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Original Article

The association of the *CMIP* rs16955379 polymorphism with dyslipidemia and the clinicopathological features of IgA nephropathy

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Abstract: Immunoglobulin A nephropathy (IgAN) is among the most common primary glomerular diseases. The prognosis in IgAN is affected by dyslipidemia, a risk factor for cardiovascular disease. The c-Maf inducing protein (CMIP) gene has been found to be associated with lipid metabolism. But the association between the *CMIP* rs16955379 single nucleotide polymorphism (SNP) and dyslipidemia or the related clinicopathological features in IgAN have not been reported thus far. The present study investigated the correlation between them. The *CMIP* rs16955379 SNP genotypes of 300 subjects with IgAN recruited from the First Affiliated Hospital of Guangxi Medical University were identified by polymerase chain reaction and direct sequencing. Compared with the control (normal lipid) group, the dyslipidemia group with IgAN had higher blood uric acid, serum creatinine, blood urea nitrogen and urinary protein quantity, higher proportions of mesangial cell proliferation and renal tubular atrophy/interstitial fibrosis (IFTA), and a lower estimated glomerular filtration rate and serum albumin. The frequencies of the *CMIP* rs16955379 SNP TT genotype and T allele in the dyslipidemia group were higher than in the control group. Triglyceride, apolipoprotein A1 (ApoA1), ApoA1/B, incidences of mesangial cell proliferation, and IFTA were higher in TT genotype carriers than in CC/CT genotype carriers. Serum lipid profiles and dyslipidemia were significantly associated with renal dysfunction and IFTA. IgAN patients with the TT genotype were more likely to have dyslipidemia, renal dysfunction and IFTA ($P < 0.05$ for all above). These results indicate that *CMIP* rs16955379 SNP may be a genetic susceptibility gene for dyslipidemia and poor renal outcome in IgAN.

Keywords: IgA nephropathy, CMIP, single nucleotide polymorphism, dyslipidemia

Introduction

Immunoglobulin A nephropathy (IgAN) is one of the most common primary glomerular diseases in the world [1, 2]. In China, IgAN accounts for 30 to 40 percent of primary glomerular diseases, and about a third of untreated patients eventually progress to end-stage renal disease (ESRD) [3]. A 30-year study of 1,012 patients at a single center in Japan showed that IgAN is not a benign disease, with about 50% of patients progressing to ESRD within 30 years despite treatment [4]. The life expectancy of patients with a clear diagnosis of IgAN was reduced by 10.1 years compared with the general population [5]. IgAN has become a worldwide public health issue that threatens human health due to its high prevalence, disability rate, morbidity, impact on quality of life, poor prognosis, cost of care, and medical resource utilization. The high cost of treatment and burden on public health care resources is particularly problematic. IgAN is a complex disease that involves multiple genes and factors; its pathogenesis is not yet fully understood. There is much evidence that IgAN is a disease with ethnic, geographic, and familial variations [6-8]. Gene polymorphism is an important factor affecting the morbidity and progression of IgAN.

IgAN is often accompanied by abnormal lipid metabolism [9], which is a risk factor for cardiovascular events and affects the progress and prognosis of patients. Hyperlipidemia is one of

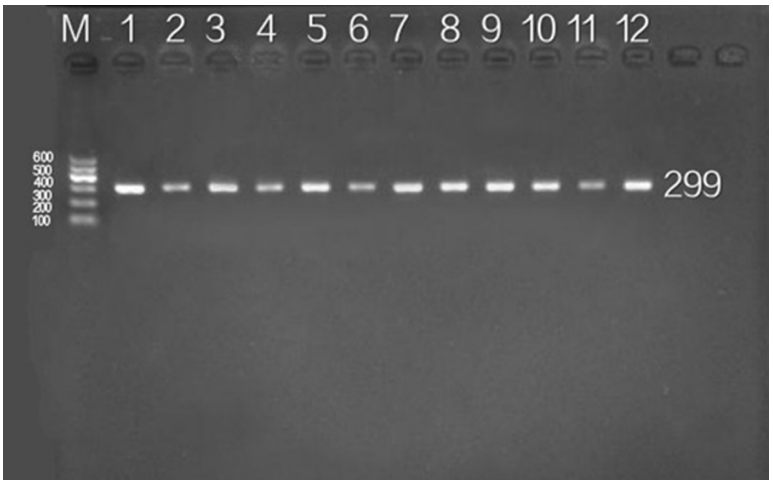

Figure 1. Electrophoresis of the PCR amplification products of CMIP rs16955379 polymorphism. Lane M: 100 bp marker ladder; Lanes 1-12: the PCR products (299 bp).

the most common types of dyslipidemia in IgAN and can cause glomerular sclerosis and renal tubular fibrosis, which increase the risk of progression in renal dysfunction [10, 11].

In recent years, genome-wide association studies (GWAS) have identified more than 100 sites associated with dyslipidemia [12]. Although previous studies have shown that CMIP polymorphisms are associated with serum lipid levels, the relationship between CMIP polymorphisms and dyslipidemia in IgAN has largely remained unknown. The purpose of this study was to research the correlation between CMIP rs16955379 and dyslipidemia or other clinicopathological features in IgAN, so as to identify a potential predictor of prognosis and judge the effectiveness of gene-targeted therapy for IgAN patients with dyslipidemia.

Materials and methods

Subjects

All subjects were patients treated in the Department of Nephrology at the First Affiliated Hospital of Guangxi Medical University between August 2014 and December 2017, who were diagnosed with IgAN by ultrasound-guided percutaneous renal biopsy. Patients were excluded from the study if they had IgAN secondary to systemic diseases such as hepatitis B, allergic purpura, systemic lupus erythematosus, cirrhosis, rheumatoid arthritis, tumors or multiple myelomas; comorbid severe primary diseases, organic diseases or mental illness; a recent history of using hormones, immunosuppressive agents, or lipid-lowering therapy. In total, 300 unrelated participants (184 males, 116 females) with IgAN were included in the study.

This study was approved by the ethics committee of the First Affiliated Hospital of Guangxi Medical University. Patient consent was obtained for all data and blood sample collections.

Collection of information

Questionnaires were used to collect information from the subjects, all of whom signed consent forms after the purpose of the survey was explained to them. Trained medical personnel interviewed the participants to obtain general information, such as name, gender, age, smoking, drinking, and medical history (e.g., disease complications such as diabetes, hypertension, hyperlipidemia, and medication history).

Collection of specimens

Fasting venous blood samples (5 mL) were obtained from all participants and were used for the evaluation of liver and kidney function, the measurement of blood lipid levels and other biochemical indicators, and the extraction of genomic DNA. The blood samples that were used to detect biochemical indices in serum were immediately cryopreserved at -80°C after sampling without anticoagulation. The samples used for DNA extraction were anti-coagulated with sodium citrate and stored at -20°C for less than 1 week.

Diagnostic criteria

The diagnosis of IgAN was based on biopsy findings, particularly at light microscopy and immunofluorescence microscopy. The deposition of IgA or IgA on immunoglobulin and its complement in the glomerular mesangial area and/or the glomerular capillary loop, glomerular mesangial cell proliferation, and mesangial matrix gathering were the main characteristics of IgAN [13, 14] (The light microscopy of renal

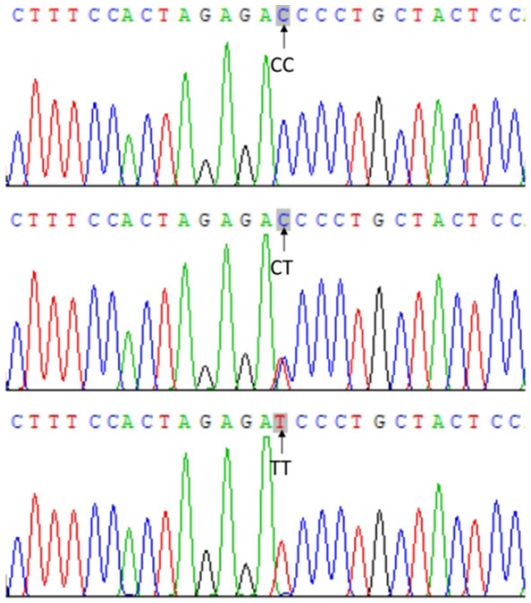

Figure 2. Partial nucleotide sequences of the CMIP rs16955379 SNP by direct sequencing. CC: CC genotypes; CT: CT genotypes; TT: TT genotypes.

