Research Article

Association between the *ACYP2* Polymorphisms and IgAN Risk in the Chinese Han Population

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Keywords

IgA nephropathy · *ACYP2* · Polymorphisms · Case-control study · Chinese Han

Abstract

Background/Aims: The association between *ACYP2* (Acylphosphatase 2) polymorphisms and immunoglobulin A nephropathy (IgAN) risk in the Chinese Han population remains unclear. We aimed to evaluate the association between *ACYP2* polymorphisms and IgAN risk by performing a case-control study. **Methods:** Eleven *ACYP2* single nucleotide polymorphisms (SNPs) from 416 IgAN patients and 495 healthy controls were genotyped using the Sequenom MassARRAY platform. Odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the association of *ACYP2* polymorphisms with IgAN risk. **Results:** We observed that rs843720 was significantly associated with an increased risk of IgAN (allele G: OR = 1.23, 95% CI: 1.01–1.49, $p = 0.036$; dominant model: OR = 1.55, 95% CI: 1.01–2.37, $p = 0.044$; log-additive model: OR = 1.43, 95% CI: 1.04–1.95, $p = 0.026$) before Bonferroni correction. The SNP rs12615793 was also significantly associated with an increased IgAN risk in the recessive model (OR = 3.33, 95% CI: 1.05–10.51, $p = 0.042$) before Bonferroni correction. **Conclusion:** These findings suggested that polymorphisms (rs843720 and rs12615793) of *ACYP2* may be pivotal in the development of IgAN. However, more functional and association studies with larger sample sizes should be performed to further validate our results in the future.

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Introduction

The immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis in the world and is characterized by the excessive deposition of IgAN in the mesangial area of glomeruli leading to mesangial proliferation and chronic glomerular inflammation [1, 2]. Previous studies have shown that about 30% of IgAN patients will progress to end-stage renal disease within 20–25 years of disease onset [3]. Poor prognostic factors for progression of renal damage in patients with IgAN include gender, older age, hypertension, severe proteinuria, renal lesions, and advanced histological involvement [4]. Furthermore, a family history of chronic nephritis, susceptibility to the common cold, preference for salty foods, frequent consumption of raw eggs, and a high intake of carbohydrates are significantly associated with increased IgAN risk [5]. To date, the exact pathogenesis of IgAN remains unclear. However, increasing lines of evidences have suggested the involvement of genetic factors in the pathogenesis of IgAN and variation in clinical manifestation. Evidence derived from experimental models of spontaneous IgAN and studies of the genetics, familial clustering, ethnic and geographic differences in prevalence support the influence of genetic factors in the development and progression of IgAN [6–9]. Previous studies have identified multiple susceptibility polymorphisms for the risk of IgAN [10–13]. Therefore, identifying genes associated with susceptibility to IgAN is particularly important and might provide a genetic target for therapeutic intervention in IgAN.

ACYP2 (Acylphosphatase 2) encodes a small cytosolic enzyme acylphosphatase (11 kDa) that can hydrolyze the phosphoenzyme intermediate of different membrane pumps, particularly the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase from sarcoplasmic reticulum of skeletal muscle [14]. These enzymes can adjust the stability of the inner environment through calcium ion transport [15]. Polak-Jonkisz et al. [16] found that the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase activity is reduced, and Ca^{2+} homeostasis is disturbed in children with chronic kidney disease. Moreover, it also exacerbates renal function deterioration. In addition, a genome-wide association study found that rs11125529 in *ACYP2* is significantly associated with telomere length [17]. Accumulating evidence prompts the view that telomere length is an indicator for organismal aging. To our best knowledge, aging is one of the contributing risk factors for kidney diseases. It was reported that telomere shortening is associated with human IgAN [18, 19]. Some association studies have demonstrated that polymorphisms in *ACYP2* are associated with the susceptibility to many diseases, such as high-altitude pulmonary edema [20], breast cancer [21], lung cancer [22], gastric cancer [23], and ischemic stroke [24].

However, to our knowledge, there are no reported studies of the association between *ACYP2* polymorphisms and the risk of IgAN among the Chinese Han population. We hypothesized that polymorphisms in *ACYP2* are associated with the risk of IgAN. To test this hypothesis, therefore, we conducted a case-control association study to evaluate the association between the *ACYP2* polymorphisms and IgAN risk in the Chinese Han population.

