significantly showed a decreasing-risk effect with IgAN (“T”, OR = 0.59, p = 0.006; “CC”, OR = 0.15, p = 0.015; “CC-CT”, OR = 0.59, p = 0.023; Log-additive, OR = 0.56, p = 0.005). Rs8044565 was correlated with the decreased susceptibility of IgAN in male (“CC”, OR = 0.27, p = 0.006) and in Lee’s grade ≥ III (“CC”, OR = 0.46, p = 0.046). We found rs8044565 was related to systolic blood pressure and urinary casts, and rs3852740 had a relationship with Serum C3 and hemoglobin (p < 0.05).

Conclusion: The present study first demonstrated that the SNPs in lncRNAs might be related to IgAN.

Introduction

With the development of modern society, especially for the change of dietary habits, chronic kidney disease with increased morbidity and mortality has attracted much attention nowadays. Immunoglobulin A nephropathy (IgAN) is a kind of autoimmune disease, accounting for 45.3% - 54.3% of primary glomerulonephritis and remains a leading cause of end-stage renal disease (ESRD) in China[1, 2]. IgAN is characterized by a single histopathological criterion of pre-dominant IgA deposits on kidney biopsy, however, renal biopsy is invasive with limitations in assessing disease activity only at the time of biopsy, which could lead to inconclusive findings and decisions[3, 4]. To date, it is gradually recognized that genetic factors play a crucial role in the development of IgAN and it may serve as potential diagnostic indicators [5-7].

As researched revealed that greater than 70% of genome is transcribed and that vast majority of transcribed DNA encodes long non-coding RNAs (lncRNAs)[8, 9]. LncRNAs are important class of noncoding RNA that are characterized by their length longer than 200nt. Accumulating evidence have suggested that lncRNAs take essential part in diverse pathological settings, including cancer, cardiovascular disease, and pathogenesis of kidney disease[9, 10]. Recent studies have also reported the relationship between lncRNAs and various kidney disease[11-13], but few about IgAN[14, 15]. Guo et al. used high-throughput RNA sequencing and qRT-PCR to test the exosomes isolated from plasma of IgAN patients and their healthy first-degree relative. The results revealed that exosomal lncRNA-G21551 was down-regulated in IgAN patients, indicating its potential to serve as a non-invasive biomarker for IgAN[14]. In the study of Zuo et al, peripheral blood mononuclear cells were collected from both IgAN patients and healthy controls to identify differentially expressed lncRNAs and mRNAs by microarray analysis and quantitative polymerase chain reaction. Their results demonstrated that differentially expressed lncRNAs and mRNAs may have a role in the development of IgAN [15]. However, there are not any genetic polymorphism research about IgAN. Thus, we designed the current study to investigate association between single nucleotide polymorphisms (SNPs) and lncRNAs.

Loc105371267, located on chromosome 16, is a lncRNA involved in the p53 network which is hardly researched. It was reported that p53 upregulation in renal resident cells may be linked to the pathogenesis of progressive IgAN[16], but the role of Loc105371267 to IgAN susceptibility remains unclear. Additionally, MRPS30-DT on chromosome 5 is broadly expressed in breast, kidney and other tissues[17]. Until now, no data have been found on the relationship between MRPS30-DT and IgAN.
Therefore, in the current study, we will conduct a case-control study to identify the association between IgAN susceptibility and six SNPs in the *Loc105371267* and *MRP30-DT* in the Chinese Han population. The study aims to identify the potential role of these SNPs in IgAN.

**Methods**

**Study participants**

The current study was included 836 unrelated subjects including 413 IgAN patients and 423 geographically ethnicity-matched healthy subjects who were collected from Xi’an Hospital of Traditional Chinese Medicine. All patients must meet the diagnostic criteria which tested by renal biopsy and the patients with other autoimmune diseases or secondary IgAN were excluded. The healthy subjects were collected from the physical examination center at the same period. The clinical information of participants were collected, including age, gender, serum albumin (ALB) level, creatinine (CREA) level, Urine red blood cell (URBC) count, hemoglobin (HB), serum uric acid (UA), fibrinogen (FIB), and pathological grade (Lee's classification).