tissues in IgAN patients shown in Figure S1). Using reference levels from the lipid profiles of 2007 Chinese adults, dyslipidemia was defined as total cholesterol (TC) level greater than 6.22 mmol/L, low density lipoprotein (LDL-C) level greater than 4.14 mmol/L, high density lipoprotein (HDL-C) level less than 1.04 mmol/L, and triglyceride (TG) level greater than 2.26 mmol/L [15-17]. Blood pressure was measured using the following method: all participants were required to rest for 5 minutes, blood pressure was measured in triplicate in a sitting position from the right arm, and the mean value was calculated. Systolic blood pressure (SBP) was the pressure at which the Korotkoff sound was first heard. Diastolic blood pressure (DBP) was the pressure at which the fifth Korotkoff sound disappeared. Diagnostic criteria for hypertension were based on the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (JNC 7) published in 2003. SBP greater than 140 mmHg (1 mmHg = 0.133 kpa) and/or DBP greater than 90 mmHg was diagnosed as hypertension [18, 19]. The normal reference ranges of serum creatinine (Scr) were those used in the First Affiliated Hospital of Guangxi Medical University since August 2014, which were defined as 59-104 μmmol/L in males and 45-84 μmmol/L in females. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 and/or Scr > 104 μmmol/L in males or Scr > 84 μmmol/L in females was considered indicative of renal dysfunction. The Oxford pathological classification (Oxford-MEST) was used to assess mesangial cell proliferation (M1 defined as having 50% of the glomerular mesangial area exceeding three mesangial cells and M0 otherwise), capillary hyperplasia (E1 defined as cell proliferation in glomerular capillaries causing narrowing of the cavity, and E0 otherwise), segmental glomerular sclerosis (S1 defined as having loops affected to any degree, without involvement of the entire glomerulus or adhesion, and S0 otherwise), and renal tubular atrophy/interstitial fibrosis (T0 defined as 0%-25%, T1 defined as 26%-50%, and T2 defined as > 50%) [20, 21].

Selection of SNP

Haploview4.2 software was used, and the Tagger program was run to choose the SNP. Next, SNP information was obtained from the National Center for Biotechnology Information (NCBI) SNP database (dbSNP Build 150, http://www.ncbi.nlm.nih.gov/SNP/). The minimum allele frequency (MAF) of the selected SNP was > 1%. A search of the literature showed that the selected SNP may be related to lipid metabolism [22]. Based on these factors, we chose CMIP rs16955379 SNP as the label site.

DNA amplification and genotyping

Genomic DNA was separated from peripheral blood leukocytes by phenol chloroform extraction [23-25]. Using gene sequences in the NCBI database, we used Primer5.0 software to design specific primers and compared them. Primer sequences were designed by a Shanghai biology engineering company for *CMIP* rs16955379F (GGGATTGCGTACATGGTGTC) and for *CMIP* rs16955379R (TGTGCTGTCTCGAAGGTGAT). The PCR reaction was performed in a total volume of 25 μL, containing 12.5 μL MIX, 8.5 μL water, 1 μL upstream primers, 1 μL downstream primers, and 2 μL of the DNA sample. The PCR program started at 94°C for 5 min; each cycle consisted of denaturing at 94°C for 30 s, annealing at 55°C for 30 s, and elongation at 72°C for 35 s. A total of 35 cycles were completed. The amplification was completed with a final extension at 72°C for 7 min. Marker and DNA samples were loaded in a 2.0% agarose gel (1X TBE agarose powder, buf-

Table 1. General clinical and pathological characteristics in the control group and dyslipidemia group of IgAN patients

Parameter	Control	*Dyslipidemia*	t/X^2	*P*
Number	164	136		
Male/female	103/61	81/55	0.33	0.565
Age (year)	35.06±6.69	35.96±10.62	1.623	0.107
Smoking [n *(%)*]	4 (2.4)	48 (35.3)	56.01	*P* < 0.0001
Drinking [n *(%)*]	3 (1.8)	35 (25.7)	35.92	*P* < 0.0001
Height (cm)	162.08±6.90	165.34±8.16	-3.143	0.002
Weight (kg)	57.97±9.12	66.36±13.85	-5.078	*P* < 0.0001
BMI (kg/m^2)	23.03±2.92	24.05±3.40	-4.642	*P* < 0.0001
SBP (mmHg)	119.53±14.44	138.72±18.35	-8.309	*P* < 0.0001
DBP (mmHg)	72.53±11.34	85.72±12.04	-8.168	*P* < 0.0001
Pulse pressure (mmHg)	47.00±8.16	53.00±13.95	-3.713	*P* < 0.0001
BUN (mmol/L)	4.92±1.50	7.33±3.30	-6.626	*P* < 0.0001
Scr (umol/L)	82.00±32.91	138.42±92.13	-5.62	*P* < 0.0001
UA (umol/L)	340.24±96.15	443.03±135.96	-6.214	*P* < 0.0001
eGFR *(*ml/min/1.73 m^2*)*	96.78±38.09	69.02±38.51	5.54	*P* < 0.0001
Hb (g/L)	124.90±13.31	124.26±26.52	0.215	0.83
ALB (g/L)	39.33±5.10	34.93±8.30	4.52	*P* < 0.0001
24 h Upro (g)	0.92±1.04	2.48±2.04	-6.672	*P* < 0.0001
Hypertension [n *(%)*]	17 (10.4)	77 (56.6)	73.921	*P* < 0.0001
renal dysfunction [n *(%)*]	30 (18.3)	85 (62.5)	61.464	*P* < 0.0001
Urine protein				
< 1 g/d [n *(%)*]	125 (76.2)	31 (22.8)		
1-3.5 g/d [n *(%)*]	30 (18.3)	74 (55.4)		
> 3.5 g/d [n *(%)*]	9 (5.5)	31 (22.8)	85.488	*P* < 0.0001
Mesangial cell proliferation				
M0 [n *(%)*]	116 (85.3)	76 (55.9)		
M1 [n *(%)*]	48 (14.7)	60 (44.1)	7.115	0.008
Hyperplasia of capillaries.				
E0 [n *(%)*]	146 (89.0)	124 (91.2)		
E1 [n *(%)*]	18 (11.0)	12 (8.8)	0.383	0.536
Segmental glomerulosclerosis				
S0 [n *(%)*]	84 (51.2)	56 (41.2)		
S1 [n *(%)*]	80 (48.8)	80 (58.8)	3.013	0.083
IFTA				
T0 [n *(%)*]	134 (81.7)	72 (52.9)		
T1 [n *(%)*]	26 (15.9)	48 (35.3)		
T2 [n *(%)*]	4 (2.4)	16 (11.8)	30.049	*P* < 0.0001

24 h Upro, 24-hour urinary protein quantitative; ALB, albumin; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; IFTA, tubular atrophy/interstitial fibrosis; SBP, systolic blood pressure; Scr, serum creatinine; UA, uric acid.

fer and nucleic acid dye type I), and 1X TBE running buffer was used in the electrophoresis chamber. The run was approximately 30 to 40 min but was adjusted as needed, according to the distance traveled through the gel. A gel imaging system was used to capture images of the gel for analysis (electrophoresis gel of PCR products shown in **Figure 1**). All PCR products were sent to the Shanghai bioengineering company for direct sequencing to determi-

Table 2. Comparison of genotype and allele frequency between the control group and dyslipidemia group of IgAN patients

Group	n	Genotype			Allele	
		CC	CT	TT	C	T
IgAN	300	168 (56.0)	112 (37.3)	20 (6.7)	448 (74.7)	152 (25.3)
HWE (P)	0.82					
Dyslipidemia	136	62 (45.6)	60 (44.1)	14 (10.3)	184 (67.6)	88 (32.4)
Control group	164	106 (64.6)	52 (31.7)	6 (3.7)	264 (80.5)	64 (19.5)
χ^2		12.793			12.961	
P		0.002			*P* < 0.0001	

ne the genotypes (partial nucleotide sequences of the CC, CT and TT genotypes shown in **Figure 2**).

Statistical analysis

All statistical analyses were performed using SPSS, version 17.0 (SPSS, Chicago, IL, USA). Data with a normal distribution (i.e., data for most of the measurement variables) were presented as the mean ± standard deviation. Data with a non-normal distribution, such as serum TG levels, were presented as the median and quartile. Qualitative data (e.g., gender, smoking, drinking, pathological stages) were presented as percentages.

Clinical indicators in the dyslipidemia group versus the control group and blood lipid levels in the CC/CT genotype carriers versus the TT genotype carriers were compared by t-test. Pathological stages between the dyslipidemia group and the control group, and the genotype distribution between the CC/CT genotype carriers and the TT genotype carriers were analyzed using a Chi-square test. The association between genotypes and the Oxford pathological classification was evaluated by analysis of covariance (ANCOVA). Allele frequency was confirmed by direct counting, and the standard goodness-of-fit test was verified by the Hardy-Weinberg equilibrium (HWE). The correlation risk factors of dyslipidemia were analyzed using the binary non-conditional logistic regression method, and the influence of lipid level factors was analyzed by a multiple linear regression analysis. The level of statistical significance was set at $P < 0.05$.