Materials and Methods

Subjects

In this study, 416 patients diagnosed with IgAN by renal biopsy were enrolled from the First Affiliated Hospital of Xi'an Jiaotong University. 495 unrelated healthy controls were randomly selected from those who went to the aforementioned hospital for medical examination during the same period. Renal biopsy pathological diagnostic criteria established by Zou (2011) were used as diagnostic criteria for IgAN. All the selected individuals are ethnic Han Chinese with no genetic relationship and their ancestors had lived in the region for at

Table 1. The primer sequences for genotyping SNPs in *ACYP2*

SNP-ID	2nd-PCR	1st-PCR	UEP-SEQ
rs6713088	ACGTTGGATGGTCACCAAAACACGTAATG	ACGTTGGATGACACACAGACTCCTTCAC	gaggcCAGAATGGTCCACTAGAGA
rs12621038	ACGTTGGATGGGCATAAGTTTATTGCCTC	ACGTTGGATGATTGTGCTAGGCACCTTAGG	ccATTGCCTCAGCTAGACT
rs1682111	ACGTTGGATGGCCAGTGGGAATGCAAAATG	ACGTTGGATGGAATTGCTGGGTATTGTC	tgctATGCAAAATGAAACAGACACTT
rs843752	ACGTTGGATGGAGACAACATAATGGAGGTC	ACGTTGGATGTCCTCTTTTCAGAAACCTGC	cGAGTTTGGGTTTGAGGT
rs843645	ACGTTGGATGACAGTGCCTTTAGCAAGGTG	ACGTTGGATGGAATCTGAATACACCTAC	TCATAGGCACTACTGTATC
rs11125529	ACGTTGGATGCCGAAGAAAAGAAGATGAC	ACGTTGGATGGAGCTTAGTTGTTACAGATG	AGAAAAGAAGATGACTAAACAT
rs12615793	ACGTTGGATGATCTTGGCCCTTGAAGAA	ACGTTGGATGTTTGAGCTTAGTTGTTAC	AAATTGAGTGACAAATATAAATAC
rs843711	ACGTTGGATGTGCCTTGTGGGAATTAGAGC	ACGTTGGATGGACAAAGGACCTTACAATC	gggaTCAGGGAACAGTGCAAA
rs11896604	ACGTTGGATGTGTCTCTGACCTAGCATGTA	ACGTTGGATGAAGTCAGAATAGTGCTTAC	GTTAAGCTTGCAAGGAG
rs17045754	ACGTTGGATGGAAATCAGGGATATTAGTGC	ACGTTGGATGCTGTAAAGTTCTGGCATGG	caggTATTACAGTTCCTAGAGTTA
rs843720	ACGTTGGATGAGTCAGAGCTAGACCTCTGG	ACGTTGGATGCTTCACAACTCCTGTAAG	ccccAATCTGTCTCAGGCTCTT

SNP, single nucleotide polymorphism; PCR, polymerase chain reaction primer; UEP, unique base extension primer. Sequences are written in the 5' → 3' (left to right) orientation.

least three generations. Patients with Henoch-Schönlein purpura, systemic lupus erythematosus, allergic purpura, chronic liver diseases, ankylosing spondylitis renal damage, and other secondary IgAN were excluded through detailed clinical and laboratory examinations. The patients were recruited without age, sex, or disease stage restriction.

DNA Extraction

A 5-mL sample of peripheral venous blood was collected in EDTA vacutainer tube from each participant on an empty stomach in the morning and then placed at –80 °C for cryo-preservation. Genomic DNA was isolated from whole blood using the GoldMag DNA Purification Kit (GoldMag Co. Ltd., Xi'an, China) according to the manufacturer's protocol and preserved at –20 °C [25]. The extracted DNA was assessed for concentration and purity utilizing an ultraviolet spectrophotometer (NanoDrop 2000; Thermo Fisher Scientific, Waltham, MA, USA) [26]. The purity was monitored by the $(OD_{260}-OD_{320})/(OD_{280}-OD_{320})$ ratio. The DNA concentration was diluted to 10 ng/μL for polymerase chain reaction amplification.

Single Nucleotide Polymorphism Selection and Genotyping

Eleven single nucleotide polymorphisms (SNPs; rs6713088, rs12621038, rs1682111, rs843752, rs843645, rs11125529, rs12615793, rs843711, rs11896604, rs17045754, and rs843720) in the *ACYP2* gene with minor allele frequency >0.05 in the Chinese Han Beijing population from the HapMap database and previously reported [20–24] were selected for analysis in our study. The primers of SNPs were designed by the Sequenom MassARRAY Assay Design 3.0 Software (Sequenom, San Diego, CA, USA). The sequences of primers corresponding to each SNP are shown in Table 1. Genotyping of the 11 SNPs were conducted using the Sequenom MassARRAY platform (Sequenom) according to the standard protocol recommended by the manufacturer [27]. Sequenom Typer 4.0 software was used for data management and analysis.