We designed this protocol in compliance with the Ethics Committee of the Xi’an Hospital of Traditional Chinese Medicine and the guidelines of the Declaration of Helsinki. All participants were provided and signed up the written informed consent.

**Selection and genotyping of SNPs**

We identified six SNPs in *LOC105371267* and *MRP30-DT* with a minor allele frequency (MAF) > 0.05 in the 1000 Genomes Projects ([http://www.internationalgenome.org/](http://www.internationalgenome.org/)). Fasting peripheral blood of all participants were collected in anticoagulant tubes and stored at -80 °C. We extracted DNA by using the whole blood genomic DNA extraction kit (GoldMag, China) in accordance with manufacturer's protocol provided, and the DNA content was measured by spectrometry (NanoDrop 2000 spectrophotometer, Thermo Scientific, USA). Multiplexed SNP MassEXTEND assay was designed by Agena MassARRAY Assay Design Software (version 3.0, Agena Bioscience, USA). Moreover, Agena MassARRAY RS100 was used to detect SNP genotyping. Data were analyzed using Agena Typer Software (version 4.0, Agena Bioscience, USA).

**Bioinformatics analysis**

The current study analyzed and predicted the possible function effects on these candidate SNPs by using online softwares, HaploReg v4.1 ([https://pubsbroad institute.org/mammals/haploreg/haploreg.php](https://pubsbroad institute.org/mammals/haploreg/haploreg.php)) and SNP info Web Server ([https://snpinfo.niehs.nih.gov/snpinfo/index.html](https://snpinfo.niehs.nih.gov/snpinfo/index.html)).

**Statistical analysis**

SPSS software (version 20.0) was used for data analysis. The independent sample T-test or χ² test was used to examine the differences of basic parameters between the cases and controls. Hardy-Weinberg equilibrium (HWE) was tested by χ² test for each SNP selected in the current study. The IgAN risk associated with genotyping was estimated by odds ratios (ORs) with 95% confidence intervals (CIs) for five different genetic models. The difference in clinical characteristics among different genotypes was analyzed using the ANOVA test. The SNP-SNP interactions in the risk of IgAN were analyzed by multifactor dimensionality reduction (MDR) (version 3.0.2). For all test, a two-tailed p-value < 0.05 was considered statistically significant.

**Results**

**Basic characteristic of the participants**
The current study was included 413 IgAN patients (267 males and 146 females) and 423 healthy controls (275 males and 148 females). The mean age of cases and controls were 33.21 ± 12.07 and 33.34 ± 10.11 years, and there were no significant differences in age and gender between cases and controls group \( (p = 0.861, p = 0.942\), respectively). Demographic and clinical characteristics were listed in Table 1, including age, gender, pathological grade, urine red blood cell (RBC), urine casts, serum albumin (ALB), creatinine (CREA), serum uric acid (UA), hemoglobin (HB) and fibrinogen (FIB). Significant differences were observed in urine RBC, urine casts, ALB, CREA, UA, HB and FIB between two groups (all \( p < 0.001\).

**Association of genetic polymorphism with IgAN risk**

Basic information of the SNPs in LOC105371267 and MRPS30-DT were presented in Table 2. All of genetic polymorphisms were complied with a Hardy-Weinberg equilibrium \( (p > 0.05\). Significantly in Table 3, rs8044565 in Loc105371267 was presented the decreased risk with IgAN adjusted by age and gender (CC vs TT, OR = 0.43, 95% CI = 0.23-0.84, \( p = 0.012\); Recessive model, OR = 0.43, 95% CI = 0.23-0.82, \( p = 0.011\)). However, another SNPs in Loc105371267 and MRP30-DT showed no statistical significance with IgAN risk.

**Stratification analysis of SNPs with IgAN risk**

Then we did stratified analysis of selected SNPs with IgAN risk. The results shown in table 4 indicated that in the subgroup of \( \geq 35\) years, rs3931698 in Loc105371267 was significantly associated with the increased risk of IgAN risk (GT vs TT, OR = 1.78, 95% CI = 1.03-3.07, \( p = 0.038\), while rs8044565 in Loc105371267 showed decreased risk with IgAN (T vs C, OR = 0.59, 95% CI = 0.40-0.86, \( p = 0.006\); CC vs TT, OR = 0.15, 95% CI = 0.03-0.69, \( p = 0.015\); Dominant model, OR = 0.59, 95% CI = 0.97-0.93, \( p = 0.023\); Recessive model, OR = 0.17, 95% CI = 0.04-0.08, \( p = 0.025\); Log-additive, OR = 0.56, 95% CI = 0.38-0.84, \( p = 0.005\)).