Results

In this study population, the ratio of males to females was 1.59:1, the age (mean ± standard deviation) was 35.23± 11.72 years, and the levels of Scr and eGFR were 118.16±114.90 μmol/L and 84.09± 38.66 ml/min/1.73 m^2, respectively. Among the study participants, 94 (31.3%) had comorbid hypertension, and 115 (38.3%) had accompanying renal dysfunction. Regarding pathological features, 192 patients (64.0%) were in the M0 stage of mesangial cell hyperplasia, and 108 patients (36.0%) were in the M1 stage according to the Oxford classification. A total of 270 patients (90.0%) had capillaries in E0, and 30 (10.0%) had capillaries in E1. There were 164 patients (54.7%) with segmental glomeruli in the S0 stage and 136 in S1 (45.3%). As for IFTA, 206 patients (68.7%) were in T0, 74 patients (24.6%) were in T1 stage, and 20 patients (6.7%) were in T2 stage.

Comparison between the dyslipidemia group and the control group in general clinical and pathological indexes

As shown in **Table 1**, there was no significant difference in gender or age distribution between the dyslipidemia and the normal group ($P > 0.05$). The dyslipidemia group had significantly greater height, weight, body mass index (BMI), SBP, DBP, pulse pressure, blood urea nitrogen (BUN), Scr, uric acid (UA), 24-hour urinary protein quantitative (24 h Upro), ratio of hypertension, ratio of renal dysfunction, mesangial cell proliferation and IFTA compared with the control group in IgAN ($P < 0.05$). The eGFR and albumin (ALB) in the dyslipidemia group were significantly lower in the dyslipidemia group than in the control group ($P < 0.05$). There was no statistically significant difference between the 2 groups in hemoglobin, the degree of hyperplasia of capillaries, and focal segmental glomerulosclerosis ($P > 0.05$).

Comparison between the dyslipidemia group and the control group in genotypes and allele frequencies

As shown in **Table 2**, the genotype distribution and allele frequency for *CMIP* rs16955379 SNP were consistent with the HWE law ($P > 0.05$), indicating that the selected population was rep-

Table 3. Comparison of blood lipid levels between different allele carriers with IgAN

Genotype	N	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ApoB
IgAN								
CC+CT	280	5.12±2.31	1.10 (0.9)	1.29±0.46	3.01±1.96	1.30±0.55	0.76±0.51	1.70±0.67
TT	20	5.37±1.64	4.42 (3.5)	1.00±0.28	2.89±1.49	1.29±0.07	0.97±0.12	1.51±0.24
t/z		-0.54	-2.478	2.374	0.243	0.12	1.02	-0.707
P		0.596	0.033	0.019	0.808	0.905	0.31	0.481

ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HLD-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 4. Comparison of blood lipid levels in different alleles carriers in the control group versus the dyslipidemia group of IgAN patients

Genotype	N	TC (mmol/L)	TG (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	ApoA1 (g/L)	ApoB (g/L)	ApoA1/ApoB
IgAN/Control group								
CC+CT	158	4.55±0.74	0.855 (0.5)	1.45±0.42	2.62±0.59	1.41±0.66	0.74±0.10	1.74±0.70
TT	6	4.45±0.20	0.830 (0.3)	1.39±0.02	2.69±0.20	1.35±0.05	0.83±0.17	1.82±0.20
t/z		1.407	-1.129	0.243	-1.261	0.155	4.772	-1.098
P		0.162	0.233	0.809	0.21	0.877	*P* < 0.0001	0.275
IgAN/Dyslipidemia								
CC+CT	122	5.86±3.25	1.650 (2.0)	1.09±0.43	3.52±2.82	1.23±0.20	0.78±0.43	1.58±0.46
TT	14	5.60±1.78	4.865 (3.8)	0.91±0.22	3.94±1.67	1.13±0.07	1.18±0.30	1.15±0.10
t/z		0.272	-2.245	1.42	0.698	-2.765	0.95	-6.767
P		0.786	0.025	0.159	0.487	0.008	0.346	*P* < 0.0001

Table 5. The relationship between the different genotypes or alleles and the Oxford pathological classification in IgAN

Genotype/allele	M0 n *(%)*	M1 n *(%)*	E0 n *(%)*	E1 n *(%)*	S0 n *(%)*	S1 n *(%)*	T0 n *(%)*	T1 n *(%)*	T2 n *(%)*
CC	114 (67.1)	56 (32.9)	156 (91.8)	14 (8.2)	80 (47.1)	90 (52.9)	128 (75.3)	38 (22.4)	4 (2.3)
CT	72 (65.5)	38 (34.5)	98 (89.1)	12 (10.9)	46 (41.8)	64 (58.2)	76 (69.1)	22 (20.0)	12 (10.9)
TT	8 (40.0)	12 (60.0)	16 (80.0)	4 (20.0)	12 (60.0)	8 (40.0)	6 (30.0)	12 (60.0)	2 (10.0)
χ^2		5.781		2.497		2.429			23.978
P		0.056		0.287		0.297			*P* < 0.0001
CC+CT	186 (66.4)	94 (33.6)	256 (89.3)	26 (10.7)	126 (45.0)	154 (55.0)	204 (72.9)	60 (21.4)	16 (5.7)
TT	8 (40.0)	12 (60.0)	16 (80.0)	4 (20.0)	12 (60.0)	8 (40.0)	6 (30.0)	12 (60.0)	2 (10.0)
χ^2		5.583		1.370		1.691			17.041
P		0.018		0.242		0.193			*P* < 0.0001

resentative of the entire group and could be used for further statistical analysis. The frequencies of the C allele and T allele in patients with IgAN were 74.7% and 25.3% respectively; the frequencies of the CC, CT and TT genotypes were 56.0%, 37.3% and 6.7% respectively. The frequencies of the genotypes and alleles in the dyslipidemia group versus the control group were significantly different, and the frequencies of the TT genotype and the T allele in the dyslipidemia group were higher than they were in the control group ($P < 0.05$).

Relationship between alleles and blood lipid levels

As shown in **Tables 3** and **4**, in patients with IgAN, the TG level in the *CMIP* rs16955379 SNP TT genotype carriers was higher than in the CC/CT genotype carriers, but the level of

Table 6. Analysis of risk factors related to dyslipidemia in patients with IgAN

Risk factors	Dyslipidemia	
	OR (95% CI)	*P*
Age	1.473 (1.237-1.755)	*P* < 0.0001
Height	1.21 (1.11-1.31)	*P* < 0.0001
BMI		
< 24 kg/m^2	1	
≥ 24 kg/m^2	3.08 (1.31-7.28)	0.01
Smoking		
No	1	
Yes	15.57 (2.84-85.20)	0.002
Drinking		
No	1	
Yes	2.87 (0.06-0.12)	0.995
Hypertension		
No	1	
Yes	12.34 (3.86-39.48)	*P* < 0.0001
ALB	1.63 (1.28-2.07)	*P* < 0.0001
UA	1.018 (1.002-1.034)	0.024
Renal dysfunction		
No	1	
Yes	17.57 (5.98-51.62)	*P* < 0.0001
24 h Upro	7.57 (2.95-19.44)	*P* < 0.0001
Mesangial cell proliferation		
No	1	
Yes	33.39 (17.41-64.05)	*P* < 0.0001
Hyperplasia of capillaries.		
No	1	
Yes	0.067 (0.004-1.112)	0.059
Segmental glomerulosclerosis		
No	1	
Yes	17.78 (2.92-10.82)	0.002
Genotypes		
CC	1	
CT	3.619 (0.775-16.911)	0.102
TT	47.807 (3.440-664.4420)	0.004
C/not-C carrier		
CC+CT	1	
TT	46.25 (8.72-245.42)	*P* < 0.0001

OR and 95% CI were obtained from the unconditional logistic regression model after adjustment for age, gender, body mass index, smoking status, alcohol consumption, and hypertension. ALB, albumin; BMI, body mass index; CI, confidence interval; OR, odds ratio; UA, uric acid.

HDL-C in the TT genotype carriers was lower than in the CC/CT genotype carriers ($P < 0.05$). Within the dyslipidemia group, the TT genotype carriers had a higher level of TG and lower levels of ApoA1 and ApoA1/B compared with the CC/CT genotype carriers. In the control group, the levels of ApoB in the TT gene carriers were higher than in CC/CT genotype carriers ($P < 0.05$).

