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 $\geq$ 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 biosy 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 *MRP30-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.[18]. 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 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/>). 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 manufacture'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 theses candidate SNPs by using online softwares, HaploReg v4.1 (<https://pubsbroadinstitute.org/mammas/haploreg/haploreg.php>) and SNP info Web Server (<https://snpin fo.niehs.nih.gov/snpinfo/index.html>).

Statistical analysis

SPSS software (version 20.0) was used for data analysis. The independent sample T-test or χ^2 test was used to examine the differences of basic parameters between the cases and controls. Hardy-Weinberg equilibrium (HWE) was tested by χ^2 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 ≥ 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 (β 2-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 μ L) was significantly higher in urinary casts level than TC (5.57 ± 21.28 μ L) and CC (3.70 ± 15.28 μ L) genotype. Meanwhile, for rs3852740 in *Loc105371267*, it was indicated that GG genotype ($1.22 \pm .041$ g/L) was higher in serums C3 level than CG (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 CG (128.92 ± 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 analyzation 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 lncRNA *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 lncRNA 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)	<i>p</i>
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		<i>p</i> -value for HWE	Haploreg 4.1
					Cases	Controls		
rs3931698	LOC105371267	Chr16: 53070825	Intron	G/T	0.144	0.139	1	Enhancer histone marks; DNase; Motifs changed
rs8044565	LOC105371267	Chr16: 53073990	Intron	C/T	0.230	0.261	0.450	Motifs changed;
rs3852740	LOC105371267	Chr16: 53078171	Intron	G/C	0.212	0.217	0.668	Promoter histone marks; Enhancer histone marks; DNase; Proteins bound; Motifs changed;
rs111577197	LOC105371267	Chr16: 53083155	Intron	T/C	0.195	0.193	0.438	Enhancer histone marks; Motifs changed;
rs16901963	MRPS30-DT	Chr5: 44783102	Intron	T/A	0.390	0.391	0.307	Motifs changed; Selected eQTL hits
rs2118763	MRPS30-DT	Chr5: 44787546	Intron	T/C	0.057	0.067	0.702	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	
						OR (95% CI)	p^a	OR (95% CI)	p^b
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 *LOC105371267* associated with IgAN risk in the subgroup tests of age.

SNP ID	Model	Allele/genotype	Case	Control	OR (95% CI)	<i>p</i>	Case	Control	OR (95% CI)	<i>p</i>
Age, years			> 35			≤ 35				
rs3931698	Allele	G	49	39	1.00		70	78	1.00	
		T	261	291	1.40 (0.89- 2.20)	0.143	446	436	0.88 (0.62- 1.24)	0.462
	Genotype	TT	110	131	1.00		191	182	1.00	
		GG	4	5	1.04 (0.27- 4.05)	0.951	3	3	0.93 (0.19- 4.70)	0.945
		GT	41	29	1.78 (1.03- 3.07)	0.038	64	72	0.86 (0.58- 1.29)	0.469
	Dominant	TT	110	131	1.00		191	182	1.00	
		GG-GT	45	34	1.67 (1.00- 2.81)	0.052	67	75	0.87 (0.59- 1.28)	0.473
	Recessive	GT-TT	151	160	1.00		255	254	1.00	
		GG	4	5	0.91 (0.24- 3.51)	0.892	3	3	0.97 (0.19- 4.87)	0.972
	Log-additive	-	-	-	1.44 (0.92- 2.25)	0.106	-	-	0.88 (0.61- 1.27)	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 (0.78- 1.34)	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 (0.27- 1.23)	0.157
		CT	50	67	0.66 (0.41- 1.06)	0.087	109	90	1.34 (0.93- 1.94)	0.118
	Dominant	TT	99	87	1.00		134	147	1.00	
		CC-CT	52	78	0.59 (0.37- 0.93)	0.023	121	111	1.19 (0.84- 1.69)	0.327
	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 (0.25- 1.08)	0.078
	Log-additive	-	-	-	0.56 (0.38-	0.005	-	-	1.01 (0.76-	0.934

0.84)

1.34)

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				Female			
rs8044565	Allele	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	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	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	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)	<i>p</i>	Case	Control	OR (95% CI)	<i>p</i>
Pathological grade			≥ III				< III			
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
<i>p</i>	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 ± .041	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
<i>p</i>	0.721	0.886	0.658	0.011	0.723	0.546	0.022	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 χ^2 value	<i>p</i> 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 χ^2 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).