By the stratification of gender shown in Table 5, we observed that in the subgroup of male, rs8044565 in Loc105371267 was associated with the decreased IgAN risk (CC vs TT, OR = 0.27, 95% CI = 0.11-0.69, \( p = 0.006\); Recessive model, OR = 0.27, 95% CI = 0.11-0.70, \( p = 0.007\)). As well, by the stratification of Lee's grade shown in Table 6, rs8044565 in Loc105371267 was also showed to be correlated with decreased IgAN risk (CC vs TT, OR = 0.46, 95% CI = 0.21-0.98, \( p = 0.046\); Recessive, OR = 0.44, 95% CI = 0.21-0.95, \( p = 0.036\)).

**Genotypes and clinical characteristics**

Additionally, we analyzed the relationship between different genotypes of SNPs and clinical characteristics in LOC105371267 and MRPS30-DT, including systolic blood pressure (SBP), diastolic blood pressure (DBP), urinary casts, serum C3, creatinine (CREA), serum uric acid (UA), hemoglobin (HB), urine beta 2 microglobulin (β2-MG). As shown in Table 7, we observed that in Loc105371267 rs8044565, the “TC” genotype (91.80 ± 19.89 mmHg) had a higher level of DBP than TT (89.82 ± 20.93 mmHg) and CC (77.64 ± 26.73 mmHg) genotype, and the TT genotype (18.46 ± 41.23 μL) was significantly higher in urinary casts level than TC (5.57 ± 21.28 μL) and CC (3.70 ± 15.28 μL) genotype. Meanwhile, for rs3852740 in Loc105371267, it was indicated that GG genotype (1.22 ± .041 g/L) had higher level of DBP than GG genotype (1.05 ± 0.25 g/L) and CC (1.04 ± 0.25 g/L) genotype; GG genotype (137.45 ± 18.06 g/L) had higher HB level than CC (129.92 ± 23.78 g/L) and CC (124.33 ± 24.22 g/L) genotype. However, another SNPs in Loc105371267 and MRP30-DT showed no statistical significance with characteristics of IgAN.

**SNP-SNP interactions**

We used MDR analysis to assess the effect of SNP-SNP interaction among 4 selected SNPs in LOC105371267 (Table 8). In total, we found a three-locus mode including rs8044565, rs3852740, rs111577197 were the best model (cross-validation consistency = 9/10, testing balanced accuracy = 0.464, \( p = 0.006\). Obviously, there were interactions between locus and locus presented in a dendrogram and the Fruchterman-Reingold in Figure 1 (A and B, respectively).
Discussion

IgAN is a complex autoimmune disease with pathogenesis needed to be clarified. Accumulating evidence indicated that genetic and environmental factors take essential part in the development of IgAN. Previous studies revealed that some genetic variations, such as FCRL3, DRB1 and DEFA[19-21], were significantly associated with the risk of IgAN, but are few reported in long non-coding RNA (lncRNA) which have attracted much attention for their functions in gene regulation nowadays[22]. More importantly, it was reported that lncRNA was associated with IgAN, however, there has been found no data to demonstrate the genetics polymorphisms about IgAN.

We designed this case-control study to detect the association between genetic polymorphisms in two lncRNAs and the susceptibility to IgAN. The results revealed that only Loc105371267 had an association with IgAN and rs8044565 variants in Loc105371267 might serve as a potential protective factor to IgAN in the overall. Interestingly, our further stratified analysis showed that LOC105371267 rs3931698 variants was associated with the susceptibility to IgAN in the subgroup ≤35 years, while LOC105371267 rs8044565 variants reduced the risk of IgAN. We also found that rs8044565 was decreased the risk of IgAN in females as well as it was significantly associated with Lee's grade. In view of the complicated pathogenic factors of IgAN, SNP-SNP interaction studies may help discover the risk factors for IgAN[23]. Accordingly, we analyzed the potential SNP-SNP interactions in LOC105371267 by MDR. The analysis indicated a strong interaction between the rs8044565, rs3852740 and rs111577197 regarding association with IgAN. To the best of our knowledge, it is the first time to demonstrate the effects of the relationships between these SNPs in lncRNA and the IgAN risk.

