

Research Article

Significant impact of +105 A>C promoter polymorphism in IL-18 cytokine in patients with kidney stone disease

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ABSTRACT

Background: Inflammation may be one cause of nephrolithiasis and the interleukin-18 (IL-18) encoding gene polymorphisms at +105 A>C has been implicated in several inflammation related diseases. The aim of this study was to test whether IL-18+105 A>C polymorphisms could act as genetic marker for renal stone disease. A case-control study was conducted to observe the genotype distribution of IL-18+105 A>C, to elucidate the possible role of this SNP as risk factor in renal stone development and to examine its correlation with the clinico-pathologic variables.

Methods: Using the Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP) technique, we tested the genotype distribution of 160 nephrolithiasis patients in comparison with 200 disease free controls from the same geographical region.

Results: We observed significant differences of IL-18+105 A to C between the controls and patients with odds ratio 5.4 ($P = 0.001$). The prevalence of the variant genotypes AC + CC in the patients was higher than that in the controls (45% v/s 30%) and showed a significant association ($P = 0.003$). Moreover, the frequency per copy of the C allele of IL-18+105 A>C was found to be implicated more in patient group 0.27 as against only 0.16 in controls ($P = 0.0003$). Further, males and subjects with <45 years of age in patient group were significantly associated with variant genotype ($P < 0.05$).

Conclusion: Thus, it is evident from our study that IL-18+105 A>C is implicated in renal stone disease, and that the rare, C related allele is connected with higher susceptibility to nephrolithiasis.

Keywords: Genetic markers, Inflammation, Nephrolithiasis, Gene polymorphisms, IL-18+105 A>C

INTRODUCTION

Renal stone formation (or nephrolithiasis) is a common problem worldwide with an increasing incidence in

Westernized societies. Urinary stones have plagued humans since the earliest records of civilization. Calcium oxalate stones, or stones which contain calcium phosphate, are the most common type of urolithiasis, occurring in 70-80% of stone sufferers the majority are

idiopathic. The prevalence of kidney stones increased in American adults from 3.8% (1976-1980) to 5.2% (1988-1994).¹ Self-reported kidney stones were noted in 4.7% of American adults.² In our region Kashmir (North India) the patients with nephrolithiasis are highly prevalent here and are managed in our only tertiary care hospital.

Urolithiasis is a multifactorial disease for which genetic and environment are confounding factors.³ It is seen that 50-70% stone disease patients have a first relative degree with urolithiasis.⁴ An autosomal dominant mode of inheritance among families having stone history has been supported suggesting the role of several candidate genes.⁵ Several genes like Vitamin D Receptor (VDR); Vascular Endothelial Growth Factor (VEGF), E-cadherin, p21, androgen-oestrogen receptor genes, calcitonin receptor (CTR) and cytokines have been proposed as candidates in this search for an association.⁶

The contribution of subtle alterations in gene sequence to kidney stone susceptibility can only be determined once genotype-phenotype correlations have been established. The study of genetic polymorphisms promises to help define pathophysiological mechanisms, to identify individuals at risk for disease and to suggest novel targets for drug treatment. Based on SNPs, a population genetic approach provides a new way of identifying the genes associated with disease. Inflammation may be one cause of urolithiasis.⁷ Calcium oxalate, calcium phosphate and uric acid crystals interacting with the tubular epithelium may lead to the retention and accumulation of crystalline material in the kidney, provoking an inflammatory response and the formation of renal stones.⁸ Furthermore, oxalate increases the production of inflammatory cytokines and free radicals, which can cause cell death, crystal deposition in the renal tubules and, eventually, growth of calcium oxalate stones.^{9,10} Cytokine gene polymorphisms, such as the IL-1b polymorphism, are associated with urolithiasis formation.¹¹ IL-18 is secreted by activated monocytes/ macrophages, and is a pleiotropic cytokine involved in the regulation of innate and acquired immune responses, playing a key role in autoimmune, inflammatory and infectious disease.¹² IL-18 expression and serum levels in inflammation-related diseases have been published. It has been shown that patients with acute kidney graft rejection have higher IL-18 levels than patients without rejection or with acute tubular necrosis.¹³ IL-18 is considered a biomarker for the early detection of acute kidney injury.¹⁴ IL-18 is constitutively expressed by the intercalated cells of the late distal convoluted tubule, the connecting tubule and the collecting duct of the healthy human kidney.¹⁵ Kretowski et al. were the first to report evidence of an association between type I diabetes and IL-18 polymorphisms at the promoter.¹⁶ Previous studies have provided evidence that IL-18+105 A/C polymorphisms may play a role in rheumatoid arthritis.¹⁷

This study is aimed to test whether IL-18+105 A/C Single Nucleotide Polymorphism (SNP) which is

suggested to cause differences in transcription factor binding and to have an impact on IL-18 activity¹⁸ and thus could be a marker of susceptibility for renal stone disease. Allelic frequencies in a normal population would be compared with those in patients with renal stone by screening for IL-18+105 A/C Single Nucleotide Polymorphism (SNP) by PCR-RFLP technique.