The correlation between genotype or allele and the Oxford pathological classification

As shown in **Table 5**, there was a statistically significant difference in the incidence of IFTA between the dyslipidemia and control groups in IgAN ($P < 0.05$). The percentages of mesangial cell proliferation and IFTA were different among the three genotypes. The proportion of patients with IFTA in T1 and T2 was significantly higher in the TT genotype carrier group versus the CC genotype group. The incidences of mesangial cell proliferation and IFTA were significantly higher in TT genotype carriers than in CC/CT genotypes carriers ($P < 0.05$, respectively). However, the proportions of patients with mesangial cell proliferation, capillary hyperplasia and segmental glomerular sclerosis lesions were not significantly different among the CC, CT and TT genotypes. There was also no statistical difference between TT and CC/CT genotypes carriers in the incidence of capillary proliferation, segmental glomerular sclerosis lesions ($P > 0.05$).

Analysis of risk factors related to dyslipidemia in patients with IgAN

As shown in **Table 6**, logistic regression analysis showed that patient age [odds ratio (OR) = 1.473, 95% CI = 1.237-1.755, $P < 0.0001$], smoking (OR = 15.57, 95% CI = 2.84-85.20, $P = 0.002$), height (OR = 1.21, 95% CI = 1.11-1.31, $P < 0.0001$), BMI greater than 24 kg/m^2 (OR = 3.08, 95% CI = 1.31-7.28, $P = 0.010$), high blood pressure (OR = 12.34, 95% CI = 3.86-39.48, $P < 0.0001$), 24-hour urinary protein level (OR = 7.57, 95% CI = 2.95-19.44, $P <$

Table 7. Relationship between dyslipidemia and relative factors in patients with IgAN

Lipid	Risk factor	B	Std.error	Beta	*t*	*P*
TC	Drinking	3.785	0.397	0.568	9.539	*P* < 0.0001
	UA	-0.006	0.001	-0.338	-4.724	*P* < 0.0001
	ALB	-0.119	0.026	-0.372	-4.612	*P* < 0.0001
	Age	-0.052	0.012	-0.269	-4.158	*P* < 0.0001
	BUN	0.366	0.096	0.400	3.803	*P* < 0.0001
	Scr	-0.012	0.003	-0.374	-3.532	0.001
	Mesangial cell proliferation	-0.797	0.239	-0.164	-3.331	0.001
	Smoking	-1.478	0.447	-0.249	-3.310	0.001
	DBP	0.045	0.015	0.262	3.013	0.003
	24 h Upro	0.300	0.119	0.162	2.534	0.012
	eGFR	-0.011	0.005	-0.184	-2.323	0.021
	Weight	0.271	0.123	1.408	2.213	0.028
	Segmental glomerulosclerosis	-0.521	0.242	-0.113	-2.157	0.032
	Hypertension	-1.436	0.711	-0.288	-2.020	0.045
TG	Drinking	2.368	0.276	0.509	8.586	*P* < 0.0001
	IFTA	1.199	0.179	0.416	6.681	*P* < 0.0001
	Smoking	-1.313	0.310	-0.317	-4.231	*P* < 0.0001
	Scr	-0.010	0.002	-0.446	-4.228	*P* < 0.0001
	TT Genotype	1.321	0.313	0.198	4.216	*P* < 0.0001
	ALB	0.073	0.018	0.326	4.057	*P* < 0.0001
	Urine protein	0.267	0.069	0.287	3.865	*P* < 0.0001
	Age	-0.033	0.009	-0.248	-3.857	*P* < 0.0001
	BUN	0.234	0.067	0.367	3.501	0.001
	Mesangial cell proliferation	0.512	0.166	0.151	3.081	0.002
	Height	-0.199	0.069	-0.945	-2.874	0.005
	Weight	0.230	0.085	1.709	2.697	0.008
	Renal dysfunction	0.630	0.234	0.191	2.689	0.008
	Hyperplasia of capillaries	-0.738	0.283	-0.133	-2.609	0.010
	eGFR	-0.008	0.003	-0.195	-2.477	0.014
	BMI	-0.491	0.233	-0.987	-2.114	0.036
HDL-C	Hyperplasia of capillaries.	0.899	0.097	0.571	9.250	*P* < 0.0001
	Mesangial cell proliferation	-0.316	0.057	-0.328	-5.523	*P* < 0.0001
	TT Genotype	-0.434	0.108	-0.229	-4.031	*P* < 0.0001
	BUN	0.073	0.023	0.405	3.183	0.002
	DBP	0.011	0.004	0.317	3.019	0.003
	Renal dysfunction	-0.232	0.081	-0.247	-2.873	0.005
	Smoking	-0.304	0.107	-0.259	-2.849	0.005
	UA	-0.001	0.000	-0.210	-2.431	0.016
	BMI	-0.169	0.080	-1.199	-2.117	0.036
	24 h Upro	-0.057	0.028	-0.155	-2.015	0.046
LDL-C	ALB	-0.142	0.024	-0.523	-5.988	*P* < 0.0001
	Drinking	1.789	0.366	0.315	4.890	*P* < 0.0001
	UA	-0.006	0.001	-0.365	-4.523	*P* < 0.0001
	IFTA	-0.718	0.238	-0.204	-3.021	0.003
	Mesangial cell proliferation	-0.598	0.220	-0.144	-2.711	0.007
	Age	-0.027	0.012	-0.164	-2.344	0.020
	24 h Upro	0.247	0.109	0.157	2.262	0.025
	Urine protein	-0.191	0.092	-0.169	-2.082	0.039
	Segmental glomerulosclerosis	-0.484	0.237	-0.123	-2.046	0.042
APOA1	Segmental glomerulosclerosis	-0.879	0.098	-0.804	-8.983	*P* < 0.0001

	eGFR	-0.014	0.002	-0.968	-8.961	$P < 0.0001$
	Renal dysfunction	-0.898	0.134	-0.806	-6.697	$P < 0.0001$
	DBP	0.034	0.005	0.918	6.341	$P < 0.0001$
	Genotypes	-0.559	0.091	-0.591	-6.138	$P < 0.0001$
	Hyperplasia of capillaries	0.668	0.140	0.348	4.759	$P < 0.0001$
	Rise of DBP	-1.282	0.314	-0.976	-4.077	$P < 0.0001$
	BMI	-0.480	0.131	-3.109	-3.670	$P < 0.0001$
	BUN	0.132	0.036	0.629	3.618	$P < 0.0001$
	UA	0.002	0.001	0.466	3.614	$P < 0.0001$
	Scr	-0.004	0.001	-0.586	-3.019	0.003
	Mesangial cell proliferation	-0.361	0.120	-0.320	-3.000	0.003
	Hypertension	1.318	0.451	1.117	2.920	0.004
	Height	-0.091	0.034	-1.145	-2.667	0.009
	Weight	0.116	0.048	2.538	2.396	0.018
	ALB	0.025	0.011	0.323	2.342	0.021
	Rise of SBP	-0.888	0.383	-0.719	-2.321	0.022
APOB	Drinking	0.577	0.078	0.391	7.446	$P < 0.0001$
	DBP	0.020	0.003	0.576	6.135	$P < 0.0001$
	Segmental glomerulosclerosis	-0.308	0.058	-0.306	-5.269	$P < 0.0001$
	IFTA	-0.330	0.065	-0.339	-5.053	$P < 0.0001$
	Rise of SBP	-1.137	0.228	-1.001	-4.979	$P < 0.0001$
	Renal dysfunction	0.393	0.080	0.383	4.909	$P < 0.0001$
	Mesangial cell proliferation	-0.323	0.072	-0.312	-4.501	$P < 0.0001$
	Pulse pressure	0.015	0.004	0.358	3.477	0.001
	Gender	-0.358	0.110	-0.352	-3.252	0.002
	BMI	0.348	0.110	0.320	3.149	0.002
	Hypertension	0.846	0.269	0.779	3.139	0.002
	24 h Upro	0.062	0.025	0.163	2.489	0.014
	Rise of DBP	-0.459	0.188	-0.379	-2.443	0.016
	Scr	-0.002	0.001	-0.296	-2.351	0.021
	Genotypes	-0.126	0.054	-0.144	-2.311	0.023
	BUN	0.047	0.022	0.243	2.151	0.034
APOA1/B	Hyperplasia of capillaries.	1.104	0.158	0.469	7.006	$P < 0.0001$
	Renal dysfunction	-0.978	0.151	-0.716	-6.497	$P < 0.0001$
	eGFR	-0.011	0.002	-0.596	-6.026	$P < 0.0001$
	Genotypes	-0.431	0.102	-0.371	-4.211	$P < 0.0001$
	24 h Upro	-0.189	0.047	-0.373	-4.029	$P < 0.0001$
	BUN	0.159	0.041	0.617	3.876	$P < 0.0001$
	Segmental glomerulosclerosis	-0.367	0.110	-0.274	-3.339	0.001
	ALB	0.036	0.012	0.387	3.064	0.003
	Scr	-0.004	0.001	-0.539	-3.034	0.003
	Rise of DBP	-0.990	0.353	-0.615	-2.805	0.006
	IFTA	0.334	0.123	0.258	2.721	0.008
	DBP	0.014	0.006	0.311	2.347	0.021
	Gender	0.453	0.207	0.334	2.185	0.031
	Mesangial cell proliferation	0.279	0.135	0.202	2.067	0.041
	Pulse pressure	-0.016	0.008	-0.293	-2.015	0.046

24 h Upro, 24-hour urinary protein quantitative; ALB, albumin; BMI, body mass index; BUN, blood urea nitrogen; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IFTA, tubular atrophy/interstitial fibrosis; SBP, systolic blood pressure; Scr, serum creatinine; UA, uric acid.

