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Original Paper

Rs1520220 and Rs2195239 Polymorphisms of IGF-1 Gene Associated with Histopathological Grades in IgA Nephropathy in Northwestern Chinese Han Population

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Key Words
Insulin-like growth factor-1 • Single-nucleotide polymorphisms • IgA nephropathy • Susceptibility • Case-control study

Abstract
Background/Aims: Insulin-like growth factor-1 (IGF-1) plays important roles in cellular proliferation, differentiation, and growth. Previous studies showed that single-nucleotide polymorphisms (SNPs) of IGF-1 are associated with various diseases. This case-control study aimed to examine the relationship between IGF-1 polymorphisms and IgA nephropathy (IgAN) risk in a Chinese Han population. ***Methods:*** We recruited 351 IgAN patients and 310 healthy controls from Northwestern China. Sequenom MassARRAY was utilized to examine the genotypes of two common IGF-1 SNPs (rs1520220 and rs2195239). Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by the Chi square test to evaluate the associations between IGF-1 and IgAN. ***Results:*** Our study demonstrated that IGF-1 gene rs1520220 and rs2195239 polymorphisms did not confer susceptibility to IgAN. We found no correlation between gender, blood pressure, proteinuria, eGFR, and IgAN in both SNPs. However, the rs1520220 and rs2195239 variants were correlated with M1 and E1 in patients with IgAN (M0/M1: CC vs. CG+GG: OR = 1.62, P = 0.04; E0/E1: CC vs. CG+GG: OR = 1.95, P = 0.004; GG vs. GC+CC: OR = 1.90, P = 0.004, respectively). ***Conclusion:*** These results indicate

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that IGF-1 gene polymorphisms play crucial roles in the histopathological progression of IgAN in the Chinese Han population.

Introduction

IgA nephropathy (IgAN) is a common form of primary glomerulonephritis worldwide [1] and approximately 50% of patients progress to end-stage renal disease [2]. Mesangial depositions of IgA along with the complement C3, IgG, and /or IgM are thought to be common characteristics, although the intensity of the latter is relatively low [1, 3]. However, the exact pathogenesis remains unknown. Genome-wide association studies have reported that multiple gene polymorphisms are correlated with the susceptibility to IgAN [4-9], including HLA-DQB1/DRB1, CFHR1, CFHR3, and HORMAD2 gene variants; our former studies also showed that IL-10 [10] and IFN-γ [11] polymorphisms were associated with the development of IgAN. These findings indicate that genetic factors are associated with the development and progression of IgAN.

Insulin-like growth factor-1 (IGF-1) is a soluble peptide that belongs to IGFs that regulate many biologic processes, including cell proliferation, differentiation, and cell growth. IGF-1 also plays a role in the development, structural maintenance, and maturation of the kidney [12]. In addition, IGF-1 as a progression factor for glomerular mesangial cells can regulate mesangial cell proliferation and extracellular matrix production [12-15]. IGF-1 can also decrease collagen accumulation and ameliorate tubular apoptosis in injured kidney tissues [16, 17]. A previous study showed that mRNA expression of IGF-1 was elevated and associated with pathological changes in patients with IgAN [18]. The GH/IGF system is expressed in the kidney [12]. In the kidney, IGF-1 was expressed in the Henle loop and collecting duct, while its receptor is also present in the glomeruli [15]. Additionally, pathological changes of IGF expression have been observed in IgAN [19]. Despite these findings, the exact function of IGF-1 in the kidney remains unknown.

Recently, polymorphisms in IGF-1 were reported to be associated with various diseases, including breast cancer [20], gastric cancer [21], coronary artery disease [22], and childhood IgAN [23]. However, no studies have evaluated IGF-1 polymorphisms in Chinese IgAN patients. Therefore, we examined the association of IGF-1 polymorphisms (rs1520220 and rs2195239) with IgAN susceptibility in a Northwestern Chinese Han population.

Materials and Methods

Ethics statement

The study protocol was approved by the Xi'an Jiaotong University Ethical Committee. Written informed consent was obtained from all participants.

Study population

This current hospital-based study recruited patients with IgAN from Northwestern China who visited the First and Second Affiliated Hospital of Xi'an Jiaotong University in March 2009 to April 2014. All patients were pathologically confirmed by renal biopsy. The age- and sex-matched healthy controls were enrolled after healthy examinations in the same hospitals during the same period. Participants were excluded if they had secondary IgAN, such as diabetes, lupus nephritis, and other conditions, or if they were not Han Chinese. Demographic and clinical characteristics were collected, including age, gender, 24-h urine protein, blood pressure, serum creatinine level, blood urea nitrogen, serum albumin level, serum IgA level, and histopathological grade (Oxford classification [24]).

