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3′UTR SNPs in the *LPP* gene associated with Immunoglobulin A nephropathy risk in the Chinese Han population

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ABSTRACT

The purpose of this study was to investigate the relationship between *Lipoma preferred partner* (*LPP*) gene polymorphisms and the risk of Immunoglobulin A nephropathy (IgAN) in the Chinese Han population. In this case-control study, we genotyped three single nucleotide polymorphisms (SNPs) of the *LPP* gene in 357 IgAN cases and 384 controls, using Agena Bioscience MassARRAY technology and assessed their association with IgAN using the χ^2 test and genetic model analysis. The odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess risk and were adjusted for age and gender by logistic regression. In the allele model, there were significant associations between *LPP* rs1064607 (OR = 1.24; 95% CI = 1.01–1.53; $p = 0.041$), rs3796283 (OR = 1.32; 95% CI = 1.08–1.63; $p = 0.008$), and rs2378456 (OR = 1.29; 95% CI = 1.05–1.59; $p = 0.016$), as well as an increased risk of IgAN. In the dominant model, the "G/C-C/C" genotypes of rs1064607 ($p = 0.023$), the "G/A-G/G" genotypes of rs3796283 ($p = 0.0013$) and the "G/C-C/C" genotypes of rs2378456 ($p = 0.00052$) were risk factors for IgAN. The results of the stratified analysis showed that rs3796283 and rs2378456 were connected with susceptibility to IgAN in different subgroups. Our data may provide new evidence to research the etiology of IgAN.

1. Introduction

With the development of society and the changes of modern lifestyles and dietary habits, chronic kidney disease with considerable morbidity and mortality has gradually attracted attention. Immunoglobulin A nephropathy (IgAN) is one of the most common manifestations of primary glomerulonephritis and is a leading cause of renal failure [1,2]. It is estimated that > 40% of IgAN patients will eventually face end-stage kidney disease [3]. It is interesting that the prevalence of IgAN varies from population to population. IgAN is most common in the Asian population, with a prevalence rate as high as 3.7% [4] and is of intermediate prevalence among Europeans (up to 1.3%) [5] but is rare among Africans [6]. Increasing evidence suggests that multiple genetic and environmental factors contribute to the risk of developing IgAN [7].

The *LPP* gene is located on chromosome 3q27-q28 and encodes a member of the zyxin family of enzymes that regulate cytoskeletal tissue, cell movement and mechanosensing [8]. A previous study has demonstrated that *LPP* can inhibit collective cell migration by a certain molecular pathway and that loss of *LPP* may serve as a prognostic marker of increasing malignancy [9]. *LPP* is involved in the formation of invadopodia and is required for regulation of metastasis in breast cancer [10]. Moreover, a meta-analysis showed that *BCL6-LPP* gene polymorphisms are correlated with renal function-related characteristics among East Asian populations [11]. Based on the above studies, we concluded that the role of the *LPP* gene in the occurrence and development of IgAN cannot be neglected. However, little is known about the relationship between *LPP* genetic polymorphisms and susceptibility to IgAN.

To investigate a potential relationship between *LPP* SNPs and the etiology of IgAN in a Chinese Han population, we genotyped three SNPs in *LPP* (rs1064607, rs3796283 and rs2378456) and performed an integrated association analysis in a case-control study.

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2. Materials and methods

2.1. Subjects

We consecutively recruited 357 IgAN patients and 384 healthy people as the control group from the Hospital. All participants are Han people in northwest China. All patients were diagnosed with IgAN by pathological biopsy and had not received any systematic treatment before blood sampling. In addition, we excluded patients with primary and secondary nephropathy, infectious diseases, autoimmune diseases and cancer. We excluded healthy controls with major diseases such as impaired vital organs, central nervous system diseases, endocrine diseases and metabolic diseases. Detailed clinical information was collected for each patient, including age, gender, a diagnosis of dropsy, Urine red blood cell count, Casts, 24 hour urine protein, serum creatinine level, blood urea nitrogen, serum uric acid, serum albumin level, serum cholesterol level, serum IgA level, serum C3 level, serum C4 level, serum uric acid, hemoglobin, fibrinogen and histopathological grade (Lee's classification).

This study was approved by the Ethics Committee of the Hospital. All participants signed a written informed consent.

