Original Paper

Association Between *IFN-γ* Gene Polymorphisms and IgA Nephropathy in a Chinese Han Population

Jie Gao^a Lintong Wei^a Xinghan Liu^b Li Wang^a Dan Niu^c Tianbo Jin^d
Ganglian Yao^a Meng Wang^b Qiaoling Yu^e Rongguo Fu^a

^aDepartment of Nephrology; ^bDepartment of Oncology, Second Affiliated Hospital; ^cDepartment of Nephrology, First Affiliated Hospital of Xi'an Jiaotong University; ^dNational Engineering Research Center for Miniaturized Detection Systems, School of Life Sciences, Northwest University; ^eDepartment of Pathology, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China

Key Words

IgA nephropathy • *IFN-γ* • Risk • Case-control study

Abstract

Background/Aims: *IFN-γ* was reported to be involved in the development and progression of Immunoglobulin A nephropathy (IgAN), however, few studies have investigated the association between *IFN-γ* polymorphisms and IgAN. Therefore, we performed a case-control study to assess the association between *IFN-γ* polymorphisms and the risk of IgAN. **Methods:** Sequenom MassARRAY was used to genotype two SNPs (rs1861494 and rs2430561) in 351 patients with IgAN and 310 healthy controls. Associations were evaluated as odd ratios (OR) with 95% confidence intervals (CI). **Results:** No association was found between *IFN-γ* rs1861494 and IgAN risk or clinical parameters. For rs2430561, the AA genotype was more common in patients with IgAN, compared with controls (AT vs. AA: OR = 0.57, P = 0.035). *IFN-γ*-rs2430561 T allele may be a protective factor for IgAN susceptibility (T vs. A: OR = 0.59, P = 0.04). Subgroup analysis based on clinical features revealed no significant association between rs2430561 polymorphism and clinical data such as gender, 24-h urine protein, blood pressure, Oxford classification and estimated glomerular filtration rate. IgAN patients had a higher *IFN-γ* serum level than healthy controls and patients with rs1861494 AA genotype had a higher *IFN-γ* serum level compared with those with AG/GG genotypes. **Conclusions:** *IFN-γ* polymorphisms may be involved in the development and progression of IgAN.

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J. Gao, L. Wei and X. Liu contributed equally to this study and therefore share first authorship.

Rongguo Fu, MD, PHD

Department of Nephrology, Second Affiliated Hospital of Xi'an Jiaotong University,
Xi'an, Shaanxi Province 710004 (China)
Tel. +86-029-87679917, Fax +86-029-87678634, E-Mail pipifu@126.com

Introduction

As the most common glomerulonephritis, Immunoglobulin A nephropathy (IgAN) is mediated by deposits of IgA immune complexes, either alone or with IgG, IgM, or both, in the mesangium [1]. In patients with IgAN, antigenic determinants in truncated IgA1 hinge region glycans are exposed and recognized by naturally occurring IgA1 and/or IgG antibodies, leading to immune complex formation and deposition, resulting in IgAN [2]. IgAN usually occurs in adolescents and young adults, mainly males, having a male-to-female ratio of 2:1 in America and 1:1 in Asia [3, 4]. In Asia, 40% of native-kidney biopsies were diagnosed as IgAN, compared with 20% in Europe, 5-10% in the United States, and less than 5% in Central Africa [5]. Besides, proteinuria is an independent indicator for those with severe renal pathological injuries but show mild clinical characteristics, and indicate that these IgAN patients should undergo renal biopsies [6]. As for renal survival, study also reveals that hyperuricemia and the activation of complement (mainly the deposition of C3 in mesangium) are independent risk factors for renal survival in patients with IgAN [7]. Although the pathogenesis is not clear, recent studies have suggested that immune response, immune mediators, and heredity are associated with the susceptibility to IgAN [8, 9]. Among these factors, genetic factors play an import role in the development and progression of IgAN [10]. Our previous studies also found that *Megsin* [11], *MCP-1/CCR2* [12] and *TLR1* [13] gene polymorphisms were associated with IgAN susceptibility in a Chinese Han population. However, the rs699 variant in *AGT* gene and rs5186 polymorphism in *ATRI* genes did not confer the risk with IgAN [14].