METHODS

Study subjects: A total of 360 samples were included in this study which comprised of 200 age and gender matched controls having no infection or any disease whatsoever and 160 confirmed cases of nephrolithiasis who attended Department of Urology, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar (India). Blood samples were taken from both the groups and a written pre informed consent was obtained from all cases and controls. Demographic and clinic-pathological characteristics of each patient were recorded in a questionnaire. This study was approved by the institutional ethics committee.

DNA extraction

Genomic DNA was isolated using standard *Proteinase-K* digestion, phenol/chloroform extraction, and ethanol precipitation method from whole-blood samples of both nephrolithiasis cases and controls. PCR was performed in 25 µl or 50 µl reaction volume containing template genomic DNA (10-50 ng), 40µM each of dATP, dCTP, dGTP, dTTP; 1µM primer, 1 unit of Taq DNA polymerase (Biotools, B & M Labs), 1x Taq DNA Polymerase buffer (with 1.5 Mm of MgCl₂) (Biotools, B & M Labs, Madrid, Spain) in nuclease free de-ionized water. IL-18 +105 A>C was detected using the primers forward primer (5'-TGT TTA TTG TAG AAA ACC TGG AAT T-3') and IL-18+105 A>C reverse primer (5'-CCTCTA CAGTCAGAA TCAGT-3') (Genscript, Piscataway, NJ), under the following reaction conditions: initial denaturation at 96°C for 5 minutes, followed by 36 cycles of 95°C for 30 seconds, 50°C for 30 seconds, 72°C for 30 seconds, and 72°C for 7 minutes as the final extension step. The 148-bp PCR product (10 µl) was digested overnight with Taq I (Fermentas, Inc., Glen Burnie, MD) 5 U in an appropriate buffer at 37°C to generate fragments of 148 bp, 123 bp, and 25 bp. The Taq1 endonuclease-specific recognition site is present in the 148-bp PCR product sequence, which is exclusive to carriers of the IL-18+105 C allele. Therefore, a single 148-bp band characterizes the homozygous AA allele of the IL-18 gene and bands of 123 bp and 25 bp represent the homozygous CC allele. Heterozygotes exhibited all 3 bands.

The digested fragments were separated by electrophoresis in 3.0% agarose gel and visualized with ethidium bromide. For quality control, each PCR reaction used distilled water instead of DNA as a negative control, and more than 10% of the samples were analyzed twice.

Statistical analysis

The cases and controls were compared using the Chi square test for categorical variables like sex and gender status of the demographic variables or Fisher exact tests when expected frequencies were small. A goodness-of-fit Chi square test was used to determine whether the polymorphisms were in Hardy-Weinberg equilibrium between cases and controls. Odds Ratios (ORs) were used as estimates of the relative risk and 95% Confidence Intervals (CIs) were calculated to estimate the association between certain genotypes or other related risk factors of kidney stone diseases. Statistical significance was considered when $P \leq 0.05$.

RESULTS

A total of 160 confirmed nephrolithiasis cases and 200 stone free healthy controls were successfully studied for polymorphic analysis of IL-18+105 A>C. The cases included 106 (66.2%) males and 54 (33.8%) female patients and the controls consisted of 613 (68%) males and 64 (32%) females (Table 1). The cases and controls were frequency matched in terms of their age and sex. The mean age was 40 ± 10 years for the cases and 38 ± 11 years for the controls and there was no significant gender related difference. The control subjects <45 years of age in control group were 90 of 200 (45%) as against 90 of 160 (56.2%) in cases while as ≥ 45 years of age in control group were 110 of 200 (55%) as against 70 of 160 (43.8%) in cases (Table 1).

On the basis of sonographical and X-ray evidence, 80 (50%) of the patients had left nephrolithiasis, 60 (37.5%) were diagnosed with right kidney stone and 20 (12.5%) were harboring stones bilaterally in kidneys. When the patients were stratified into different locations of hydronephrosis, we observed right nephrolithiasis with hydronephrosis (HDN) in 54 patients (35%), right nephrolithiasis without HDN 08 patient (5%), left nephrolithiasis with HDN 64 patients (40%), and left nephrolithiasis without HDN 08 patients (5%), bilateral nephrolithiasis 24 (15%) patients (Table 1).