2.2. SNP selection and genotyping

Three SNPs in the 3′UTR region of *LPP* were selected from the dbSNP database (http://www.hapmap.org/index.html.en) and the SNP Consortium database (http://snp.cshl.org/) for analysis. The lower frequency alleles were coded as the minor allele. All of the SNPs had minor allele frequencies (MAFs) > 5% in the 1000 Genomes population (http://www.internationalgenome.org/). Genomic DNA was extracted from whole blood samples with the GoldMag-Mini Purification Kit (GoldMagCo. Ltd. Xi'an, China), and DNA concentrations were measured with the NanoDrop2000 (Thermo Scientific, Waltham, Massachusetts, USA). Agena Bioscience MassARRAY Assay Design 3.0 software was used to design a multiplexed SNP Mass EXTENDED assay [12–14]. Primers for amplification and single-base extension were showed in Supplementary Table 1. Genotyping was performed on the Agena Bioscience MassARRAY RS1000 platform. Data management and analysis were performed with the Agena Bioscience Typer 4.0 Software [15,16]. The genotyping method was referenced from previous association studies [17–21].

2.3. Statistical analysis

Statistical analysis was performed with Microsoft Excel (Microsoft, Redmond, WA, USA) and SPSS package version 20.0 (SPSS, Chicago, IL, USA). Genotype frequencies for each SNP were tested for departure from HWE using the Chi-square test on controls. Allele and genotype frequencies in the cases and controls were compared using Chi-square tests [22]. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the effects of the polymorphisms on IgAN risk with logistic regression analysis after adjusting for age and gender in four models (co-dominant, dominant, recessive, and log-additive) [23]. All p values in this study were two-sided, and $p < 0.05$ was considered statistically significant.

2.4. Bioinformatics analysis

We used the online bioinformatics database HaploReg v4.1 to evaluate and annotate the potential functions of the selected SNPs (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php).

3. Results

3.1. Demographics and clinical characteristics of study participants

A total of 357 patients and 384 control subjects were recruited into the study. The characteristics of IgAN patients and control subjects are shown in Table 1. The average age of the participants was 32.44 ± 11.80 years (patients) and 51.16 ± 11.49 years (controls). There was no significant difference in age distribution between patients and controls ($p = 0.495$). However, there is a significant difference in gender distribution between the two groups ($p = 0.036$). Therefore, we adjusted for age and gender with logistic regression for further analysis. Among the entire patient group, the mean urine RBC is 255.39 ± 36.49 n/μL, the mean BUN is 9.05 ± 0.82 mM, the mean urine CREA is 145.75 ± 8.55 μmol/L and the mean UA is 380.87 ± 11.41 μmol/L. According to Lee's glomerular grading system, 33.6% of patients were below Grade III and 60.2% were above Grade III. In addition, variance analysis of all the clinical indicators among patients and the different genotypes with respect to SNPs are shown in Supplementary Table 2.

3.2. Basic information of selected SNPs

All SNP call rates (> 95%) were considered high enough to perform subsequent analysis. Basic information on the SNPs in *LPP* is shown in Table 2, including the gene, chromosome, position, role, alleles, minor allele frequency (MAF) and functional effects. We predicted the functional elements of these candidate SNPs using HaploRegv4.1. The results showed that the SNPs of *LPP* were related to the regulation of

Table 1
Characteristics of the study population.

Section a

	Cases (N = 357)	Controls (N = 384)	p[a]
Age			0.495
Mean ± SD	32.44 ± 11.80	51.16 ± 11.49	
Sex, n (%)			0.036
Male	233 (65.3%)	278 (72.4%)	
Female	124 (34.7%)	106 (17.6%)	
Pathological grade, n (%)			
Unknown	22 (6.2%)		
< III	120 (33.6%)		
≥ III	215 (60.2%)		

Section b

	Mean ± SD	Total
Dropsy	0.60 ± 0.05	240
Urine RBC (n/μL)	250.12 ± 28.82	234
Casts (n/μL)	5.77 ± 1.33	230
Upr (g/day)	2.71 ± 0.34	347
ALB (g/L)	33.99 ± 0.43	347
CHO (mmol/L)	6.13 ± 1.01	341
Serum IgA (g/L)	2.75 ± 0.07	333
C3 (g/L)	1.03 ± 0.01	329
C4 (g/L)	0.02 ± 0.01	329
BUN (mmol/L)	8.20 ± 0.32	348
CREA (μmol/L)	145.75 ± 8.55	348
UA (μmol/L)	380.87 ± 11.41	284
HB (g/L)	129.4 ± 2.86	342
FIB (g)	17.76 ± 13.97	291

RBC = Red blood cell, Upr = urine protein, ALB = serum albumin, CHO = serum cholesterol, C3 = serum C3, C4 = serum C4, BUN = blood urea nitrogen, CREA = creatinine, UA = serum uric acid, HB = hemoglobin, and FIB = fibrinogen.