Statistical Analysis

Whether the genotype frequency distribution of control was consistent with Hardy-Weinberg equilibrium was estimated using the χ^2 test. The difference in the distribution of allele frequencies between cases and controls were compared by the χ^2 test, and the odds ratio (OR) and 95% confidence interval (CI) indicated relative risk. Genetic model and haplotype analyses were applied using unconditional multivariate logistic regression analysis

Table 2. Basic characteristic of cases and controls in this study

Variables	Cases	Controls	<i>p</i> value
Total	416	495	
Gender			<0.001
Female	145 (34.9)	315 (63.6)	
Male	271 (65.1)	180 (36.4)	
Age, years	33.35±12.13	54.48±9.44	<0.001

Data are presented as *n* (%) or mean ± SD. *p* values were calculated using Pearson's χ^2 test for gender and Student's *t* test for age. *p* < 0.05 indicates statistical significance.

to evaluate the correlation between polymorphisms and IgAN risk. Moreover, we performed Bonferroni correction to eliminate the probability of false-positive findings in the genetic model analyses. Pairwise linkage disequilibrium (LD) between each SNP, quantified as D' and r^2 , was measured by the Haploview software version 4.2 (Broad Institute, Cambridge, MA, USA). The Haploview software was used to test the association between statistically inferred haplotypes and IgAN risk. All statistical analyses were performed with Microsoft Excel (Microsoft Corp., Redmond, WA, USA) and Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA). *p* value <0.05 was considered to indicate that a difference was statistically significant, and all statistical tests were two-sided at a test level of $\alpha = 0.05$. Besides, the *p* value <0.004 (0.05/11) indicates statistical significance after Bonferroni correction.

Results

Characteristics of Subjects

The characteristics of cases and controls enrolled in this study are shown Table 2. This study recruited 911 subjects, including 416 IgAN patients (145 females and 271 males) and 495 healthy controls (315 females and 180 males). There was a significant difference between the case and control groups with respect to gender distribution (*p* < 0.05). The average age of IgAN patients was 33.35 ± 12.13 years compared with 54.48 ± 9.44 years in controls, which also showed statistically significant difference (*p* < 0.05). In order to eliminate those residual confounding effects, the variables of age and gender were adjusted in later multivariate unconditional logistic regression analysis.

Allele Distributions of ACYP2 Polymorphisms

The allele distribution of the selected SNPs in cases and controls is shown in Table 3. The genotypic distribution of all SNPs in the control group conformed to Hardy-Weinberg equilibrium (*p* > 0.05). We found that the frequency of rs843720 G allele in cases (38.5%) was higher than in the controls (33.7%), and the G allele of rs843720 was significantly associated with an increased the risk of IgAN (OR = 1.23, 95% CI: 1.01–1.49, *p* = 0.036). However, there was no significant difference in other allele distributions of ACYP2 polymorphisms between IgAN patients and controls.

Genetic Model Analyses

Genetic model analysis indicated that the AA genotype of rs12615793 was significantly associated with an increased risk of IgAN, compared to the GG and AG genotypes (adjusted

Table 3. Allele distribution of *ACYP2* polymorphisms and association with IgAN risk

SNP-ID	Position	Band	Alleles A/B	Role	HWE- <i>p</i>	Case (MAF)	Control (MAF)	ORs	95% CI	<i>p</i>
rs6713088	54345469	2p16.2	G/C	Intron	0.778	0.409	0.397	1.05	0.87–1.27	0.606
rs12621038	54391113	2p16.2	T/C	Intron	0.786	0.449	0.457	0.97	0.80–1.16	0.715
rs1682111	54427979	2p16.2	A/T	Intron	0.832	0.323	0.303	1.10	0.90–1.34	0.362
rs843752	54446587	2p16.2	G/T	Intron	0.569	0.263	0.269	0.97	0.79–1.20	0.793
rs843645	54474664	2p16.2	G/T	Downstream	1.000	0.246	0.261	0.93	0.75–1.15	0.488
rs11125529	54475866	2p16.2	A/C	Downstream	0.092	0.195	0.180	1.10	0.87–1.40	0.416
rs12615793	54475914	2p16.2	A/G	Downstream	0.242	0.212	0.191	1.13	0.90–1.43	0.283
rs843711	54479117	2p16.2	C/T	Downstream	0.124	0.460	0.454	1.03	0.85–1.24	0.778
rs11896604	54479199	2p16.2	G/C	Downstream	0.249	0.214	0.194	1.13	0.90–1.42	0.290
rs17045754	54496757	2p16.2	C/G	Intron	0.297	0.197	0.185	1.08	0.86–1.37	0.507
rs843720	54510660	2p16.2	G/T	Intron	0.422	0.385	0.337	1.23	1.01–1.49	0.036

SNP, single nucleotide polymorphism; A, minor alleles; B, major alleles; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; OR, odds ratio; 95% CI: 95% confidence interval. *p* < 0.05 indicates statistical significance. *p* value < 0.004 (0.05/11) indicates statistical significance after Bonferroni correction.

Fig. 1. Haplotype block map for the eleven SNPs in *ACYP2*. The LD between each pair of SNPs is standardized *D'*, bright red corresponding to very strong LD, white corresponding to no LD, and pink corresponding to intermediate LD.