The distribution of IL-18+105 A>C genotypes and its allele frequency in cases and controls are shown in Table 2. Owing to the very low frequency of the 'CC' genotype and an increased risk associated with AC and CC genotypes, AC + CC was compared against AA. IL-18+105 A>C SNP frequencies of AA, AC and CC genotypes among controls were 140 (70%), 54 (28%) and 04 (02%) while in nephrolithiasis cases genotype frequencies were 88 (55%), 58 (36.3%) and 14 (8.7%) respectively with Odds Ratio (OR) = 5.4; 95% Confidential Interval (CI) = 3.74-8.50 (Table 3). The cases had a higher frequency of the rare allele (AC + CC = 45.2%) than the controls (30%) and this difference showed statistically significant association with AC + CC

combination against AA with an OR of 1.9 (0.8-3.8) ($P = 0.001$) (Table 3). The frequency of mutant per copy of C allele observed in cases was 0.27 (26.9%) and 0.16 (16.0%) in controls. This observation showed a highly statistical significance of rare allele (C) between cases and controls ($P = 0.0003$) with OR = 1.9 (CI = 1.0-4.0) (Table 3).

Table 1: Demographic variables in nephrolithiasis cases and controls.

	Controls n (%)	Cases n (%)	
Overall subjects	200	160	
Sex			
Male	136 (68)	106 (66.2)	0.7
Female	64 (32)	54 (33.8)	
Age group			
<45	90 (45)	90 (56.2)	0.03
≥ 45	110 (55)	70 (43.8)	
Dwelling			
Rural	80 (40)	60 (37.5)	0.6
Urban	120 (60)	100 (62.0)	
Location of stone in kidney			
Left kidney		80 (50.0)	
Right kidney		60 (37.5)	
Bilateral		20 (12.5)	
Hydronephrosis		132 (82.5)	
NoHydronephrosis		28 (17.5)	
Clinical details of pain			
Right flank pain		48 (30%)	
Left flank pain		48 (30%)	
Bilateral flank pain		28 (17.5%)	
Lower abdominal pain		02 (1.25%)	
Dysuria			
Right flank pain with dysuria		10 (6.25%)	
Left flank pain with dysuria		10 (6.25%)	
Dysuria with haematuria		02 (1.25%)	
Dysuria only		04 (2.5%)	
Haematuria			
Left flank pain with haematuria		06 (3.75%)	
Scrotal pain with haematuria		02 (1.25%)	

When classified further into groups, our study interestingly found higher number of rare allele (AC + CC) in male patients as compared to females with OR = 2.0 ($P = 0.004$) (Table 2). Moreover, patients with <45 years of age were more significantly associated with combined (AC + CC) against AA (OR = 2.8; 95% CI = 2.04-6.18) ($P < 0.002$). We also found that variant genotypes (AC + CC) were associated significantly in patients with hydronephrosis ($P < 0.05$) as compared to those without any hydronephrosis. Association of variant allele with other clinic-pathological characteristics is

given in the Table 2. ORs were assessed using, recessive dominant, co-dominant and additive inheritance models. The inheritance model with the lowest P value is

considered appropriate for the individual SNP data. Hence recessive inheritance model is appropriate for analysis of IL-18+105 A>C polymorphism (Table 4).

Table 2: Genotypic frequency of IL18+105 A>C cases and controls.

	Control n (%)	AA n (%)	AC + CC n (%)	Cases n (%)	AA n (%)	AC + CC n (%)	OR (95%CI)	P value
Overall genotype	200	140 (70)	60 (30)	160	88 (55)	72 (45)	1.9 (0.8-3.8)	0.003
Sex								
Male	136 (68)	92 (65.7)	42 + 02	106 (66.2)	54 (61.4)	42 + 12	2.0 (0.8-4.2)	0.004
Female	64 (32)	48 (34.3)	14 + 02	54 (33.8)	34 (38.6)	18 + 02	1.7 (0.7-3.9)	0.15
Age group								
<45	90 (45)	70 (50)	18 + 02	90 (56.2)	50 (56.8)	32 + 08	2.8 (0.8-4.2)	0.002
≥45	110 (55)	70 (50)	38 + 02	70 (43.8)	38 (43.1)	22 + 10	1.4 (0.7-4.0)	0.20
Dwelling								
Rural	80	60 (42.8)	18 + 02	60	40 (45.5)	18 + 02	1.5 (0.5-4.0)	0.27
Urban	120	80 (57.1)	38 + 02	100	48 (54.5)	40 + 12	2.1 (0.8-4.2)	0.005
Location								
Left kidney				80	50 (56.8)	24 + 06	1.5 (0.8-4.0)	0.13
Right kidney				60	30 (34.0)	26 + 04	1.6 (0.8-4.3)	
Bilateral				20	08 (9.0)	08 + 04	4.1 (2.1-7.0)	
Hydronephrosis								
Yes				132	80 (90.9)	42 + 10	3.8 (1.8-6.9)	0.02
No				28	08 (9.09)	16+04		

Table 3: Genotypic and allelic frequencies of IL-18+105 A>C in cases and controls.