Table 1. Primers used for this study

SNP_ID	1st-PCRP	2nd-PCRP	UEP_SEQ
rs1520220	ACGTTGGATGAGCTGTCTGTGGTATTCACG	ACGTTGGATGAAGGGCATGTATAGGTGGAC	TGACAGGCCCTTAGTACTTTT
rs2195239	ACGTTGGATGACTCACAGTGAAATGGTTGG	ACGTTGGATGTGGACACCCTCAATCAATGG	GAACCATTTTCAGCATGTT

Table 2. Allelic frequency distributions between rs1520220 and rs2195239 polymorphisms and IgAN risk. OR: odds ratio, 95% CI: 95% confidence interval

SNP	Allele		Case		Control		Chi-square	P
	A	B	A count	B count	A count	B count		
rs1520220	G	C	309	393	248	372	2.08	0.15
rs2195239	C	G	291	411	240	380	1.003	0.32

DNA extraction and genotyping

Tubes containing ethylene diaminetetraacetic acid were used to collect approximately 2 mL peripheral venous blood samples from each participant. The samples were centrifuged at 1500 rpm for 10 min, and then stored at −80°C. The DNA was extracted using the GoldMag DNA Purification Kit (GoldMag Co. Ltd, Xi'an City, China) according to the manufacturer's instructions. The purity and concentration of DNA were measured utilizing an ultraviolet spectrophotometer (Nanodrop, Thermo Scientific, Waltham, MA, USA). Sequenom MassARRAY RS1000 was used to detect the genotypes of two common IGF-1 polymorphisms. Corresponding primers used for each SNP are listed in Table 1. Sequenom Typer 3.0 Software (San Diego, CA, USA) was used for data analyses.

Statistical analyses

SPSS software (version 20, SPSS, Inc., Chicago, IL, USA) was used for statistical analyses. SNP frequencies in control subjects were tested for departure from Hardy-Weinberg Equilibrium. The Student *t*-test or the Chi square test (χ^2 test) was used to examine the differences in the distributions of demographic characteristics between patients and controls. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by χ^2 test to evaluate the associations between IGF-1 and IgAN. All tests were two-tailed and $P < 0.05$ was considered statistically significant. Five genetic models were used in our study: allelic model, co-dominant model, recessive model, dominant model, and over-dominant model.

Results

Demographic and characteristics of participants

As shown in Supplemental Table 1 (for all supplemental material see www.karger.com/doi/10.1159/000486914), our study consisted of 351 patients with IgAN (229 males and 122 females, mean age of 32 ± 11.9 years) and 310 age- and sex-matched healthy controls (186 males and 124 females, mean age of 35 ± 12.6 years). There were no statistically significant differences between cases and healthy controls in age ($P = 0.45$) and gender ($P = 0.16$). Hypertension was defined as blood pressure ≥140/90 mmHg and/or diastolic pressure ≥90 mmHg on three occasions at diagnosis and 24-h urine protein was divided into 2 groups, <3.5 and ≥3.5 g. Among the 351 patients, 221 showed mesangial cell proliferation, 196 were classified as E1, and 103 patients showed segmental sclerosis. Additionally, approximately 230, 73, and 48 IgAN patients were classified as T0, T1, and T2.

Allelic frequency distributions of IGF-1 between IgAN and healthy controls

The allelic frequencies of rs1520220 and rs2195239 are shown in Table 2. The frequencies of the rs1520220 G allele (44.0%) and rs2195239 C allele (41.4%) in IgAN

patients were slightly higher than in the healthy control groups. However, there was no statistical significant difference in the frequency distribution of the rs1520220 and rs2195239 alleles between IgAN patients and controls (P = 0.15 and 0.32, respectively).

Genotype associations between IGF-1 gene polymorphisms and IgAN risk

Genotype frequency distributions of rs1520220 and rs2195239 variants are shown in Table 3. The detection rates of genotypes were 100%. Both SNPs in healthy controls were in Hardy-Weinberg equilibrium (P = 0.42, and P = 0.40, respectively). The genotype frequency distribution of the rs1520220 polymorphism was as follows: 37.1% (CC), 45.8% (CG), and 17.1% (GG) in healthy controls and 32.5% (CC), 47.0% (CG), and 20.5% (GG) in patients. The genotype frequency distribution of rs2195239 was 38.7% (GG), 45.2% (CG), and 16.1% (CC) in healthy controls and 34.5% (GG), 48.1% (CG), and 17.4% (CC) in patients. However, both rs1520220 and rs2195239 variants showed no susceptibility to IgAN in the Northwestern Chinese Han population in all genetic models (CC vs. CG+GG in dominant model: OR = 1.23, 95%CI = 0.89–1.69, P = 0.21; GG vs. GC+CC: OR = 1.20, 95%CI = 0.87–1.65, P = 0.26).