[a] p values were calculated from the two-sided chi-square test. $p < 0.05$ indicates statistical significance.

Table 2
Basic information for candidate SNPs.

SNP ID	Gene	Chr.	Position	Role	Alleles A/B	MAF		*p*-HWE	OR (95% CI)	p^a	HaploReg
						Case	Control				
rs1064607	*LPP*	3	188595672	3′UTR	C/G	0.416	0.365	0.661	1.24 (1.01–1.53)	**0.041***	DNase, selected eQTL hits
rs3796283	*LPP*	3	188602952	3′UTR	G/A	0.483	0.414	0.674	1.32 (1.08–1.63)	**0.008***	Enhancer histone marks, motifs changed, selected eQTL hits
rs2378456	*LPP*	3	188603007	3′UTR	C/G	0.517	0.453	0.608	1.29 (1.05–1.59)	**0.016***	Enhancer histone marks, motifs changed

SNP: single nucleotide polymorphism, Alleles A/B: minor/major alleles; MAF, minor allele frequency; OR: odds ratio, CI: confidence interval, HWE: Hardy–Weinberg equilibrium.
[a] *p* values were calculated using the two-sided chi-squared test (the major allele of each SNP was a reference allele).
* Bold indicates statistical significance. ($p < 0.05$)

DNase, enhancer histones, changed motifs, and/or selected eQTL hits, suggesting they might exert associated biological influences in the patients.

3.3. Association of LPP polymorphisms with IgAN risk

The Chi-square test was used to compare the frequency distributions of alleles between cases and controls (Table 2). The results showed that the 'C' allele of rs1064607 was a risk allele for IgAN (OR = 1.244, 95% CI = 1.008–1.534, $p = 0.041$). Similarly, the rs3796283-G and rs2378456-C alleles were risk alleles for IgAN (rs3796283-G: OR = 1.323, 95% CI = 1.077–1.625, $p = 0.008$; rs1064607-C: OR = 1.292, 95% CI = 1.048–1.593, $p = 0.016$).

Then, we classified the major allele of each SNP as a reference allele and assessed the association between each different genotype and IgAN risk in four genetic models (Table 3). In the dominant model, the following genotypes were associated with increased IgAN risk: the "G/C-C/C" genotypes of rs1064607 (OR = 1.58; 95% CI = 1.06–2.35; $p = 0.023$); the "G/A-G/G" genotypes of rs3796283 (OR = 2.00; 95% CI = 1.30–3.05; $p = 0.0013$); and the "G/C-C/C" genotypes of rs2378456 (OR = 1.90; 95% CI = 1.20–2.98; $p = 0.00052$). These three SNPs also enhanced IgAN susceptibility in other models.

3.4. Stratification analysis of LPP polymorphisms and risk for IgAN

We divided the subjects into four subgroups based on their gender and histopathological grade (Table 4). In the stratified analysis by gender, two SNPs associated with IgAN susceptibility in the male subgroup: rs3796283 in the dominant model (OR = 1.80; 95% CI = 1.11–2.92; $p = 0.017$ for the "G/A-G/G" genotype) and the log-additive model (OR = 1.45, 95% CI = 1.05–1.98, $p = 0.019$), and rs2378456 in the dominant model (OR = 1.84; 95% CI = 1.10–3.08; $p = 0.019$ for the "G/C-C/C" genotype) and the log-additive model (OR = 1.38, 95% CI = 1.00–1.91, $p = 0.046$). However, only rs3796283 associated with IgAN risk in the female subgroup in the dominant model (OR = 2.80; 95% CI = 1.16–6.75; $p = 0.019$ for the "G/A-G/G" genotype) and the log-additive model (OR = 1.78, 95% CI = 1.01–3.13, $p = 0.041$). In the stratified analysis by histopathological grade, we observed a significant association between the SNPs of *LPP* and increased IgAN risk for the ≥Lee's III group in the co-dominant, dominant and log-additive models (all *p* values were < 0.05). For the < Lee's III group, in the dominant model, the "G/A-G/G" genotypes of rs3796283 were associated with increased IgAN risk (OR = 2.06; 95% CI = 1.12–3.79; $p = 0.021$).