Loc105371267, located on chromosome 16, is a p53-regulated lncRNA which remains unclear in IgAN risk. In recent years, evidence has emerged that dysfunction of the p53 network is associated with the development of autoimmune disease[24-26]. Thus, it is significance to detect the association between LOC105371267 and IgAN. In current study, we firstly investigated the association between 4 polymorphisms in the LOC105371267 with IgAN risk among Chinese Han population. The results provided an evidence that rs8044565 in LOC105371267 was significantly associated with reduced IgAN risk in different genetic models. Therefore, it may serve as an important protective role for IgAN which needed to be further verified.

Given the current aging society in China, age in IgAN patients is an important factor to consider. Previous cohort study in 2019 indicated that the mean age at diagnosis of IgAN was 32.9 years[3]. Thus, to detect the genetics effect of age in IgAN, we did an analysis stratified by age at 35 years, it showed that genotype “GG” in LOC105371267 rs3931698 was contributed to the IgAN susceptibility (OR = 1.78, 95% CI = 1.03-3.07), p = 0.038) in the group of age ≥35 years, while LOC105371267 rs8044565 significantly association with the reduced IgAN risk at the same subgroup. At the same time, the genotype “CC” in rs8044565 showed the decreasing risk-effect with IgAN (OR = 0.27, 95% CI = 0.11-0.69, p = 0.006). It probably revealed that rs8044565 in LOC105371267 might perform a protective effect in the group of male who were older than 35 years.

Besides, several studies have showed that SNPs have strong susceptibility to IgAN in Lee's grade[27-29]. In the current study, we observed that the genotype “CC” (OR = 0.46, 95% CI = 0.21-0.98, p = 0.046) in LOC105371267 rs8044565 was significantly related with the reduced IgAN risk under the stratification of Lee's grade > III. Clinical characteristics can be regarded as indicators for IgAN[30]. Thus, we determined the correlation between SNPs and clinical characteristics in IgAN. We observed that LOC105371267 rs8044565 was related to diastolic blood pressure, urinary casts and LOC105371267 rs3852740 was related to serum C3 and hemoglobin. We speculate that SNPs in LOC105371267 may correlate with clinical indicators, which needed to verify by investigating the more indicators in the further study.

Several intrinsic limitations to our study should be considered. First, the selection bias in this case-control study was its hospital-based design, and it may not be representative of the general population. Second, environmental exposure was not available, which limited us to further analyze the potential interaction of gene-environment on IgAN risk. Importantly, further functional assay of our present study provided scientific evidence about LOC105371267 with IgAN in the future study.
Conclusion

To summarize, the current study investigated the SNPs in IncRNA LOC105371267 and MRPS30-DT with the risk of IgAN. The results revealed that only LOC105371267 variants significantly associate with the IgAN risk and rs8044565 may be a protective factor which need to be further verified in the larger samples study. Notably, our results was firstly detected the relationship between IncRNA and IgAN risk. Besides, a new insight for the molecular mechanism in the development of IgAN was provided.

Declarations

Ethics approval and consent to participate

This study strictly obeyed the World Medical Association Declaration of Helsinki, which was also approved by the Ethical Committee of the Xi’an Hospital Of Traditional Chinese Medicine. Written informed consent was obtained from each study participant.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

Not applicable.

Author Contributions

Xiaoyan Chen and Wen Cao drafted the manuscript. Haiyue Li and Yuanwei Liu performed the DNA extraction and genotyping; Jianfeng Liu and Jiamin Wu performed the data analysis; Danning Shi, Zichao Xiong and Yao Sun performed the sample collection and information recording; Wen Cao and Xiaoyan Chen conceived and supervised the study.

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Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Code availability

Any code involved in the study is available.

Consent to participate

All participants were provided and signed up the written informed consent.