Tumor necrosis factor (TNF) signaling is involved in renal injury progression in patients with IgAN, and *TNF- α TNFA2/2* genotype has been found to correlate with IgAN progression [15]. Similarly, interleukin-18 (*IL-18*), another proinflammatory cytokine, was found to be highly expressed in patients with IgAN, and the *IL-18-607A/C* AA genotype correlated with an increased risk of IgAN in a Chinese Han population [16]. Interferon- γ (*IFN- γ*), which is induced by IL-18, plays an important role in the pathogenesis of IgAN [17]. Yano et al. found that *IFN- γ* expression in peripheral blood mononuclear cells of patients with IgAN was elevated compared with healthy controls, and the higher *IFN- γ* serum level was significantly associated with the decline in glomerular filtration rate and severity of renal histopathologic grade [18]. However, a previous study suggested that *IFN- γ* could inhibit the growth of mesangial cells, which had a protective effect against renal injury [19]. More recently, Wang et al. found that the *IFN- γ* rs2430561 AA genotype may be a susceptibility factor for IgAN, but it had no association with pathological types of IgAN [20]. Compared with healthy controls, *IFN- γ* 114 allele and 114+/+ genotypes were more predominant in the IgAN group in Japanese population (60 vs. 45%, $P < 0.01$) [21].

To date, few studies have investigated the association between *IFN- γ* gene polymorphisms and IgAN risk. Therefore, we performed this case-control study to evaluate the relationship between *IFN- γ* gene polymorphisms (rs1861494 and rs2430561) and susceptibility to IgAN and clinical parameters in the Chinese Han population.

Materials and Methods

Ethics statement

The study protocol was approved by the ethics committee of the Second Affiliated Hospital of Xi'an Jiaotong University. Written informed consent was obtained from all participants after a full explanation of the study. The experimental protocol was implemented in accordance with the approved guidelines.

Subjects

Three hundred fifty-one patients with IgAN (229 males and 122 females, mean age of 32 ± 11.9 years) who were confirmed by renal biopsy were enrolled from northwestern China at the First and Second Affiliated Hospital of Xi'an Jiaotong University from March 2009 to April 2014. Three hundred ten

Table 1. Primers used for this study

SNP_ID	1st-PCR	2nd-PCR	UEP_SEQ
rs1861494	ACGTTGGATGAGGTGAGT	ACGTTGGATGAGGGACA	TGCTTCTCAGTACT
	TGACAAATCCAG	ATGAGAGAACTGC	CCC
rs2430561	ACGTTGGATGTCAAGGAA	ACGTTGGATGGTGAACCC	AAAAACAAAAA
	TTCCCTGCCTCG	CCATCTCAACGA	ACAAAAAAT

healthy subjects (186 males and 124 females, mean age of 35 ± 12.6 years) were recruited as controls from individuals who visited these hospitals for routine health examinations. All participants were of Chinese Han descent and lived in or near Xi'an City. Patients with comorbidities such as diabetes mellitus, lupus nephritis, and other secondary IgAN were excluded. Demographic and clinical details, including age, sex, 24-h urine protein, blood pressure, estimated glomerular filtration rate (eGFR), serum creatinine level (Scr), blood urea nitrogen (BUN), serum albumin level (ALB), serum IgA level, serum C3 level, and Oxford classification were collected.

DNA extraction and genotyping and measure of IFN- γ serum levels

Blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) and stored at -80°C after centrifugation at 1,500 rpm for 10 min. Genomic DNA was extracted from whole blood by using the GoldMag DNA purification kit (GoldMag Co. Ltd, Xi'an City, China) and its purity and concentration were determined using an ultraviolet spectrophotometer (Nanodrop, Thermo Scientific, Waltham, MA, USA). Two IFN- γ polymorphisms (rs1861494 and rs2430561) were selected for association testing. MassARRAY Assay Design 3.0 software (Sequenom, San Diego, CA, USA) was used to design multiplexed MassEXTEND assay. Genotyping was performed using Sequenom MassARRAY RS1000 following the standard protocol. The primers used for genotyping are provided in Table 1. Sequenom Typer 3.0 software was used for data analysis. ELISA kits (Elabscience Biotechnology Co., Ltd) were used to measure IFN- γ serum levels of controls ($n = 100$) and patients ($n = 100$) according to the manufacture instruction.

Statistical analysis

Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, IL, USA). Testing for Hardy-Weinberg Equilibrium (HWE) was performed using an exact test. The allele and genotype frequencies of cases and controls were compared by a χ^2 test. For analyzing the association between IFN- γ polymorphisms and IgAN, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression adjusted for age and sex. Five genetic models (incompletely dominant, dominant, recessive, overdominant, and log-additive) were evaluated for association of IFN- γ polymorphisms with risk of IgAN. P -values < 0.05 were considered significant, and all statistical tests were two-sided. IFN- γ serum levels were displayed as (mean $\pm$ standard deviation). We used F test to determine whether the homogeneity of variance between the two independent samples existed, and then performed student t test.