0.0001), renal dysfunction (OR = 17.57, 95% CI = 5.98-51.62, $P < 0.0001$), degree of mesangial proliferation (OR = 33.39, 95% CI = 17.41-64.05, $P < 0.0001$), and segmental glomerular sclerosis (OR = 17.78, 95% CI = 2.92-10.82, $P = 0.002$) were positively correlated with dyslipidemia in IgAN. In addition, patients carrying *CMIP* rs16955379 TT genotypes had an increased risk of dyslipidemia in IgAN, with a 46.25-fold higher risk of dyslipidemia in TT genotype carriers than in CC/CT genotype carriers with IgAN (OR = 46.25, 95% CI = 8.72-245.42, $P < 0.0001$) and a 47.807-fold higher risk of dyslipidemia versus CC genotype carriers in IgAN (OR = 47.807, 95% CI = 3.44-664.44, $P = 0.004$).

Influence of blood lipid profile in patients with IgAN

A multiple linear regression analysis showed that the levels of TG and HDL-C were significantly associated with the TT genotype of *CMIP* rs16955379 in patients with IgAN ($P < 0.05$, **Table 7**). The levels of ApoA1, ApoB, and ApoA1/B were related to the CC, CT, and TT genotypes, while the levels of TG and HDL-C were closely related to the TT genotype. TT genotype carriers had a higher risk of dyslipidemia (i.e., abnormal levels of TG and HDL-C) ($P < 0.05$). Furthermore, blood lipid levels in patients with IgAN were linearly correlated with smoking, drinking, blood pressure, BMI, renal dysfunction, and renal pathological stage ($P < 0.05$).

Discussion

Dyslipidemia is one of the most important risk factors in the development of atherosclerosis, coronary heart disease, hypertension, stroke, and other cardiovascular diseases. Cardiovascular diseases are a common cause of death in patients with chronic kidney disease (CKD) [26]. The overall prevalence of dyslipidemia in Chinese adults is about 41.9%, and dyslipidemia is more common in men than in women [27]. The prevalence of dyslipidemia in patients with CKD is 2 to 4 times greater than in the general population. Moreover, the prevalence of dyslipidemia in dialysis patients is over 60% [28]. In this study of 300 patients with IgAN, there were 136 cases of dyslipidemia and 164 cases with normal blood lipid. The prevalence of dyslipidemia was about 45.3%, and the prevalence in men was higher than in women. Therefore, an improvement of blood lipid levels in patients with dyslipidemia is beneficial in reducing the morbidity and mortality of cardiovascular events. Some studies have shown that the mechanism of dyslipidemia in IgAN may be related to the following factors: decreased plasma colloid osmotic pressure caused by hypoalbuminemia, which could stimulate the synthesis of LDL, lipoprotein, and apolipoprotein in the liver; excitement of the sympathetic nerve; enhanced activity of hormone-sensitive lipase (HSL) in adipocytes, leading to increased adipose mobilization; increased endotoxin; decreased activity of LPL; hepatic lipase (HL); reduced density of lipoprotein receptors, which can disturb the degradation of TG, and so on [29]. The presence of these factors may increase the incidence and mortality of cardiovascular accidents in patients with IgAN.

Dyslipidemia is considered an independent risk factor for CKD and is associated with a poor prognosis [30, 31]. Studies have shown that HDL-C and hypercholesterolemia are associated with an increased risk of proteinuria and that hypercholesterolemia plays an important role in reducing eGFR [32]. The risk of cardiovascular events increases by 30% when eGFR is reduced by 30% in patients with CKD [33]. In conclusion, the increase in TG and LDL-C, and the reduction of HDL-C are closely related to the progress of CKD [34-36]. A cohort study showed that eGFR tended to increase in patients treated with statins, and renal function was significantly improved [37]. A study in rats showed that atorvastatin can reduce the risk and the degree of renal function damage, proteinuria, and glomerular cell proliferation induced by bovine gamma globulin (BGG) [38]. In the current study, patients were divided into the dyslipidemia group and the control group. The dyslipidemia group had a lower level of eGFR, a higher level of Scr, and a higher incidence of renal dysfunction compared with the control group, which suggests a positive correlation between the incidence of dyslipidemia and renal dysfunction in patients with IgAN. Patients with both IgAN and dyslipidemia were more likely to suffer from renal dysfunction. Therefore, dyslipidemia in patients with IgAN alerts the clinician to the possibility of renal dysfunction, and measures to correct dyslipidemia and renal dysfunction should be pursued

as early as possible. The mechanism of dyslipidemia-induced renal dysfunction was hypothesized to be lipid nephrotoxicity more than 30 years ago. Proteinuria, low levels of ALB, and hyperlipidemia may lead to atherosclerotic glomerulosclerosis. In the early stage of glomerular injury, a series of lesions, such as inflammation, could increase the permeability of the glomerulus, and decrease the activity of lipoprotein lipase, resulting in hyperlipidemia. Charge affinity of cyclic LDL-C and the glycosaminoglycan in the glomerular basement membrane further enhance the permeability of the glomerular basement membrane. A large number of viral lipoproteins can stimulate the proliferation of glomerular mesangial cells. The proximal renal tubules reabsorb some of the filtered lipoproteins if the pH value in the proximal tubule is close to the isoelectric point of the apolipoprotein, and formation of the intracavitary apolipoprotein precipitate results in the development of renal tubular interstitial disease [39]. But opposite findings were reported in a Dutch study by Voskamp and colleagues [40], indicating that there was no significant correlation between dyslipidemia or lipid levels and renal replacement therapy or death in CKD patients.

In this study, the Oxford classification method of IgAN was used to compare the pathological stages. Prior studies have shown that the Oxford classification and MEST score may predict prognosis of at the early stage of IgAN [21]. In this study, comparisons of pathological types between the dyslipidemia group and control group in IgAN showed that the dyslipidemia group had a higher proportion of patients with mesenchymal cell proliferation and IFTA compared with the control group, suggesting that hyperlipidemia may further aggravate renal dysfunction. The pathological mechanism of lipid-initiated renal impairment may involve an increase in lipid in the endothelium, which causes the deposition and oxidation of LDL-C, a larger mononuclear macrophage infiltration lesion area, and greater cell formation in the lesion area. The proliferation of mesangial cells, the growth of the mesangial matrix, and renal tubular interstitial lesions are also involved in this process. It has been hypothesized that dyslipidemia can cause an excessive expression of fat cell factors, angiotensin, inflammation factors such as interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α), causing renal interstitial fibrosis [41]. Further study is needed to determine whether the pathological changes of mesangial cell proliferation, renal tubular atrophy, and interstitial fibrosis in patients with IgAN complicated with dyslipidemia are caused by the above mechanisms. In addition, studies have shown that renal interstitial fibrosis and IFTA are all related to a poor prognosis in IgAN [42]. Combined with findings from other studies, the results of our research support the idea that dyslipidemia may affect IgAN pathological types and can strongly influence mesangial cell proliferation and IFTA, which was one of the factors associated with disease progression and poor prognosis in IgAN.