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Tables

Table 1 Basic characteristic of IgAN cases and healthy controls in this study
| Characteristics                          | Controls (n = 423) | Cases (n = 413) | p  |
|-----------------------------------------|-------------------|----------------|----|
| Age, years (mean ± SD)                  | 33.34 ± 10.11     | 33.21 ± 12.07  | 0.861 |
| > 35 years old                          | 165 (39%)         | 155 (38%)      |    |
| ≤ 35 years old                          | 258 (61%)         | 258 (62%)      |    |
| Gender                                  |                   |                | 0.942 |
| Male                                    | 275 (65%)         | 267 (65 %)     |    |
| Female                                  | 148 (35%)         | 146 (35%)      |    |
| Pathological grade                      |                   |                |    |
| ≥ III                                   | 423 (100%)        | 263 (64%)      |    |
| < III                                   | 423 (100%)        | 136 (33%)      |    |
| Clinical index                          |                   |                |    |
| Urine RBC (µL)                          | 26.17 ± 141.94    | 195.42 ± 371.96 | < 0.001 |
| Urine casts (µL)                        | 0.38 ± 0.58       | 4.93 ± 19.14   | < 0.001 |
| ALB (g/L)                               | 46.95 ± 2.97      | 35.95 ± 9.50   | < 0.001 |
| CREA (µmol/L)                           | 67.24 ± 15.51     | 154.03 ± 173.05 | < 0.001 |
| UA (µmol/L)                             | 340.83 ± 94.75    | 383.88 ± 114.60 | < 0.001 |
| HB (g/L)                                | 150.87 ± 17.89    | 126.49 ± 23.98 | < 0.001 |
| FIB (g)                                 | 3.03 ± 0.24       | 3.78 ± 1.28    | < 0.001 |

RBC, Red blood cell; ALB, Serum albumin; CREA, Creatinine; UA, Serum uric acid; HB, Hemoglobin; FIB, Fibrinogen

Table 2 Basic information for Loc105371267 SNPs
| SNP ID     | Gene       | Chr:Position     | Role   | Alleles (A/B) | MAF     | p-value for HWE | Haploreg 4.1 |
|-----------|------------|------------------|--------|---------------|---------|-----------------|---------------|
| rs3931698 | LOC105371267 | Chr16: 53070825 | Intron | G/T           | 0.144   | 0.139           | Enhancer histone marks; DNAse; Motifs changed |
| rs8044565 | LOC105371267 | Chr16: 53073990 | Intron | C/T           | 0.230   | 0.261           | Motifs changed; |
| rs3852740 | LOC105371267 | Chr16: 53078171 | Intron | G/C           | 0.212   | 0.217           | Promoter histone marks; Enhancer histone marks; DNAse; Proteins bound; Motifs changed; |
| rs111577197| LOC105371267 | Chr16: 53083155 | Intron | T/C           | 0.195   | 0.193           | Enhancer histone marks; Motifs changed; |
| rs16901963 | MRPS30-DT  | Chr5: 44783102  | Intron | T/A           | 0.390   | 0.391           | Motifs changed; Selected eQTL hits |
| rs2118763 | MRPS30-DT  | Chr5: 44787546  | Intron | T/C           | 0.057   | 0.067           | Motifs changed |

SNP, Single nucleotide polymorphisms, MAF, minor allele frequency, HWE, Hardy–Weinberg equilibrium.

Table 3 Association analysis between the SNPs and IgAN risk
| SNP ID     | Gene     | Model            | Genotype | Case | Control | Without adjusted | Adjusted by age and gender |
|-----------|----------|------------------|----------|------|---------|------------------|--------------------------|
| rs8044565 | LOC105371267 | Genotype | TT       | 233  | 234     | 1                | 1                        |
|           |          | CC               | 14       | 32   | 0.44    | (0.23-0.84)      | 0.014                    | 0.43                     | (0.23-0.84)              | 0.012                    |
|           |          | CT               | 159      | 157  | 1.02    | (0.76-1.35)      | 0.907                    | 1.02                     | (0.76-1.35)              | 0.912                    |
|           |          | Dominant         | TT       | 173  | 189     | 1                | 1                        |
|           |          | CC-CT            | 233      | 234  | 0.91    | (0.70-1.21)      | 0.548                    | 0.92                     | (0.70-1.21)              | 0.540                    |
|           |          | Recessive        | CT-TT    | 14   | 32      | 1                | 1                        |
|           |          | CC               | 392      | 391  | 0.44    | (0.23-0.83)      | 0.012                    | 0.43                     | (0.23-0.82)              | 0.011                    |
|           |          | Log-additive     | -        | -    | -       | -                | -                        | -                        | 0.84                     | (0.67-1.06)              | 0.139                    | 0.84                     | (0.67-1.06)              | 0.133                    |