Table 3
Association between SNPs and risk of IgAN in multiple inheritance models.

SNP	Model	Genotype	Control	Case	OR (95% CI)	p^a	AIC	BIC
rs1064607	Co-dominant	G/G	157 (40.9%)	117 (33.1%)	1	0.073	669.6	692.6
		G/C	174 (45.3%)	178 (50.4%)	1.55 (1.02–2.36)			
		C/C	53 (13.8%)	58 (16.4%)	1.68 (0.94–3.00)			
	Dominant	G/G	157 (40.9%)	117 (33.1%)	1	**0.023***	667.6	686.1
		G/C-C/C	227 (59.1%)	236 (66.9%)	1.58 (1.06–2.35)			
	Recessive	G/G-G/C	331 (86.2%)	295 (83.6%)	1	0.320	671.8	690.2
		C/C	53 (13.8%)	58 (16.4%)	1.31 (0.77–2.22)			
	Log-additive	–	–	–	1.35 (1.02–1.78)	**0.035***	668.4	686.8
rs3796283	Co-dominant	A/A	134 (34.9%)	92 (25.9%)	1	**0.0048***	664.3	687.3
		G/A	182 (47.4%)	183 (51.5%)	1.92 (1.22–3.00)			
		G/G	68 (17.7%)	80 (22.5%)	2.21 (1.26–3.85)			
	Dominant	A/A	134 (34.9%)	92 (25.9%)	1	**0.0013***	662.6	681
		G/A-G/G	250 (65.1%)	263 (74.1%)	2.00 (1.30–3.05)			
	Recessive	A/A-G/A	316 (82.3%)	275 (77.5%)	1	0.120	670.5	689
		G/G	68 (17.7%)	80 (22.5%)	1.46 (0.91–2.35)			
	Log-additive	–	–	–	1.52 (1.15–2.00)	**0.0027***	664	682.4
rs2378456	Co-dominant	G/G	117 (30.6%)	72 (22.1%)	1	**0.019***	635.3	658.1
		G/C	185 (48.3%)	171 (52.5%)	1.85 (1.14–2.99)			
		C/C	81 (21.1%)	83 (25.5%)	2.00 (1.14–3.51)			
	Dominant	G/G	117 (30.6%)	72 (22.1%)	1	**0.0052***	633.4	651.6
		G/C-C/C	266 (69.5%)	254 (77.9%)	1.90 (1.20–2.98)			
	Recessive	G/G-G/C	302 (78.8%)	243 (74.5%)	1	0.220	639.7	657.9
		C/C	81 (21.1%)	83 (25.5%)	1.33 (0.84–2.11)			
	Log-additive	–	–	–	1.42 (1.07–1.88)	**0.013***	635.0	653.3

ORs: odds ratios; CI: confidence interval; AIC: Akaike's Information criterion; BIC: Bayesian Information criterion.
[a] *p* values were adjusted by gender and age.
* Bold indicates statistical significance. ($p < 0.05$)

Table 4
Stratification analysis of the association of SNPs with IgAN in multiple inheritance models.