IgAN has familial aggregation, with mostly autosomal dominant inheritance. Familial clustering accounts for 10%-15% of cases of IgAN. There is also racial diversity in IgAN. The incidence of IgAN is highest in Asians and Indians, followed by those of white European ethnicity; the lowest incidence of IgAN is in people of African ancestry [43, 44]. There are also geographic differences in IgAN prevalence. The incidence of IgAN in Asia is far higher than it is in North America, Europe and other regions and accounts for 30% to 50% of primary glomerular disease in that region. Studies have shown that Asian patients are more likely to progress to ESRD, the main primary glomerulonephrosis in that region [45]. Familial aggregation, ethnic diversity, and regional heterogeneity in IgAN suggest that genetic factors play a crucial role in the pathogenesis and progression of IgAN. A recent study showed close connections between the CMIP gene (c-Maf inducing protein, GeneID: ID80790, HGNC: 24319, MIM: 610112, Location: 16q23.2-q23.3, also known as TCMIP) and the level of blood lipids (eg, HDL-C), and the risk of type 2 diabetes mellitus (T2DM) and acute myocardial infarction (MI). The CMIP gene has also been associated with speech disorders in previous studies [46]. Research from Strawbridge and colleagues [47] has shown that CMIP, PLXND1, VEGFA and ZNRF3-KREMEN1 and gene loci related to the waist-hip ratio after adjusting for the body weight index (WHRadjBMI) are nominally associated with lipid solution, which regulates the spontaneity and/or stimulation of fat cells. These may be due to the influence on the NFκB

signal, the size of fat cell, and the Wnt signal. The CMIP gene is located on chromosome 16 at 16q23, which encodes the c-Maf inducible protein, which is a factor in the T cell signaling pathway. In addition, the CMIP gene can be encoded with the different subtypes *CMIP* rs2925979, *CMIP* rs3924153, *CMIP* rs16955379 and *CMIP* rs56823429 [48, 49]. A study from Japan showed that *CMIP* rs16955379 (C > T, 16q23.2) was associated with decreased HOMA-β and beta-cell function of insulin and increased fasting blood glucose [22]. In particular, the increase in fasting blood glucose in males with T2DM was associated with an increased risk of dyslipidemia, so this site may increase the risk of T2DM by affecting blood lipid and blood glucose levels. A case-control study of the Chinese Han population showed that those with *CMIP* rs16955379 had a lower genetic risk of T2DM, possibly due to its negative correlation between the red blood cell phospholipid alpha linolenic acid (ALA) and T2DM in that community. The interaction between those two factors may regulate the risk of T2DM in the Chinese population [50]. The current study builds on gene polymorphism, the genetic susceptibility of CMIP in IgAN, and related research in dyslipidemia, to elucidate the relationship between the *CMIP* rs 16955379 SNP and dyslipidemia in IgAN. An interesting finding of the study was that the TT genotype and T allele frequency in the dyslipidemia group were higher than in the control group with IgAN. Dyslipidemia in patients with IgAN who were TT genotype carriers had higher TG and lower ApoA1, ApoA1/B level versus CC/TT genotype carriers. A large number of studies has shown that low ApoA1, ApoA1/B levels and high ApoB levels are risk factors for atherosclerosis and stroke, suggesting an increased risk of adverse cardiovascular events [51, 52]. If the long-term disorder of lipid metabolism is not corrected, it will likely cause lipid deposition in the glomerular basement membrane and affect its permeability, which will aggravate renal arteriosclerosis and renal tubular interstitial disease. Our study found that carriers of the *CMIP* rs16955379 TT genotype in IgAN were prone to development of dyslipidemia, which was mainly shown in the reduced TG levels and ApoA1, ApoA1/B, and affected the progress and prognosis of IgAN. However, further study is needed to confirm whether the poor prognosis of TT genotype carriers in IgAN was due to lipid metabolic disorders increasing the risk of the occurrence of cardiovascular complications or whether it was due to dyslipidemia effects on the kidney itself.

Studies have shown that kidney pathological changes and the progression of IgAN are associated with gene polymorphisms, and the Oxford MEST of the various indicators of IgAN prognosis was different: IFTA were independent predictors of ESRD [53]. However, mesangial hyperplasia was associated with the acceptance of immunosuppressive agents in patients and was a weak prognostic indicator. The results of our study showed *CMIP* rs16955379 SNP was associated with the stage of mesangial proliferation and IFTA. Patients with IgAN who carried the TT genotype were more likely to have the M1 or T2 stage of mesangial proliferation and IFTA than patients in IgAN who carried the CC/CT genotypes. There may be a positive correlation between the *CMIP* rs16955379 TT genotype and the severity of the pathological type in IgAN. Patients with the TT genotype had more severe mesangial cell proliferation and IFTA, which could lead to further deterioration and progression of IgAN and a poorer outcome.

Dyslipidemia is mainly affected by the environment, blood glucose, genes, other factors, and/or interactions among those factors [54-56]. A cross-sectional study of gene loci in the Chinese population showed that 12 of the 25 loci that were analyzed were closely associated with abnormal blood lipid levels, indicating that genetic differences may influence susceptibility to abnormal lipid levels. Those study findings suggest that genetic mutations are very important to the occurrence of dyslipidemia [57]. The logistic regression analysis in this study suggests that the risk of dyslipidemia in TT genotype carriers with IgAN is 46.25 times higher than in CC/CT genotype carriers with IgAN. TT genotype carriers with IgAN have a higher risk of dyslipidemia compared with CC/CT genotype carriers with IgAN. Early intervention and management of blood lipids in TT genotype carriers with IgAN may reduce the incidence of adverse events caused by dyslipidemia, but a larger cohort study with long-term follow-up is required for confirmation. The results of linear regression analysis of different factors indicated that the *CMIP* rs16955379 SNP genotype and allele, blood pressure, BMI, renal dysfunction and pathological type all affect the risk of dys-

lipidemia in the patients with IgAN. The risk of dyslipidemia was increased with the presence of the TT gene, the elevation of blood pressure and BMI, renal dysfunction, and the stage of the Oxford classification. The multitude of factors that affect blood lipid levels, such as gene polymorphisms, blood pressure, renal function, and pathological type, may also affect the progress and prognosis of IgAN, but the interaction still needs to be confirmed.

Limitations

To be sure, there are some limitations in our research. First, our sample size was limited, and a larger sample size is needed to confirm our conclusion. Secondly, our study was a cross-sectional study that did not prospectively compare blood lipid results between cohorts and did not demonstrate the effects on long-term outcomes. Thirdly, the selected SNP site is only one of the CMIP genes and therefore does not represent all loci. Fourthly, we did not research diet in the study, so we could not eliminate the effects of diet on dyslipidemia. These limitations need to be addressed in future studies that include more SNP sites in the CMIP gene and the use of different genetic models.

Conclusion

Our study suggests that dyslipidemia can increase the risk of renal dysfunction and renal tubular atrophy/interstitial fibrosis in IgAN. The prevalence of dyslipidemia, renal dysfunction, and renal tubular and interstitial lesions in patients with the *CMIP* rs16955379 TT genotype were higher, indicating disease progression and a poor prognosis of IgAN. *CMIP* rs16955379 SNP is closely associated with serum lipid levels, dyslipidemia, renal dysfunction and tubular atrophy/interstitial fibrosis in IgAN.

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Disclosure of conflict of interest

None.

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References

[1] Fabiano RC, Pinheiro SV and Simões E Silva AC. Immunoglobulin A nephropathy: a pathophysiology view. Inflamm Res 2016; 65: 757-770.

[2] Al Hussain T, Hussein MH, Al Mana H, Akhtar M. Pathophysiology of IgA nephropathy. Adv Anat Pathol 2017; 24: 56-62.

[3] Zhou FD, Zhao MH, Zou WZ, Liu G and Wang H. The changing spectrum of primary glomerular diseases within 15 years: a survey of 3331 patients in a single Chinese centre. Nephrol Dial Transplant 2009; 24: 870-876.

[4] Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, Itabashi M, Takei T, Uchida K and Nitta K. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One 2014; 9: e91756.

[5] Hastings MC, Bursac Z, Julian BA, Villa Baca E, Featherston J, Woodford SY, Bailey L and Wyatt RJ. Life expectancy for patients from the southeastern united states with IgA nephropathy. Kidney Int Rep 2018; 3: 99-104.

[6] Magistroni R, D'Agati VD, Appel GB and Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. Kidney Int 2015; 88: 974-989.

[7] Wyatt RJ and Julian BA. IgA nephropathy. N Engl J Med 2013; 368: 2402-2414.

[8] Yeo SC, Liu X and Liew A. Complement factor H Gene polymorphism rs6677604 and the risk, severity and progression of IgA nephropathy: a systematic review and meta-analysis. Nephrology (Carlton) 2017; [Epub ahead of print].

[9] Zhang L, Li ZH, Yin Y, Duan CR, Xun M, Wu TH, Zhang Y and Ding YF. Clinical characteristics of children with an initial onset of IgA nephropathy with nephrotic syndrome. Zhongguo Dang Dai Er Ke Za Zhi 2015; 17: 786-791.

[10] Syrjanen J, Mustonen J and Pasternack A. Hypertriglyceridaemia and hyperuricaemia are risk factors for progression of IgA nephropathy. Nephrol Dial Transplant 2000; 15: 34-42.