Correlation between IGF-1 gene polymorphisms and clinical variables in patients with IgAN

We further investigated the relationships between rs1520220 and rs2195239 polymorphisms and IgAN susceptibility stratified by gender, blood pressure, 24-h urine protein, eGFR, and pathological classifications. As shown in Supplemental Table 2–5, we found no correlation between gender, blood pressure, 24-h urine protein, eGFR, and IgAN in both rs1520220 and rs2195239 polymorphisms in all genetic models. However, the rs1520220 and rs2195239 variants were correlated with mesangial cell (M1) and endothelial cell (E1) proliferation, and E1 in patients with IgAN (M0/M1: CC vs. CG+GG: OR = 1.62, 95%CI = 1.03–2.56, P = 0.04; E0/E1: CC vs. CG+GG: OR=1.95, 95%CI = 1.24–3.06, P = 0.004; GG vs. GC+CC: OR = 1.90, 95%CI = 1.227–2.97, P = 0.004, respectively in Table 4).

Table 3. Genotype frequency distributions between rs1520220 and rs2195239 polymorphisms and IgAN risk. OR: odds ratio, 95% CI: 95% confidence interval

SNP	Model	Genotype	Control	Case	OR (95% CI)	P
HWE:0.42 rs1520220	Codominant	C/C	115(37.1%)	114(32.5%)	1.00	
		C/G	142(45.8%)	165 (47%)	1.17(0.83-1.65)	0.36
		G/G	53 (17.1%)	72 (20.5%)	1.37(0.88-2.13)	0.16
	Dominant	C/C	115(37.1%)	114(32.5%)	1.00	0.21
		C/G-G/G	195(62.9%)	237(67.5%)	1.23(0.89-1.69)	
	Recessive	C/C-C/G	257(82.9%)	279(79.5%)	1.00	0.26
		G/G	53 (17.1%)	72 (20.5%)	1.25(0.84-1.85)	
	Overdominant	C/C-G/G	168(54.2%)	186 (53%)	1.00	0.76
		C/G	142(45.8%)	165 (47%)	1.05(0.77-1.43)	
HWE:0.40 rs2195239	Codominant	G/G	120(38.7%)	121(34.5%)	1.00	
		C/G	140(45.2%)	169(48.1%)	1.20(0.85-1.68)	0.53
		C/C	50 (16.1%)	61 (17.4%)	1.21(0.77-1.90)	
	Dominant	G/G	120(38.7%)	121(34.5%)	1.00	0.26
		C/G-C/C	190(61.3%)	230(65.5%)	1.20(0.87-1.65)	
	Recessive	G/G-C/G	260(83.9%)	290(82.6%)	1.00	0.67
		C/C	50 (16.1%)	61 (17.4%)	1.09(0.73-1.65)	
	Overdominant	G/G-C/C	170(54.8%)	182(51.9%)	1.00	0.44
		C/G	140(45.2%)	169(48.1%)	1.13(0.83-1.53)	

Table 4. Association between genotype distribution and Oxford classification in patients with IgAN. OR = odds ratio, 95% CI = 95% confidence interval

	rs1520220				rs2195239			
Oxford classification	CC	CG+GG	OR(95% CI)	P	GG	GC+CC	OR (95% CI)	P
M(M0/M1)	51/63	79/158	1.62(1.03-2.56)	0.04	44/77	86/144	0.96(0.61-1.51)	0.85
E(E0/E1)	63/51	92/145	1.95(1.24-3.06)	0.004	66/55	89/141	1.90(1.22-2.97)	0.004
S(S0/S1)	81/33	167/70	1.03(0.63-1.68)	0.91	84/37	164/66	0.91(0.57-1.48)	0.71
T(T0/T1/T2)	72/31/11	158/42/37	0.62(0.36-1.06)	0.08	81/29/11	149/44/37	0.83(0.48-1.42)	0.49
			1.53(0.74-3.18)	0.25			1.83(0.89-3.78)	0.10