CI, confidence interval; OR: odds ratio; SNP, single nucleotide polymorphism

\( p \)-values were calculated by unconditional logistic regression analysis with adjustment for age and gender.

\( p < 0.05 \) indicates statistical significance.

Table 4. The SNPs of \textit{LOC105371267} associated with IgAN risk in the subgroup tests of age.
| SNP ID   | Model   | Allele/genotype | Case | Control | OR (95% CI) | p   | Case | Control | OR (95% CI) | p   |
|---------|---------|-----------------|------|---------|-------------|-----|------|---------|-------------|-----|
| Age, years |         |                 |      |         |             |     |      |         |             |     |
| > 35    |         |                 |      |         |             |     |      |         |             |     |
| ≤ 35    |         |                 |      |         |             |     |      |         |             |     |
| rs3931698 | Allele | G               | 49   | 39      | 1.40        | 0.143 | 70   | 78      | 0.88        | 0.462 |
|         |         | T               | 261  | 291     | 1.40 (0.89-2.20) |   | 446  | 436     | 0.88 (0.62-1.24) |   |
| Genotype | TT      |                 | 110  | 131     | 1.00        |     | 191  | 182     | 1.00        |     |
|         |         | GG              | 4    | 5       | 1.04        | 0.951 | 3    | 3       | 0.93        | 0.945 |
|         |         | GT              | 41   | 29      | 1.78 (1.03-3.07) | 0.038 | 64   | 72      | 0.86        | 0.469 |
| Dominant | TT      |                 | 110  | 131     | 1.00        |     | 191  | 182     | 1.00        |     |
|         |         | GG              | 4    | 5       | 1.04        | 0.951 | 3    | 3       | 0.93        | 0.945 |
|         |         | GT              | 41   | 29      | 1.78 (1.03-3.07) | 0.038 | 64   | 72      | 0.86        | 0.469 |
| Recessive | GT-TT   |                 | 151  | 160     | 1.00        |     | 255  | 254     | 1.00        |     |
|         |         | GG              | 4    | 5       | 0.91        | 0.892 | 3    | 3       | 0.97        | 0.972 |
| Log-additive | -    |                 |      |         | 1.44 (0.92-2.25) | 0.106 | -    | -       | 0.88        | 0.498 |
| rs8044565 | Allele | C               | 54   | 89      | 1.00        |     | 377  | 384     | 1.00        |     |
|         |         | T               | 248  | 241     | 0.59 (0.40-0.86) | 0.006 | 133  | 132     | 1.03        | 0.856 |
| Genotype | TT      |                 | 99   | 87      | 1.00        |     | 134  | 147     | 1.00        |     |
|         |         | CC              | 2    | 11      | 0.15 (0.03-0.69) | 0.015 | 12   | 21      | 0.58        | 0.157 |
|         |         | CT              | 50   | 67      | 0.66 (0.41-1.06) | 0.087 | 109  | 90      | 1.34        | 0.118 |
| Dominant | TT      |                 | 99   | 87      | 1.00        |     | 134  | 147     | 1.00        |     |
|         |         | CC              | 2    | 11      | 0.15 (0.03-0.69) | 0.015 | 12   | 21      | 0.58        | 0.157 |
|         |         | CT              | 50   | 67      | 0.66 (0.41-1.06) | 0.087 | 109  | 90      | 1.34        | 0.118 |
| Recessive | CT-TT   |                 | 149  | 154     | 1.00        |     | 243  | 237     | 1.00        |     |
|         |         | CC              | 2    | 11      | 0.17 (0.04-0.80) | 0.025 | 12   | 21      | 0.52        | 0.078 |
| Log-additive | -    |                 |      |         | 0.56 (0.38-0.80) | 0.005 | -    | -       | 1.01        | 0.934 |
CI, confidence interval; OR: odds ratio; SNP, single nucleotide polymorphism

*p < 0.05 indicates statistical significance.