[11] Jia X, Pan X, Xie J, Shen P, Wang Z, Li Y, Wang W and Chen N. The importance of sensitive screening for abnormal glucose metabolism in

patients with IgA nephropathy. Clin Nephrol 2016; 85: 30-37.
[12] Aulchenko YS, Ripatti S, Lindqvist I, Boomsma D, Heid IM, Pramstaller PP, Penninx BW, Janssens AC, Wilson JF, Spector T, Martin NG, Pedersen NL, Kyvik KO, Kaprio J, Hofman A, Freimer NB, Jarvelin MR, Gyllensten U, Campbell H, Rudan I, Johansson A, Marroni F, Hayward C, Vitart V, Jonasson I, Pattaro C, Wright A, Hastie N, Pichler I, Hicks AA, Falchi M, Willemsen G, Hottenga JJ, de Geus EJ, Montgomery GW, Whitfield J, Magnusson P, Saharinen J, Perola M, Silander K, Isaacs A, Sijbrands EJ, Uitterlinden AG, Witteman JC, Oostra BA, Elliott P, Ruokonen A, Sabatti C, Gieger C, Meitinger T, Kronenberg F, Döring A, Wichmann HE, Smit JH, McCarthy MI, van Duijn CM, Peltonen L; ENGAGE Consortium. Loci influencing lipid levels and coronary heart disease risk in 16 European population cohorts. Nat Genet 2009; 41: 47-55.
[13] Soares MF. An update on pathology of IgA nephropathy. J Bras Nefrol 2016; 38: 435-440.
[14] Roberts IS. Pathology of IgA nephropathy. Nat Rev Nephrol 2014; 10: 445-454.
[15] Pan L, Yang Z, Wu Y, Yin RX, Liao Y, Wang J, Gao B, Zhang L; China National Survey of Chronic Kidney Disease Working Group. The prevalence, awareness, treatment and control of dyslipidemia among adults in China. Atherosclerosis 2016; 248: 2-9.
[16] Gu W, Liu J, Wang Z, Liu Y and Wen S. ADRB2 polymorphisms and dyslipidemia risk in Chinese hypertensive patients. Clin Exp Hypertens 2017; 39: 139-144.
[17] Joint Committee for Developing Chinese guidelines on Prevention and Treatment of Dyslipidemia in Adults. Chinese guidelines on prevention and treatment of dyslipidemia in adults. Zhonghua Xin Xue Guan Bing Za Zhi 2007; 35: 390-419.
[18] Delgado J, Jacobs EA, Lackland DT, Evans DA and de Leon CF. Differences in blood pressure control in a large population-based sample of older African Americans and non-Hispanic whites. J Gerontol A Biol Sci Med Sci 2012; 67: 1253-1258.
[19] Borden WB, Maddox TM, Tang F, Rumsfeld JS, Oetgen WJ, Mullen JB, Spinler SA, Peterson ED and Masoudi FA. Impact of the 2014 expert panel recommendations for management of high blood pressure on contemporary cardiovascular practice: insights from the NCDR PINNACLE registry. J Am Coll Cardiol 2014; 64: 2196-2203.
[20] Shin DH, Lim BJ, Han IM, Han SG, Kwon YE, Park KS, Lee MJ, Oh HJ, Park JT, Han SH, Kang SW and Yoo TH. Glomerular IgG deposition predicts renal outcome in patients with IgA nephropathy. Mod Pathol 2016; 29: 743-752.
[21] Barbour SJ, Espino-Hernandez G, Reich HN, Coppo R, Roberts IS, Feehally J, Herzenberg AM, Cattran DC; Oxford Derivation, North American Validation and VALIGA Consortia; Oxford Derivation North American Validation and VALIGA Consortia. The MEST score provides earlier risk prediction in IgA nephropathy. Kidney Int 2016; 89: 167-175.
[22] Sakai K, Imamura M, Tanaka Y, Iwata M, Hirose H, Kaku K, Maegawa H, Watada H, Tobe K, Kashiwagi A, Kawamori R and Maeda S. Replication study for the association of 9 east Asian GWAS-derived loci with susceptibility to type 2 diabetes in a Japanese population. PLoS One 2013; 8: e76317.
[23] Aung LH, Yin RX, Wu DF, Cao XL, Hu XJ and Miao L. Proprotein convertase subtilisin/kexin type 9 gene E670G polymorphism interacts with alcohol consumption to modulate serum lipid levels. Int J Med Sci 2013; 10: 124.
[24] Zhang QH, Yin RX, Gao H, Huang F, Wu JZ, Pan SL, Lin WX and Yang DZ. Association of the SPTLC3 rs364585 polymorphism and serum lipid profiles in two Chinese ethnic groups. Lipids Health Dis 2017; 16: 1.
[25] Sun JQ, Yin RX, Shi GY, Shen SW, Chen X, Yuan B, Huang F, Wang W, Lin WX and Pan SL. Association of the ARL15 rs6450176 SNP and serum lipid levels in the Jing and Han populations. Int J Clin Exp Pathol 2015; 8: 12977-12994.
[26] Kuwahara M, Takehara E, Sasaki Y, Azetsu H, Kusaka K, Shikuma S and Akita W. Effects of cardiovascular events on end-stage renal disease and mortality in patients with chronic kidney disease before dialysis. Ther Apher Dial 2016; 20: 12-19.
[27] Huang Y, Gao L, Xie X and Tan SC. Epidemiology of dyslipidemia in Chinese adults: meta-analysis of prevalence, awareness, treatment, and control. Popul Health Metr 2014; 12: 28.
[28] Khurana M and Silverstein DM. Etiology and management of dyslipidemia in children with chronic kidney disease and end-stage renal disease. Pediatr Nephrol 2015; 30: 2073-2084.
[29] Hopewell JC, Haynes R and Baigent C. The role of lipoprotein(a) in chronic kidney disease. J Lipid Res 2018; 59: 577-585.
[30] Yang YR, Lv JC, Jiang L, Zhang YM, Song YH, Li RS and Zhang H. Clinicopathologic characteristics and outcomes of IgA nephropathy in elder patients. Beijing Da Xue Xue Bao Yi Xue Ban 2008; 40: 401-404.
[31] Kimura G, Kasahara M, Ueshima K, Tanaka S, Yasuno S, Fujimoto A, Sato T, Imamoto M, Ko-

sugi S and Nakao K. Effects of atorvastatin on renal function in patients with dyslipidemia and chronic kidney disease: assessment of clinical usefulness in CKD patients with atorvastatin (ASUCA) trial. Clin Exp Nephrol 2017; 21: 417-424.

[32] Liu DW, Wan J, Liu ZS, Wang P, Cheng GY and Shi XZ. Association between dyslipidemia and chronic kidney disease: a cross-sectional study in the middle-aged and elderly Chinese population. Chin Med J (Engl) 2013; 126: 1207-1212.

[33] Mafham M, Emberson J, Landray MJ, Wen CP and Baigent C. Estimated glomerular filtration rate and the risk of major vascular events and all-cause mortality: a meta-analysis. PLoS One 2011; 6: e25920.

[34] Zhang L, Li J, Yang S, Huang N, Zhou Q, Yang Q and Yu X. Clinicopathological features and risk factors analysis of IgA nephropathy associated with acute kidney injury. Ren Fail 2016; 38: 799-805.

[35] Homma K, Homma Y, Yamaguchi S, Shiina Y, Wakino S, Hayashi K, Hori S and Itoh H. Triglyceride-rich lipoproteins in chronic kidney disease patients undergoing maintenance haemodialysis treatment. Int J Clin Pract 2012; 66: 394-398.

[36] Chen SC, Hung CC, Kuo MC, Lee JJ, Chiu YW, Chang JM, Hwang SJ and Chen HC. Association of dyslipidemia with renal outcomes in chronic kidney disease. PLoS One 2013; 8: e55643.

[37] Moriyama T, Oshima Y, Tanaka K, Iwasaki C, Ochi A, Itabashi M, Takei T, Uchida K and Nitta K. Statins stabilize the renal function of IgA nephropathy. Ren Fail 2014; 36: 356-360.

[38] Katzir Z, Leibovitch E, Vaknin H, Schreiber L, Berger E, Matas Z, Fux A, Boaz M, Briliant A and Biro A. Effect of atorvastatin on IgA nephropathy in the rat. Clin Nephrol 2013; 79: 214-220.

[39] Gyebi L, Soltani Z and Reisin E. Lipid nephrotoxicity: new concept for an old disease. Curr Hypertens Rep 2012; 14: 177-181.

[40] Voskamp PW, van Diepen M, Dekker FW and Hoogeveen EK. Dyslipidemia and risk of renal replacement therapy or death in incident predialysis patients. Sci Rep 2018; 8: 3130.

[41] Singh AK and Kari JA. Metabolic syndrome and chronic kidney disease. Curr Opin Nephrol Hypertens 2013; 22: 198-203.