Discussion

IGF-1 is a peptide growth factor synthesized by many cells and tissues, including glomerular mesangial cells. In humans, the IGF-1 gene is located on chromosome 12q21. The protein encoded by this gene is similar to insulin in structure and function and is involved in regulating growth and development. A previous study showed that exposure to IGF-1 promotes cell proliferations and increase matrix production by mesangial cells [12], which may be correlate with IgAN. IgAN patients often show mesangial cell proliferation and extracellular matrix accumulation under light microscopy [3]. These functions of IGF-1 are likely mediated by activating and regulating the levels of its receptors. Al-Eisa et al. [25]. showed that IgA significantly elevated IGF-1 activity in rat glomerular mesangial cells by stimulating IGF-1R gene transcription and plays a role in the pathogenesis of IgAN. Tokunaga et al. [26]. indicated that high IGF-1 levels were correlated with renal pathology in patients with IgAN. These findings indicate that the IGF-1 gene variant an ideal candidate for identifying factors that influence IgAN susceptibility.

In this current hospital-based case-control study, we explored the relationship between the IGF-1 rs1520220 and rs2195239 polymorphisms and IgAN susceptibility. No significant associations were detected between IgAN susceptibility and the rs1520220 and rs2195239 variants in all genetic models. However, the rs1520220 and rs2195239 variants were correlated with pathologic grades in patients with IgAN. This is the first study to investigate the association of IGF-1 rs1520220 and rs2195239 polymorphisms and the susceptibility to IgAN in a Northwestern Chinese Han population.

Although increasing evidence had shown that the IGF-1 gene is crucial in various diseases, results regarding tumor development or progression are controversial. For example, rs1520220 is known to be correlated with higher levels of IGF-1; susceptible genes in several types of cancers [27, 28] were not associated with pancreatic cancer in Japanese subjects [29] and ischemic stroke patients [30]. Similar negative results were observed for rs2195239 in breast cancer [30, 31]. Until now, only one study reported the association of IGF-1 polymorphisms on childhood IgAN susceptibility in Korean subjects [23]. In the study, no associations were found between the genotype distributions of rs1520220 and rs2195239 with IgAN risk, which were similar to the results of our study. In addition, rs1520220 and rs2195239 variants were correlated with pathologic progression of patients with IgAN. These results are partly consistent with those of our study, and rs1520220 and rs2195239 variants were associated with mesangial cell (M1) and endothelial cell (E1) proliferation and E1 in patients with IgAN, respectively. We utilized Oxford classification for histopathological grading, while the other study used Lee grading. However, both studies agreed with the results of previous studies. First, the mRNA levels of profibrotic factors, such as fibronectin, laminin, and collagen IV, were up-regulated in rat kidneys by intravascular infusion of IGF-1 [15]. Second, excess IGF-1 decreased collagen degradation in diabetic nephropathy mice [32]. Finally, Davis et al [33]. reported that IGF signaling alterations had

no effects on mesangial reactions to high glucose or Ang II. Accordingly, IGF-1 appears to be related to glomerular extracellular matrix accumulation and degradation, which may cause histopathological progression of renal diseases, including IgAN.

Furthermore, we found no association between IGF-1 polymorphisms and gender, blood pressure, 24-h urine protein, and eGFR. These results are partly consistent with those of a Korean study [23], in which no relationships were found with proteinuria and podocyte foot process effacement. Different stages of disease, environmental background, and treatment protocols may explain these discrepancies. Further studies are needed to investigate whether IGF-1 is involved in the development of proteinuria or eGFR in more severe patients with IgAN.

There were some limitations to this study. Because this was a single-center study, there may have been some bias. All participants were Chinese Han, which may limit the large-scale application of our results to other countries with different ethnicities. Finally, the sample size in our study may not have been large enough to identify true differences, thus revealing unstable results. Further multicenter, larger sample size studies are needed to overcome these limitations. Additionally, the follow-up duration was short. However, this is the first study to explore the association between IGF-1 rs1520220 and rs2195239 polymorphisms and IgAN susceptibility in a Northwestern Chinese Han population.

Conclusion

In summary, the present study demonstrated that the IGF-1 gene rs1520220 and rs2195239 polymorphisms did not confer the susceptibility to IgAN in a Northwestern Chinese Han population. However, both the rs1520220 and rs2195239 variants were correlated with M1 and E1, and E1 in patients with IgAN, respectively. These results indicate that IGF-1 gene polymorphisms play a role in the development of IgAN in the Northwest Chinese Han population.

Disclosure Statement

The authors declare they have no conflict of interest.

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