Table 5. Association between SNPs and IgAN risk by stratification tests of gender

| SNP ID   | Model   | Allele/genotype | Case | Control | OR (95% CI) | p    | Case | Control | OR (95% CI) | p    |
|----------|---------|-----------------|------|---------|-------------|------|------|---------|-------------|------|      |
| Gender   | Male    | C               | 116  | 149     | 1.00        |      | 71   | 72      | 1.00        |      |      |
|          |         | T               | 406  | 401     | 0.77 (0.58-1.02) | 0.065 | 219  | 224     | 1.01 (0.69-1.47) | 0.964 |      |
| Genotype | Male    | TT              | 151  | 147     | 1.00        |      | 82   | 87      | 1.00        |      |      |
|          |         | CC              | 6    | 21      | 0.27 (0.11-0.69) | 0.006 | 8    | 11      | 0.77 (0.30-2.02) | 0.599 |      |
|          |         | CT              | 104  | 107     | 0.94 (0.66-1.34) | 0.739 | 55   | 50      | 1.17 (0.71-1.90) | 0.533 |      |
| Dominant | Male    | TT              | 151  | 147     | 1.00        |      | 82   | 87      | 1.00        |      |      |
|          |         | CC-CT           | 110  | 128     | 0.83 (0.59-1.17) | 0.292 | 63   | 61      | 1.10 (0.69-1.74) | 0.696 |      |
| Recessive| Male    | CT-TT           | 255  | 254     | 1.00        |      | 137  | 137     | 1.00        |      |      |
|          |         | CC              | 6    | 21      | 0.27 (0.11-0.70) | 0.007 | 8    | 11      | 0.73 (0.28-1.87) | 0.509 |      |
| Log-additive |       |                |      |         | 0.75 (1.56-1.00) | 0.052 |      |         | 1.01 (0.70-1.46) | 0.962 |      |

CI, confidence interval; OR: odds ratio; SNP, single nucleotide polymorphism

*p < 0.05 indicates statistical significance.

Table 6 Correlation between SNPs and IgAN susceptibility stratified by pathological grade.
| SNP ID       | Model            | Allele/genotype | Case | Control | OR (95% CI) | p    | Case | Control | OR (95% CI) | p    |
|--------------|------------------|-----------------|------|---------|-------------|------|------|---------|-------------|------|
| **Pathological grade** |                  |                 |      |         |             |      |      |         |             |      |
| rs8044565    | Allele           | C               | 122  | 221     | 1.00        |      | 61   | 221     | 1.00        |      |
|              |                  | T               | 396  | 625     | 0.87 (0.68-1.12) | 0.288 | 207  | 625     | 0.83 (0.60-1.15) | 0.270 |
|              | Genotype         | TT              | 146  | 234     | 1.00        |      | 78   | 234     | 1.00        |      |
|              |                  | CC              | 9    | 32      | 0.46 (0.21-0.98) | 0.046 | 5    | 32      | 0.45 (0.17-1.20) | 0.239 |
|              |                  | CT              | 104  | 157     | 1.07 (0.77-1.48) | 0.679 | 51   | 157     | 0.99 (0.66-1.50) | 0.981 |
|              | Dominant         | TT              | 146  | 234     | 1.00        |      | 78   | 234     | 1.00        |      |
|              |                  | CC-CT           | 113  | 189     | 0.97 (0.70-1.32) | 0.833 | 56   | 166     | 0.90 (0.61-1.33) | 0.595 |
|              | Recessive        | CT-TT           | 250  | 391     | 1.00        |      | 129  | 391     | 1.00        |      |
|              |                  | CC              | 9    | 32      | 0.44 (0.21-0.95) | 0.036 | 5    | 32      | 0.45 (0.17-1.18) | 0.106 |
|              | Log-additive     | -               | -    | -       | 0.88 (0.68-1.13) | 0.312 | -    | -       | 0.84 (0.61-1.15) | 0.275 |

*p values were calculated by logistic regression adjusted by age and gender.