Results

Demographic and clinical features of the study population

Three hundred fifty-one patients (229 males and 122 females) and 310 healthy controls (186 males and 124 females) were recruited for this study. Their demographic and clinical data are provided in Table 2. There is no significant difference between the age at diagnosis of the two groups (case: 32 ± 11.9 years; control: 35 ± 12.6 years, $P = 0.45$). Of the 351 patients, 221 were classified to M1, 196 had endocapillary hypercellularity, 103 had segmental sclerosis, and there were about 73 and 48 patients classified to T1 and T2, respectively. 79 had a urine protein ≥ 3.5 g/24 h, 157 had blood pressure $\geq 140/90$ mmHg, and 245 patients had eGFR ≥ 60 ml/min $\cdot 1.73^2$. Means of the serum albumin (ALB), serum IgA, and serum C3 in the patient group were 34.0 ± 7.98 , 2.76 ± 1.72 , and 1.06 ± 0.26 g/L, respectively.

Associations between genotype distribution and IgAN risk

As shown in Table 3, the genotype frequency distribution of the rs1861494 polymorphism was AA 38.8%, AG 47%, and GG 14.2% in patients and AA 36.8%; AG 47.4%; and GG 15.8% in controls. For the rs2430561 polymorphism, the TT genotype was not found in either group. The AA and AT genotype frequencies were 92.6% and 7.4% in IgAN group, and 87.7% and 12.3% in the control group, respectively (Table 4). Both polymorphisms were in Hardy-Weinberg equilibrium.

Table 2. Basic characteristics of the subjects

Total subjects (n=661)	IgAN	Control	P
Number (n)	351	310	
Male/Female	229/122	186/124	0.16a
Age (mean $\pm$ SD)	32 $\pm$ 11.9	35 $\pm$ 12.6	0.45b
Urine Protein (g/24h)			
<3.5	272 (77.5%)		
$\geq$ 3.5	79 (22.5%)		
blood pressure (mmHg)			
<140/90	194 (55.3%)		
$\geq$ 140/90	157 (44.7%)		
Oxford classification			
M(M0/M1)	130/221 (37.0%/63%)		
E(E0/E1)	155/196 (44.2%/55.8%)		
S(S0/S1)	248/103 (70.7%/29.3%)		
T(T0/T1/T2)	230/73/48 (65.5%/20.8%/13.7%)		
eGFR (ml/min $\cdot$ 1.73 2)			
$\geq$ 60	245 (69.8%)		
<60	106 (30.2%)		
Serum Cr (μ mol/L)	159.5 $\pm$ 146.0		
BUN (mmol/L)	8.2 $\pm$ 5.9		
Serum ALB (g/L)	34.01 $\pm$ 7.98		
Serum IgA (g/L)	2.76 $\pm$ 1.72		
Serum C3 (g/L)	1.06 $\pm$ 0.26		

^aP values was calculated from two-sided chi-square test;

^bP values were calculated by Student's t tests.

Abbreviations: IgAN = IgA Nephropathy, SCr = serum creatinine level, BUN = blood urea nitrogen, ALB = serum albumin level. eGFR = estimated Glomerular Filtration Rate.

Table 3. Relationships between IFN- γ rs1861494 polymorphism and IgA nephropathy risk

Model	Genotype	Control	Case	OR (95% CI)	P
Codominant	A/A	114 (36.8%)	136 (38.8%)	1.00	0.72
	A/G	147 (47.4%)	165 (47%)	0.94 (0.67-1.31)	
	G/G	49 (15.8%)	50 (14.2%)	0.86 (0.54-1.36)	
Dominant	A/A	114 (36.8%)	136 (38.8%)	1.00	0.60
	A/G-G/G	196 (63.2%)	215 (61.2%)	0.92 (0.67-1.26)	
Recessive	A/A-A/G	261 (84.2%)	301 (85.8%)	1.00	0.57
	G/G	49 (15.8%)	50 (14.2%)	0.88 (0.58-1.36)	
Overdominant	A/A-G/G	163 (52.6%)	186 (53%)	1.00	0.92
	A/G	147 (47.4%)	165 (47%)	0.98 (0.72-1.34)	
Log-additive	---	---	---	0.93 (0.74-1.16)	0.51

OR: odds ratio, 95% CI: 95% confidence interval.

Table 4. Relationships between IFN- γ rs430561 polymorphism and IgA nephropathy risk

Model	Genotype	Control	Case	OR (95% CI)	P
Codominant	A/A	272 (87.7%)	325 (92.6%)	1.00	0.035
	A/T	38 (12.3%)	26 (7.4%)	0.57(0.34-0.97)	
	T/T	0 (0%)	0 (0%)		
Allele	A	582 (93.9%)	676 (96.3%)	1.00	0.040
	T	38 (6.1%)	26 (3.7%)	0.59 (0.35-0.98)	

OR: odds ratio, 95% CI: 95% confidence interval.