Table 4. Genetic model analyses of the association between *ACYP2* polymorphisms and IgAN risk

SNP-ID	Model	Genotype	Case, %	Control, %	Without adjustment		With adjustment	
					OR (95% CI)	p	OR (95% CI)	p
rs6713088	Codominant	C/C	143 (34.4%)	178 (36%)	1.00	0.860	1.00	0.580
		C/G	206 (49.5%)	240 (48.6%)	1.07 (0.80–1.43)		0.95 (0.60–1.50)	
		G/G	67 (16.1%)	76 (15.4%)	1.10 (0.74–1.63)		0.72 (0.39–1.35)	
	Dominant	C/C	143 (34.4%)	178 (36%)	1.00	0.600	1.00	0.590
		C/G-G/G	273 (65.6%)	316 (64%)	1.08 (0.82–1.41)		0.89 (0.58–1.37)	
	Recessive	C/C-C/G	349 (83.9%)	418 (84.6%)	1.00	0.770	1.00	0.310
		G/G	67 (16.1%)	76 (15.4%)	1.06 (0.74–1.51)		0.75 (0.43–1.31)	
	Overdominant	C/C-G/G	210 (50.5%)	254 (51.4%)	1.00	0.780	1.00	0.810
		C/G	206 (49.5%)	240 (48.6%)	1.04 (0.80–1.35)		1.05 (0.70–1.59)	
	Log-additive	–	–	–	1.05 (0.87–1.27)	0.600	0.87 (0.64–1.17)	0.360
rs12621038	Codominant	C/C	120 (29.2%)	147 (29.8%)	1.00	0.620	1.00	0.850
		T/C	213 (51.8%)	242 (49%)	1.08 (0.80–1.46)		0.88 (0.55–1.42)	
		T/T	78 (19%)	105 (21.3%)	0.91 (0.62–1.33)		0.99 (0.55–1.80)	
	Dominant	C/C	120 (29.2%)	147 (29.8%)	1.00	0.850	1.00	0.690
		T/C-T/T	291 (70.8%)	347 (70.2%)	1.03 (0.77–1.37)		0.91 (0.58–1.43)	
	Recessive	C/C-T/C	333 (81%)	389 (78.7%)	1.00	0.400	1.00	0.790
		T/T	78 (19%)	105 (21.3%)	0.87 (0.63–1.20)		1.07 (0.64–1.80)	
	Overdominant	C/C-T/T	198 (48.2%)	252 (51%)	1.00	0.400	1.00	0.560
		T/C	213 (51.8%)	242 (49%)	1.12 (0.86–1.46)		0.88 (0.58–1.34)	
	Log-additive	–	–	–	0.97 (0.80–1.16)	0.710	0.98 (0.73–1.32)	0.910
rs1682111	Codominant	T/T	185 (44.6%)	239 (48.3%)	1.00	0.530	1.00	0.510
		T/A	192 (46.3%)	212 (42.8%)	1.17 (0.89–1.54)		1.15 (0.74–1.78)	
		A/A	38 (9.2%)	44 (8.9%)	1.12 (0.69–1.79)		1.52 (0.73–3.17)	
	Dominant	T/T	185 (44.6%)	239 (48.3%)	1.00	0.260	1.00	0.380
		T/A-A/A	230 (55.4%)	256 (51.7%)	1.16 (0.89–1.51)		1.20 (0.79–1.83)	
	Recessive	T/T-T/A	377 (90.8%)	451 (91.1%)	1.00	0.890	1.00	0.330
		A/A	38 (9.2%)	44 (8.9%)	1.03 (0.66–1.63)		1.42 (0.70–2.86)	
	Overdominant	T/T-A/A	223 (53.7%)	283 (57.2%)	1.00	0.300	1.00	0.760
		T/A	192 (46.3%)	212 (42.8%)	1.15 (0.88–1.49)		1.07 (0.70–1.62)	
	Log-additive	–	–	–	1.10 (0.90–1.35)	0.350	1.20 (0.87–1.65)	0.270
rs843752	Codominant	T/T	228 (54.8%)	262 (52.9%)	1.00	0.690	1.00	0.630
		G/T	157 (37.7%)	200 (40.4%)	0.90 (0.69–1.19)		0.81 (0.52–1.25)	
		G/G	31 (7.5%)	33 (6.7%)	1.08 (0.64–1.82)		0.91 (0.39–2.10)	
	Dominant	T/T	228 (54.8%)	262 (52.9%)	1.00	0.570	1.00	0.350
		G/T-G/G	188 (45.2%)	233 (47.1%)	0.93 (0.71–1.20)		0.82 (0.54–1.24)	
	Recessive	T/T-G/T	385 (92.5%)	462 (93.3%)	1.00	0.640	1.00	0.990
		G/G	31 (7.5%)	33 (6.7%)	1.13 (0.68–1.87)		1.00 (0.44–2.25)	
	Overdominant	T/T-G/G	259 (62.3%)	295 (59.6%)	1.00	0.410	1.00	0.350
		G/T	157 (37.7%)	200 (40.4%)	0.89 (0.68–1.17)		0.82 (0.54–1.25)	
	Log-additive	–	–	–	0.97 (0.79–1.20)	0.790	0.88 (0.63–1.23)	0.450