*p < 0.05 indicates statistical significance.

Table 7 Correlation between clinical characteristics and SNP genotypes
| SNP               | SBP (mmHg) | DBP (mmHg) | Urinary Casts (μL) | Serum C3 (g/L) | CREA (μmol/L) | UA (μmol/L) | HB (g/L) | Urine β2-MG (μg/L) |
|------------------|-----------|-----------|-------------------|---------------|---------------|------------|----------|------------------|
| rs8044565        |           |           |                   |               |               |            |          |                  |
| CC               | 121.55 ± 33.54 | 77.64 ± 26.73 | 3.70 ± 15.28 | 1.06 ± 0.28 | 92.97 ± 63.68 | 354.50 ± 140.62 | 124.86 ± 23.23 | 884.47 ± 999.78 |
| TC               | 138.35 ± 26.75 | 91.80 ± 19.89 | 5.57 ± 21.28 | 1.04 ± 0.22 | 155.22 ± 178.35 | 391.51 ± 115.08 | 125.77 ± 23.93 | 620.08 ± 893.88 |
| TT               | 139.64 ± 30.48 | 89.82 ± 20.93 | 18.46 ± 41.23 | 1.05 ± 0.25 | 152.62 ± 164.61 | 379.13 ± 113.05 | 127.57 ± 23.89 | 584.34 ± 900.57 |
|                  | 0.080                          | 0.048                          | 0.023                          | 0.836                          | 0.410                          | 0.381                          | 0.738                          | 0.505                          |
| rs3852740        |           |           |                   |               |               |            |          |                  |
| GG               | 140.30 ± 34.47 | 90.21 ± 22.33 | 1.56 ± 2.67 | 1.22 ± 1.1 | 123.61 ± 94.53 | 361.96 ± 89.4 | 137.45 ± 18.06 | 439.54 ± 759.32 |
| CG               | 140.14 ± 30.86 | 90.38 ± 20.13 | 4.52 ± 15.76 | 1.05 ± 0.25 | 155.20 ± 182.82 | 379.67 ± 100.28 | 128.92 ± 23.78 | 477.98 ± 743.99 |
| CC               | 137.73 ± 27.92 | 138.65 ± 29.20 | 5.41 ± 21.38 | 1.04 ± 0.25 | 155.82 ± 172.82 | 387.99 ± 123.47 | 124.33 ± 24.22 | 694.13 ± 974.74 |
|                  | 0.721                          | 0.886                          | 0.658                          | 0.011                          | 0.723                          | 0.546                          | 0.22                          | 0.096                          |

SBP, systolic blood pressure; DBP, diastolic blood pressure; CREA, creatinine; UA, Serum uric acid; HB, Hemoglobin; β2-MG, beta 2 microglobulin.

*p* values were calculated by Kruskal-Wallis H test.

*p* < 0.05 indicates statistical significance.

Table 8 MDR analysis of SNP-SNP interactions in relation with IgAN risk.

| Model                | Training Bal. Acc | Testing Bal. Acc | OR (95% CI)   | Testing χ² value | p value  | CVC |
|----------------------|-------------------|------------------|---------------|-----------------|----------|-----|
| rs8044565            | 0.522             | 0.482            | 1.36 (0.93-2.01) | 2.506           | 0.113    | 8/10 |
| rs8044565, rs3852740 | 0.536             | 0.454            | 1.35 (1.01-1.82) | 3.975           | 0.046    | 7/10 |
| rs8044565, rs3852740, rs111577197 | 0.550             | 0.464            | 1.50 (1.12-2.01) | 7.570           | 0.006    | 9/10 |

MDR, multifactor dimensionality reduction; Bal. Acc., balanced accuracy; CVC, cross-validation consistency; OR, odds ratio; 95% CI, 95% confidence interval.

*p* values were calculated using χ² tests. *p* < 0.05 indicates statistical significance.

**Figures**
Image not available with this version

Figure 1

There were interactions between locus and locus presented in a dendrogram and the Fruchterman-Reingold in Figure 1 (A and B, respectively).