Table 5. Genotype association analysis of *IFN- γ* variants with clinical parameters of IgA nephropathy

Variables	rs1861494				rs2430561			
	AA	AG+GG	OR(95% CI)	P	AA	AT	OR (95% CI)	P
Gender								
Female	44	78	0.84	0.45	112	10	0.84	0.68
Male	92	137	(0.53-1.32)		213	16	(0.37-1.92)	
Urine protein (g/24h)								
<3.5	104	168	1.03	0.90	253	19	1.29	0.58
≥3.5	32	47	(0.62-1.73)		72	7	(0.52-3.20)	
Blood pressure (mmHg)								
<140/90	74	120	0.94	0.80	180	14	1.06	0.88
≥140/90	62	95	(0.61-1.46)		145	12	(0.48-2.37)	
Oxford classification								
M(M0/M1)	43/93	87/128	0.68	0.09	122/203	8/18	1.35	0.50
			(0.43-1.07)				(0.57-3.20)	
E(E0/E1)	52/84	103/112	0.67	0.08	142/183	13/13	0.78	0.53
			(0.44-1.04)				(0.35-1.73)	
S(S0/S1)	102/34	146/69	1.42	0.16	231/94	17/9	1.30	0.54
			(0.88-2.30)				(0.56-3.02)	
T(T0/T1/T2)	99/24/13	131/49/35	1.54(0.89-2.68)	0.06	214/66/45	16/7/3	1.42(0.56-3.60)	0.72
			2.04(1.02-4.05)				0.89(0.25-3.19)	
eGFR (ml/min·1.73 ²)								
≥60	101	144			228	17		
<60	35	71	1.42(0.88-2.30)	0.15	97	9	1.24(0.54-2.89)	0.61

OR: odds ratio, 95% CI: 95% confidence interval.

librium in the control group (rs1861494: $P = 0.89$; +874A/T: $P = 0.25$). We did not find any meaningful association between rs1861494 polymorphism and IgAN susceptibility in any comparison (AG vs. AA: OR = 0.94, 95%CI = 0.67-1.31, $P = 0.72$; GG vs. AA: OR = 0.86, 95%CI = 0.54-1.36, $P = 0.51$; AG+GG vs. AA: OR = 0.92, 95%CI = 0.67-1.26, $P =$

0.60; GG vs. AA+AG: OR = 0.88, 95%CI = 0.58-1.36, $P = 0.57$; AG vs. AA+GG: OR = 0.98, 95%CI = 0.72-1.34, $P = 0.92$; Table 3). However, individuals carrying the rs2430561 AT genotype had a lower risk of IgAN than those with the AA genotype (OR = 0.57, 95%CI = 0.34-0.97, $P = 0.035$, Table 4). Furthermore, a significant difference was observed between the allele frequencies of patients with IgAN and healthy controls (T vs. A: OR = 0.59, 95%CI = 0.35-0.98, $P = 0.04$, Table 4).

Associations between genotype distribution and IgAN clinical variables

We further explored the possible relationships between rs1861494 and rs2430561 polymorphisms and clinical variables in patients, including sex, 24-h urine protein, blood pressure, Oxford classification and eGFR. In the patient group, the results showed that no significant associations were identified between rs1861494 and rs2430561 polymorphisms and all of the above-mentioned clinical parameters (Table 5).

Associations between genotype distribution and IFN- γ serum levels

To evaluate the influence of the two polymorphisms on the expression of *IFN- γ* , we compared the *IFN- γ* serum levels between patients and controls with different genotypes. As displayed in Table 6, *IFN- γ* serum level of patients (413.74 ± 124.18 pg/ml) was significantly differed from that of controls (328.49 ± 92.59 pg/ml) ($P < 0.0001$). Compared with patient

Table 6. Associations between genotype distribution and *IFN- γ* serum levels

SNP	Genotype	Number	IFN- γ (pg/ml)	P
Case	---	100	413.74±124.18	< 0.0001
	---	100	328.49±92.59	
rs1861494	AA	31	441.43±118.44	0.02
	AG+GG	69	385.76±89.63	
rs2430561	AT	13	432.16±141.27	0.26
	AA	87	394.87±95.13	

carrying rs1861494 AG/GG genotypes ($n = 69$), patients with AA genotypes ($n = 31$) had higher IFN- γ expressions (385.76 ± 89.63 pg/ml vs. 441.43 ± 118.44 pg/ml, $P = 0.02$). As for rs2430561 polymorphisms, we found no meaningful difference about the IFN- γ serum levels between patients with AA ($n = 87$) and AT (13) genotypes (394.87 ± 95.13 pg/ml vs. 432.16 ± 141.27 pg/ml, $P = 0.26$).