Table 4 (continued)

SNP-ID	Model	Genotype	Case, %	Control, %	Without adjustment		With adjustment	
					OR (95% CI)	p	OR (95% CI)	p
rs843645	Codominant	T/T	236 (56.7%)	270 (54.5%)	1.00	0.780	1.00	0.550
		G/T	155 (37.3%)	192 (38.8%)	0.92 (0.70–1.22)		0.84 (0.54–1.30)	
		G/G	25 (6%)	33 (6.7%)	0.87 (0.50–1.50)		0.67 (0.28–1.61)	
	Dominant	T/T	236 (56.7%)	270 (54.5%)	1.00	0.510	1.00	0.330
		G/T-G/G	180 (43.3%)	225 (45.5%)	0.92 (0.70–1.19)		0.81 (0.54–1.23)	
	Recessive	T/T-G/T	391 (94%)	462 (93.3%)	1.00	0.690	1.00	0.450
		G/G	25 (6%)	33 (6.7%)	0.90 (0.52–1.53)		0.72 (0.31–1.70)	
	Overdominant	T/T-G/G	261 (62.7%)	303 (61.2%)	1.00	0.640	1.00	0.540
		G/T	155 (37.3%)	192 (38.8%)	0.94 (0.72–1.23)		0.87 (0.57–1.34)	
	Log-additive	–	–	–	0.93 (0.75–1.15)	0.490	0.83 (0.59–1.16)	0.280
rs11125529	Codominant	C/C	271 (65.1%)	327 (66.1%)	1.00	0.180	1.00	0.290
		C/A	128 (30.8%)	158 (31.9%)	0.98 (0.74–1.30)		0.85 (0.54–1.33)	
		A/A	17 (4.1%)	10 (2%)	2.05 (0.92–4.55)		2.40 (0.66–8.81)	
	Dominant	C/C	271 (65.1%)	327 (66.1%)	1.00	0.770	1.00	0.700
		C/A-A/A	145 (34.9%)	168 (33.9%)	1.04 (0.79–1.37)		0.92 (0.59–1.42)	
	Recessive	C/C-C/A	399 (95.9%)	485 (98%)	1.00	0.067	1.00	0.160
		A/A	17 (4.1%)	10 (2%)	2.07 (0.94–4.56)		2.53 (0.70–9.19)	
	Overdominant	C/C-A/A	288 (69.2%)	337 (68.1%)	1.00	0.710	1.00	0.380
		C/A	128 (30.8%)	158 (31.9%)	0.95 (0.72–1.26)		0.82 (0.52–1.28)	
	Log-additive	–	–	–	1.11 (0.87–1.41)	0.410	1.01 (0.69–1.49)	0.950
rs12615793	Codominant	G/G	260 (62.5)	316 (64)	1.00	0.100	1.00	0.061
		A/G	136 (32.7)	167 (33.8)	0.99 (0.75–1.31)		0.76 (0.48–1.19)	
		A/A	20 (4.8)	11 (2.2)	2.21 (1.04–4.70)		3.04 (0.95–9.72)	
	Dominant	G/G	260 (62.5)	316 (64)	1.00	0.650	1.00	0.500
		A/G-A/A	156 (37.5)	178 (36)	1.07 (0.81–1.40)		0.86 (0.56–1.33)	
	Recessive	G/G-A/G	396 (95.2)	483 (97.8)	1.00	0.032	1.00	0.042
		A/A	20 (4.8)	11 (2.2)	2.22 (1.05–4.68)		3.33 (1.05–10.51)	
	Overdominant	G/G-A/A	280 (67.3)	327 (66.2)	1.00	0.720	1.00	0.150
		A/G	136 (32.7)	167 (33.8)	0.95 (0.72–1.25)		0.72 (0.46–1.12)	
	Log-additive	–	–	–	1.14 (0.90–1.44)	0.270	1.01 (0.69–1.47)	0.960
rs843711	Codominant	C/C	125 (30.2%)	139 (28.1%)	1.00	0.220	1.00	0.480
		C/T	197 (47.6%)	263 (53.1%)	0.83 (0.61–1.13)		0.77 (0.48–1.25)	
		T/T	92 (22.2%)	93 (18.8%)	1.10 (0.76–1.60)		0.72 (0.39–1.32)	
	Dominant	C/C	125 (30.2%)	139 (28.1%)	1.00	0.480	1.00	0.240
		C/T-T/T	289 (69.8%)	356 (71.9%)	0.90 (0.68–1.20)		0.76 (0.48–1.20)	
	Recessive	C/C-C/T	322 (77.8%)	402 (81.2%)	1.00	0.200	1.00	0.540
		T/T	92 (22.2%)	93 (18.8%)	1.24 (0.89–1.71)		0.85 (0.51–1.43)	
	Overdominant	C/C-T/T	217 (52.4%)	232 (46.9%)	1.00	0.096	1.00	0.560
		C/T	197 (47.6%)	263 (53.1%)	0.80 (0.62–1.04)		0.88 (0.59–1.34)	
	Log-additive	–	–	–	1.03 (0.85–1.24)	0.780	0.84 (0.62–1.14)	0.260