SNP	Model	Genotype	Male		Female		< Lee's III		≥Lee's III	
			OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a	OR (95% CI)	p^a
rs3796283	Co-dominant	C/C	1	0.051	1	0.062	1		1	
		G/C	1.71 (1.02–2.88)		2.71 (1.09–6.73)		2.12 (1.11–4.02)	0.122	1.88 (1.13–3.15)	**0.016***
		G/G	2.00 (1.05–3.81)		3.08 (0.99–9.56)		1.92 (0.85–4.33)	0.118	2.28 (1.21–4.29)	**0.010***
	Dominant	C/C	1	**0.017***	1	**0.019***	1	**0.021***	1	**0.005***
		G/A-G/G	1.80 (1.11–2.92)		2.80 (1.16–6.75)		2.06 (1.12–3.79)		1.99 (1.23–3.24)	
	Recessive	A/A-G/A	1	0.190	1	0.390	1	0.607	1	0.116
		G/G	1.46 (0.83–2.55)		1.48 (0.61–3.62)		1.20 (0.60–2.40)		1.48 (0.61–3.62)	
	Log-additive	–	1.45 (1.05–1.98)	**0.022***	1.78 (1.01–3.13)	**0.041***	1.45 (1.05–1.98)	0.065	1.54 (1.13–2.10)	**0.007***
rs2378456	Co-dominant	G/G	1	0.064	1	0.270	1		1	
		G/C	1.83 (1.06–3.17)		0.79 (0.32–1.94)		1.80 (0.90–3.59)	0.095	1.92 (1.11–3.31)	**0.020***
		C/C	1.86 (0.98–3.56)		0.40 (0.13–1.29)		1.91 (0.85–4.27)	0.117	1.98 (1.04–3.80)	**0.038***
	Dominant	G/G	1	**0.019***	1	0.380	1	0.069	1	**0.010***
		G/C-C/C	1.84 (1.10–3.08)		0.68 (0.29–1.61)		1.83 (0.95–3.52)		0.94 (1.15–3.26)	
	Recessive	G/G-G/C	1	0.370	1	0.120	1	0.437	1	0.344
		C/C	1.28 (0.74–2.21)		0.48 (0.18–1.24)		1.30 (0.67–2.50)		0.48 (0.18–1.24)	
	Log-additive	–	1.38 (1.00–1.91)	**0.046***	0.65 (0.36–1.15)	0.130	1.38 (1.00–1.91)	0.108	1.42 (1.03–1.95)	**0.032***

[a] p values were adjusted by age.
* Bold indicates statistical significance. ($p < 0.05$)

4. Discussion

To date, several studies have investigated the relationship between SNPs and IgAN susceptibility, and a wide range of SNPs have been identified in different populations. However, the pathogenesis of IgAN is uncertain. Researchers still need to identify more SNPs that are correlated with IgAN. In this study, we identified three SNPs of the *LPP* gene associated with risk of IgAN.

In recent years, a large number of genome-wide association studies have revealed many possible genetic risk factors for different types of diseases [24]. It is interesting that several *LPP*-susceptible SNPs overlap among different kinds of disease，including type 1 diabetes and Crohn's disease and, especially, several autoimmune disorders such as rheumatoid arthritis, juvenile idiopathic arthritis and vitiligo [25–27]. We believe we are the first to identify the association between *LPP* gene polymorphisms and risk of IgAN, which is also an immune-related disease. Combined with previous research, we hypothesized that the *LPP* gene may be a potential immune-related factor. However, we should be cautious about the results identified here because of the limited sample size. Further studies will investigate the underlying mechanism of the *LPP* gene.

Expression of the *LPP* gene, which was first discovered in human benign and malignant tumors, may be related to the migration and proliferation of tumor cells [28], and could also play an indispensable role in cell proliferation and transcription [29]. Petit et al. first described *LPP* promotion of lipoma formation by preferential participation in ectopic chromosome 12, and overexpression of *LPP* is involved in the development of epithelial-derived and mesenchymal-derived tumors. It can shuttle back and forth between the cell surface and the nucleus, which is the hub of genetic changes [30]. Rs1064607, rs3796283 and rs2378456 are located in the 3′UTR region of the *LPP* gene. Therefore, combining the functions of the 3′UTR and the predicted results of the database, we conjectured that *LPP* 3′UTR variations may alter translation of the *LPP* gene and lead to a higher risk of IgAN.

In this study, some limitations should be taken into account. First, all participants were recruited in the same hospital, and there were inevitable geographical limitations Second, IgAN is a multifactorial disease that is influenced by a combination of multiple genetic and environmental factors. Due to the absence of data on environmental factors, it is difficult to explore the interaction between *LPP* polymorphisms and environmental factors in the development of IgAN.

In conclusion, we provided a previously unknown association between *LPP* polymorphisms and risk of IgAN in a Chinese Han population, which may be a potential target for novel diagnostic strategies of IgAN. Further studies will focus on the interactions between the three *LPP* SNPs and environmental factors in IgAN risk and clarification of the specific functions of the *LPP* gene in the pathogenesis of IgAN.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.intimp.2019.05.053.

Declaration of Competing Interest

The authors have no conflicts of interest to report.

Acknowledgments

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