Discussion

IFN- γ is a cytokine produced by immune cells activated by bacteria, virus, or tumor cells. Normally, IFN- γ can stimulate the immune system, interfere with virus replication, and help to eradicate pathogens [22]. A study showed IFN- γ could induce the production of IL-12 in vivo to inhibit the secretion of IL-14 by T-helper 2 (Th2) cells, and further promote T-helper 1 (Th1) polarization [23]. Thus, IFN- γ plays a key role in the regulation of Th1/Th2 ratio in the immune response. In high immunoglobulin IgA (HIGA) of ddY mice, the Th1 was in excess initially, and Th2 and IgA production were markedly up-regulated with increased age, indicating that increased IgA expression was associated with Th1/Th2 imbalance [24]. IL-4, IL-10, and IL-13, which are secreted by Th2 cells, are over-expressed in patients with IgAN and induce the glycosylation of IgA1 hinge region by decreasing the mRNA levels of core-1 β 1, 3-galactosyltransferase and Cosmc [25]. The Th1/Th2 pro-inflammatory cytokine imbalance plays a pivotal role in the pathogenesis of IgAN [26].

The IFN- γ gene, with four exons and three introns, is located on chromosome 12q24 and spans approximately 5.4 kb [27]. It is suggested that polymorphisms in IFN- γ gene could affect the expression of IFN- γ and further affect the development and progression of diseases [28]. The IFN- γ rs1861494 and rs2430561 polymorphisms are located in the third and first introns, respectively, which harbor binding sites for the transcription factor nuclear factor- κ B (NF- κ B) [29]. Silva et al. demonstrated that the over-expression of NF- κ B was correlated with poor prognosis in patients with IgAN [30]. Activation of NF- κ B is also crucial in the progression of the renal pathology of IgAN [31]. In addition, the DNA sequences containing the rs2430561 and rs1861494 are the specific binding sites for the NF- κ B transcription factor. Therefore, if the pathway is affected, it may cause changes of transcription and protein expressions of IFN- γ . And also it may lead to oxidative damage, causing cellular and pathological injuries, such as mesangial cell injuries, accumulation of extracellular matrix and eventually leading to renal fibrosis.

The rs2430561 T allele is linked to the 12 CA repeat allele of IFN- γ and has an NF- κ B binding site, while the A allele is linked to the non-12 CA repeat alleles [32, 33]. As NF- κ B induces IFN- γ expression, the rs2430561 TT genotype correlates with high IFN- γ expression, whereas the AT and AA genotypes correlate with moderate and low expression respectively [34]. Chen et al. found that IFN- γ expression was increased in patients with IgAN, compared to the non-IgAN group [17]. Our results show that the IFN- γ rs2430561 AT genotype and T allele may be protective factors for general IgAN risk, and are not specific for individual IgAN clinical symptoms. The IFN- γ rs1861494 polymorphism was associated with higher Lee's grades (IV+V) of patients with IgAN. Our findings are consistent with those of Tian et al., who analyzed the rs2430561 polymorphism in 131 IgAN patients and 138 healthy controls, and reported a higher frequency of AA genotype and A allele in patient group, compared with control group [35]. A family-based association study also confirmed that rs2430561 A confer to IgAN risk, without influencing its progression [36]. In the present study, we investigated the relationship between IFN- γ rs1861494 polymorphism and IgAN, and report that the IFN- γ rs1861494 polymorphism is associated with IFN- γ serum levels. This is in line with the results that T allele of rs1861494 in IFNG gene in patients with IBD correlated with elevated expression of IFN- γ [37].

There are several limitations in this study. First, we included 661 participants, the small sample size may lack sufficient power to identify some correlations accurately. Second, the

follow-up time was too short to predict the prognosis. Third, environmental factors and racial differences may affect the IgAN susceptibility, and further gene-environment and gene-ethnicity interaction studies are essential.

Conclusion

In summary, this study demonstrates that the *IFN- γ* rs1861494 polymorphism is associated with *IFN- γ* serum levels and the *IFN- γ* rs2430561 polymorphism is correlated with general IgAN risk, and does not stratify by individual clinical features. Further studies with larger sample size will be needed to validate our conclusion.

Disclosure Statement

The authors declare that they do not have any conflict of interests.

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