Table 4 (continued)

SNP-ID	Model	Genotype	Case, %	Control, %	Without adjustment		With adjustment	
					OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
rs11896604	Codominant	C/C	259 (62.3%)	317 (64%)	1.00	0.220	1.00	0.310
		C/G	136 (32.7%)	164 (33.1%)	1.01 (0.77–1.34)		0.82 (0.53–1.29)	
		G/G	21 (5%)	14 (2.8%)	1.84 (0.92–3.68)		1.98 (0.63–6.26)	
	Dominant	C/C	259 (62.3%)	317 (64%)	1.00	0.580	1.00	0.600
		C/G-G/G	157 (37.7%)	178 (36%)	1.08 (0.82–1.41)		0.89 (0.58–1.37)	
	Recessive	C/C-C/G	395 (95%)	481 (97.2%)	1.00	0.083	1.00	0.200
		G/G	21 (5%)	14 (2.8%)	1.83 (0.92–3.64)		2.11 (0.67–6.60)	
	Overdominant	C/C-G/G	280 (67.3%)	331 (66.9%)	1.00	0.890	1.00	0.310
		C/G	136 (32.7%)	164 (33.1%)	0.98 (0.74–1.29)		0.80 (0.51–1.24)	
	Log-additive	–	–	–	1.13 (0.90–1.43)	0.290	0.99 (0.68–1.44)	0.970
rs17045754	Codominant	G/G	270 (64.9%)	325 (65.7%)	1.00	0.370	1.00	0.590
		G/C	128 (30.8%)	157 (31.7%)	0.98 (0.74–1.30)		0.86 (0.55–1.35)	
		C/C	18 (4.3%)	13 (2.6%)	1.67 (0.80–3.46)		1.54 (0.46–5.15)	
	Dominant	G/G	270 (64.9%)	325 (65.7%)	1.00	0.810	1.00	0.660
		G/C-C/C	146 (35.1%)	170 (34.3%)	1.03 (0.79–1.36)		0.91 (0.59–1.40)	
	Recessive	G/G-G/C	398 (95.7%)	482 (97.4%)	1.00	0.160	1.00	0.430
		C/C	18 (4.3%)	13 (2.6%)	1.68 (0.81–3.46)		1.62 (0.49–5.35)	
	Overdominant	G/G-C/C	288 (69.2%)	338 (68.3%)	1.00	0.760	1.00	0.450
		G/C	128 (30.8%)	157 (31.7%)	0.96 (0.72–1.27)		0.84 (0.54–1.32)	
	Log-additive	–	–	–	1.08 (0.86–1.37)	0.500	0.97 (0.66–1.42)	0.890
rs843720	Codominant	T/T	154 (37)	213 (43)	1.00	0.100	1.00	0.083
		G/T	204 (49)	230 (46.5)	1.23 (0.93–1.62)		1.45 (0.93–2.27)	
		G/G	58 (13.9)	52 (10.5)	1.54 (1.01–2.37)		2.01 (1.02–3.96)	
	Dominant	T/T	154 (37)	213 (43)	1.00	0.065	1.00	0.044
		G/T-G/G	262 (63)	282 (57)	1.29 (0.98–1.68)		1.55 (1.01–2.37)	
	Recessive	T/T-G/T	358 (86.1)	443 (89.5)	1.00	0.110	1.00	0.130
		G/G	58 (13.9)	52 (10.5)	1.38 (0.93–2.06)		1.63 (0.87–3.06)	
	Overdominant	T/T-G/G	212 (51)	265 (53.5)	1.00	0.440	1.00	0.330
		G/T	204 (49)	230 (46.5)	1.11 (0.85–1.44)		1.23 (0.81–1.86)	
	Log-additive	–	–	–	1.24 (1.02–1.51)	0.033	1.43 (1.04–1.95)	0.026

SNP, single nucleotide polymorphism; OR, odds ratio; 95% CI, 95% confidence interval. *p* value <0.05 indicates statistical significance. *p* value <0.004 (0.05/11) indicates statistical significance after Bonferroni correction.