[42] Liu LS; Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. 2010 Chinese guidelines for the management of hypertension. Zhonghua Xin Xue Guan Bing Za Zhi 2011; 39: 579-615.

[43] Moriyama T, Suzuki K, Sugiura H, Itabashi M, Tsukada M, Takei T, Koike M, Uchida K, Horita S and Taneda S. Frequency of renal disease in Japan: an analysis of 2,404 renal biopsies at a single center. Nephron Clin Prac 2010; 115: c227-c236.

[44] Gutiérrez E, Zamora I, Ballarín JA, Arce Y, Jiménez S, Quereda C, Olea T, Martínez-Ara J, Segarra A and Bernis C. Long-term outcomes of IgA nephropathy presenting with minimal or no proteinuria. J Am Soc Nephrol 2012; 23: 1753.

[45] Barbour SJ, Cattran DC, Kim SJ, Levin A, Wald R, Hladunewich MA and Reich HN. Individuals of Pacific Asian origin with IgA nephropathy have an increased risk of progression to end-stage renal disease. Kidney Int 2013; 84: 1017-1024.

[46] Newbury DF and Monaco AP. Genetic advances in the study of speech and language disorders. Neuron 2010; 68: 309-320.

[47] Strawbridge RJ, Laumen H, Hamsten A, Breier M, Grallert H, Hauner H, Arner P and Dahlman I. Effects of genetic loci associated with central obesity on adipocyte lipolysis. PLoS One 2016; 11: e0153990.

[48] Sendeyo K, Audard V, Zhang SY, Fan Q, Bouachi K, Ollero M, Rucker-Martin C, Gouadon E, Desvaux D, Bridoux F, Guellaen G, Ronco P, Lang P, Pawlak A and Sahali D. Upregulation of c-mip is closely related to podocyte dysfunction in membranous nephropathy. Kidney Int 2013; 83: 414-425.

[49] Ory V, Fan Q, Hamdaoui N, Zhang SY, Desvaux D, Audard V, Candelier M, Noel LH, Lang P, Guellaen G, Pawlak A and Sahali D. c-mip down-regulates NF-kappaB activity and promotes apoptosis in podocytes. Am J Pathol 2012; 180: 2284-2292.

[50] Zheng JS, Li K, Huang T, Chen Y, Xie H, Xu D, Sun J and Li D. Genetic risk score of nine type 2 diabetes risk variants that interact with erythrocyte phospholipid alpha-linolenic acid for type 2 diabetes in Chinese Hans: a case-control study. Nutrients 2017; 9.

[51] Dong H, Chen W, Wang X, Pi F, Wu Y, Pang S, Xie Y, Xia F and Zhang Q. Apolipoprotein A1, B levels, and their ratio and the risk of a first stroke: a meta-analysis and case-control study. Metab Brain Dis 2015; 30: 1319-1330.

[52] Mashayekhi NR, Sadrnia S, Chehrei A and Javaheri J. The correlation between serum ApoA1 and B and coronary artery disease as well as its severity. Int Cardiovasc Res J 2014; 8: 1-5.

[53] Zhu X, Li H, Liu Y, You J, Qu Z, Yuan S, Peng Y, Liu F and Liu H. Tubular atrophy/interstitial fibrosis scores of Oxford classification combined with proteinuria level at biopsy provides earlier risk prediction in IgA nephropathy. Sci Rep 2017; 7: 1100.

[54] Waterworth DM, Ricketts SL, Song K, Chen L, Zhao JH, Ripatti S, Aulchenko YS, Zhang W,

Yuan X, Lim N, Luan J, Ashford S, Wheeler E, Young EH, Hadley D, Thompson JR, Braund PS, Johnson T, Struchalin M, Surakka I, Luben R, Khaw KT, Rodwell SA, Loos RJ, Boekholdt SM, Inouye M, Deloukas P, Elliott P, Schlessinger D, Sanna S, Scuteri A, Jackson A, Mohlke KL, Tuomilehto J, Roberts R, Stewart A, Kesäniemi YA, Mahley RW, Grundy SM; Wellcome Trust Case Control Consortium, McArdle W, Cardon L, Waeber G, Vollenweider P, Chambers JC, Boehnke M, Abecasis GR, Salomaa V, Järvelin MR, Ruokonen A, Barroso I, Epstein SE, Hakonarson HH, Rader DJ, Reilly MP, Witteman JC, Hall AS, Samani NJ, Strachan DP, Barter P, van Duijn CM, Kooner JS, Peltonen L, Wareham NJ, McPherson R, Mooser V and Sandhu MS. Genetic variants influencing circulating lipid levels and risk of coronary artery disease. Arterioscler Thromb Vasc Biol 2010; 30: 2264-2276.

[55] Samson SL and Garber AJ. Metabolic syndrome. Endocrinol Metab Clin North Am 2014; 43: 1-23.

[56] Tan A, Sun J, Xia N, Qin X, Hu Y, Zhang S, Tao S, Gao Y, Yang X, Zhang H, Kim ST, Peng T, Lin X, Li L, Mo L, Liang Z, Shi D, Huang Z, Huang X, Liu M, Ding Q, Trent JM, Zheng SL, Mo Z and Xu J. A genome-wide association and gene-environment interaction study for serum triglycerides levels in a healthy Chinese male population. Hum Mol Genet 2012; 21: 1658-1664.

[57] Luo H, Zhang X, Shuai P, Miao Y, Ye Z and Lin Y. Genetic variants influencing lipid levels and risk of dyslipidemia in Chinese population. J Genet 2017; 96: 985-992.

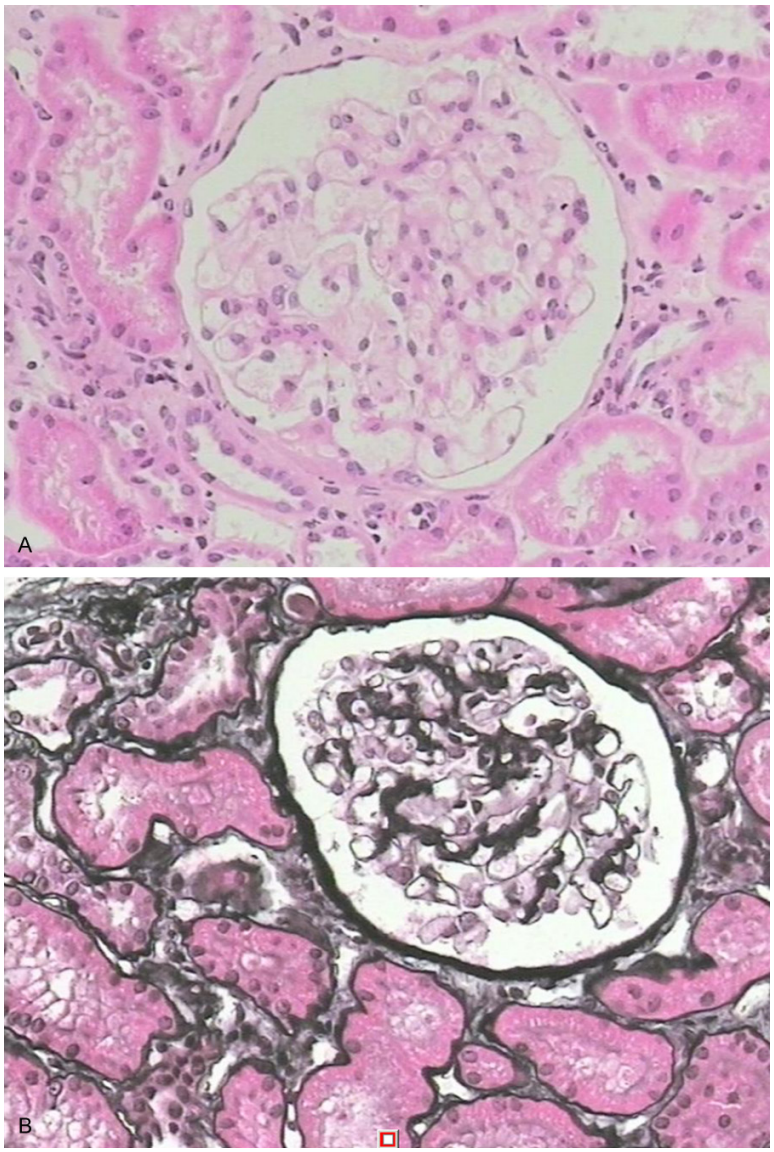

Figure S1. A and B. Light microscopy of renal tissues in IgAN patients. The deposition of IgA or IgA on immunoglobulin and its complement in the glomerular mesangial area, glomerular mesangial cell proliferation, and mesangial matrix gathering.