OR = 3.33, 95% CI: 1.05–10.51, *p* = 0.042; OR = 2.22, 95% CI: 1.05–4.68, *p* = 0.032) in the recessive model. In addition, compared with the TT genotype, the GT and GG genotypes of rs843720 were associated with 1.55-fold increased IgAN risk in the dominant model (adjusted OR = 1.55, 95% CI: 1.01–2.37, *p* = 0.044). And rs843720 was significantly associated with an increased risk of IgAN in the log-additive model (adjusted OR = 1.43, 95% CI: 1.04–1.95, *p* = 0.026; OR = 1.24, 95% CI: 1.02–1.51, *p* = 0.033) (Table 4). After Bonferroni correction, the significance of multiplex detection at the *p* < 0.004 (0.05/11) level was not retained for rs12615793 and rs843720. In addition, no association was found between other polymorphisms of ACYP2 and IgAN risk in the genetic models.

Table 5. Association between haplotypes of *ACYP2* and IgAN risk

SNP-ID	Haplotype	F_A	F_U	χ^2	p^a	Without adjustment		With adjustment	
						OR (95% CI)	p^b	OR (95% CI)	p^b
rs1682111/rs843752/	ATTGCGC	0.323	0.303	0.886	0.346	1.00	–	1.00	–
rs843645/rs11125529/	TGGCGTC	0.239	0.257	0.778	0.378	0.87 (0.67–1.12)	0.280	0.75 (0.51–1.12)	0.160
rs12615793/rs843711/	TTTCGCC	0.195	0.225	2.397	0.122	0.80 (0.62–1.05)	0.110	0.89 (0.58–1.36)	0.580
rs11896604	TTTAATG	0.194	0.179	0.696	0.404	1.02 (0.77–1.34)	0.900	0.88 (0.56–1.37)	0.570
	TTTCACC	0.014	0.011	0.406	0.524	1.16 (0.49–2.74)	0.730	1.10 (0.30–4.03)	0.890

SNP, single nucleotide polymorphism; F_A, frequency in cases; F_U, frequency in controls; OR, odds ratio; 95% CI, 95% confidence interval. ^a p values were calculated using the Pearson's χ^2 test. ^b p values were calculated using the Wald test. $p < 0.05$ indicates statistical significance.

Haplotype Analysis

Seven SNPs in the *ACYP2*, including rs1682111, rs843752, rs843645, rs11125529, rs12615793, rs843711, and rs11896604 showed significant LD, as shown in Figure 1. Five haplotypes were revealed after the combination of seven SNPs in *ACYP2*. When the putative risk genotypes were combined and used as the reference ATTGCGC haplotype, no significant difference in the haplotype frequency distributions between the IgAN patient and control groups was found ($p > 0.05$). The results are presented in Table 5.

SNP Genotypes and Clinical Indicator Levels

We compared the mean levels of clinical indicators between three genotypes of rs843720 (Table 6). There was significant difference in the mean level of HB between the GT genotype and TT genotype groups with IgAN ($p < 0.05$). However, no significant difference in the mean levels of other clinical indicators was found between the GT genotype and TT genotype groups, and the GG genotype and TT genotype groups with IgAN ($p > 0.05$).

Discussion

To date, there have been no reports on the correlation between the polymorphisms of *ACYP2* and IgAN risk. In this case-control study, we aimed to investigate the association between polymorphisms of *ACYP2* and the risk of IgAN in the Chinese Han population. The results revealed that the rs843720 G allele significantly increased the risk of IgAN, and rs843720 was associated with increased risk in both the dominant model and log-additive model before Bonferroni correction. In addition, we found that rs12615793 was also significantly associated with increased risk of IgAN in the recessive model. However, no significant difference in the distribution of allele and genotype was observed in other nine SNPs of *ACYP2* between the IgAN patients and the controls ($p > 0.05$).

ACYP2 (2p16.2) encodes a cytosolic enzyme acylphosphatase, which can adjust the stability of the inner environment of Ca^{2+} [15], and plays a role in pyruvate metabolism [28], cell differentiation [29], senescence [30], and apoptosis [31]. Recently, a genome-wide meta-analysis had successfully identified that rs11125529 was associated with shorter telomere length in the European population [17]. In humans, telomere shortening takes place in many tissues with age, and is accelerated in chronic diseases and cancer [32]. Some reports have identified that telomere shortening is associated with the progression of IgAN [18, 19]. However, we did not observe any significant association between rs11125529 and the risk of IgAN. One possibility is that rs11125529 may not correlate with shorter telomere length in

Table 6. Difference in clinical indicators between rs843720 genotypes

Clinical indicators	Total		TT		GT		p^a		p^b	
	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD	n	mean ± SD
Urine red blood cells, / μ L	227	245.3±428.64	82	239.6±439.24	113	261.58±451.27	0.735	32	202.43±310.94	0.663
Urinary type, / μ L	223	5.56±19.85	79	6.51±21.57	113	3.63±13.29	0.294	31	10.22±31.74	0.482
Urine protein quantification, g/d	338	2.21±1.72	122	2.14±1.77	170	2.25±1.68	0.561	46	2.26±1.75	0.683
Serum albumin, g/L	340	34.17±7.87	124	34.47±7.97	169	34.57±7.6	0.914	47	31.91±8.34	0.065
Serum cholesterol, mmol/L	333	5.08±2.27	121	5.05±2.08	166	5.08±2.46	0.886	46	5.16±2.1	0.756
Serum IGA, g/L	326	2.77±1.17	118	2.75±1.11	161	2.8±1.24	0.756	47	2.71±1.13	0.825
Serum C3, g/L	322	1.06±0.26	117	1.06±0.27	159	1.05±0.25	0.772	46	1.1±0.23	0.374
Serum C4, g/L	321	0.27±0.1	116	0.27±0.12	159	0.27±0.09	0.839	46	0.27±0.07	0.913
Blood urea nitrogen, mmol/L	341	8.16±5.82	124	8.11±6.68	170	8.28±5.55	0.812	47	7.82±4.24	0.780
Serum creatinine, μ mol/L	337	132.76±114.23	121	119.72±113.94	169	143.8±118.48	0.084	47	126.61±96.18	0.714
Serum uric acid, μ mol/L	277	372.6±113.44	105	357.99±115.56	130	384.96±110.09	0.069	42	370.9±116.58	0.543
Blood β_2 -microglobulin, μ g/mL	235	2.837.25±2.086.04	88	2.713.61±2.031.81	114	2.991.37±2.136.16	0.350	33	2.634.54±2.077.13	0.850
Urinary β_2 -microglobulin, ng/mL	220	635.14±929.14	86	583.14±839.63	102	694.37±1038.58	0.426	32	586.08±793.67	0.986
Hemoglobin, g/L	335	127.27±23.89	124	131.16±23.34	166	124.67±24.81	0.025	45	126.13±20.82	0.205
Fibrinogen, g/L	285	3.74±1.22	111	3.73±1.32	137	3.67±1.01	0.729	37	4.05±1.52	0.209

p values were calculated using Pearson's χ^2 test. $p < 0.05$ indicates statistical significance. ^a Difference in clinical indicators between the GT and TT groups. ^b Difference in clinical indicators between the GG and TT groups.

the Chinese Han population. There is another possibility that rs11125529 is a consequence of the IgAN rather than occurring prior to disease development. It will be necessary to reveal the detailed causes in further studies.

The results of this study demonstrated that rs843720 and rs12615793 significantly increased the risk of IgAN. Therefore, the association provided evidence that rs843720 and rs12615793 might be influential factors for telomere length and increase the risk of IgAN by affecting telomere length. However, no difference in the mean levels of clinical indicators (except for HB) was found between the wild-type and mutant types of the rs843720 groups. The finding suggested that rs843720 may increase the risk of IgAN through other mechanisms. Moreover, the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase activity was found to be reduced, and Ca^{2+} homeostasis is disturbed in children with chronic kidney disease [16]. It may be that rs843720 and rs12615793 affect the $\text{Ca}^{2+}/\text{Mg}^{2+}$ -ATPase activity and calcium homeostasis and thus affect the development of kidney disease [16]. Therefore, further studies are required to investigate the detailed mechanisms of IgAN development.

The rs843720 has been reported to be significantly correlated with increased lung cancer risk in the recessive model [22]. Moreover, previous research showed that the AA genotype of rs12615793 was associated with a decreased risk of high-altitude pulmonary edema, compared to the GG and AG genotypes [33], but allele A of rs12615793 was found to be associated with an increased risk of ischemic stroke in the Chinese Han population [24]. This suggests that polymorphisms may affect diseases differently.

This study has some limitations. First, the study sample is relatively small, which limits the ability to determine the association between *ACYP2* polymorphisms and the risk of IgAN. Second, a more closely matched population may reveal differences that were not found in this study, as the characteristics of the healthy control group were significantly different from those of the IgAN patients group. Third, many other risk factors (e.g., smoking, drinking) and clinical and pathological characteristics were not included. Finally, the biological function analyses of *ACYP2* polymorphisms were not performed.

Conclusions

In conclusion, this study indicated that rs843720 and rs12615793 are associated with increased risk of IgAN in the Chinese Han population, which suggested the two polymorphisms might play a role in the development of IgAN in the Chinese Han population. However, further analysis must be performed with a larger sample size to enhance the power of the study and expand the knowledge of the functions of *ACYP2* polymorphisms in the development of IgAN.

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Statement of Ethics

All subjects provided written informed consent to voluntarily participate in this study. This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Disclosure Statement

The authors have declared that no competing interest exists.

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