SNP	Controls (n=200)	Cases (n=160)	OR (95% CI)	P value
IL-18 A>C Genotype				
AA	140 (70%)	88 (55%)	1.0 (ref.)	
AC	56 (28%)	58 (36.3%)	1.7 (1.0- 3.5)	0.03
CC	04 (02%)	14 (8.7%)	5.4 (3.74-8.50)	0.001
IL-18 A>C Allele type				
A	336 (84%)	234 (73.1%)	1.0 (ref.)	0.0003
C	64 (16%)	86 (26.9%)	1.9 (1.0-4.0)	

Table 4: Various models of inheritance used for cases and controls.

Genotypes and alleles (patients vs. controls)	Controls (n=200)	Cases (n=160)	OR (95% CI)	P value
Recessive model (AA vs. AC+CC)				
AA	140	88	1.9 (0.4-3.2)	0.003
AC+CC	60	72		
Dominant model (AA +AC vs. CC)				
AA + AC	196	146	4.6 (1.2-7.6)	0.006
CC	04	14		
Co-dominant model (AC vs. AA+CC)				
AC	54	58	1.4 (0.4-3.0)	0.1
AA + CC	144	102		
Additive model (AA vs. CC)				
AA	140	88	5.5 (3.5-8.6)	0.001
CC	04	14		

DISCUSSION

Single Nucleotide Polymorphisms (SNP) has emerged as a tool for mapping the complex disease genes, hence making it possible to search the candidate genes as cause of stone disease for calcium metabolism.¹² A definite link has been established since past several years where nephrolithiasis has been reported due to the variations in polymorphic variants of several genes in different ethnic population based case-control studies.¹⁹

Most polymorphisms are undoubtedly functionally neutral, some affect regulation of gene expression or the function of the coded protein.²⁰ There are two polymorphisms of IL-18, -607 C/A and -137 G/C, which were suggested to cause differences in transcription factor binding and to have an impact on IL-18 activity.²¹ Kretowski et al. were the first to report evidence of an association between type I diabetes and IL-18 polymorphisms at the promoter.²² Previous studies have provided evidence that IL-18+105 A>C polymorphisms may play a role in rheumatoid arthritis.²³

This study aimed to test whether IL-18+105 A>C polymorphisms could be a marker of susceptibility to renal stone disease is the second study and first one from the subcontinent. Genotypic/allelic frequencies in a normal population were compared with those in patients with stone disease by screening for IL-18 polymorphism in +105 A>C.

The distribution analysis of three genotypes in our study revealed genotypic frequency of AA, AC and CC among controls as 140 (70%), 54 (28%) and 04 (02%) while in nephrolithiasis cases genotype frequencies were 88 (55%), 58 (36.3%) and 14 (8.7%) respectively. This report clearly demonstrates a significant association of IL-18+105 A>C genotype with the susceptibility of subjects to development of risk for renal stones ($P < 0.05$). The CC genotype frequency was significantly higher in the studied nephrolithiasis group than in the control population and appeared to be more than 5-fold genetic risk factor for kidney stones. To date, only a single study has been done in relationship to urolithiasis and IL-18+105 A>C, and much of the genetic background of patients with urolithiasis still needs to be identified. In this study the pattern of distribution of genotypic frequency in nephrolithiasis cases is compatible with this study conducted by Kuang et al. (2010).²⁴ The frequency of per copy of C allele observed in cases was observed to be 0.27 as compared to 0.16 in controls and this difference was highly significant ($P = 0.01$) and was in accordance with study conducted by Kuang et al. (2010).²⁴

Several recent studies investigating IL-18 expression and serum levels in inflammation-related diseases have been published. It has been shown that patients with acute kidney graft rejection have higher IL-18 levels than patients without rejection or with acute tubular necrosis.²⁵

IL-18 is considered a biomarker for the early detection of acute kidney injury.²⁶ IL-18 is constitutively expressed by the intercalated cells of the late distal convoluted tubule, the connecting tubule and the collecting duct of the healthy human kidney.²⁷ Since IL-18 is an early component of the inflammatory cytokine cascade, the location of its production suggests that renal intercalated cells may contribute to the immediate immune response of the kidney. Recent reports suggest that the IL-18 +105A allele haplotype is associated with inflammatory disease, but evidence failed to suggest that the C allele was associated with levels of IL-1.²

This study revealed nearly 2-fold increased risk of nephrolithiasis in carriers of the variant allele (AC + CC) in comparison to wild-type carriers (AA) ($P > 0.03$). The variant allele frequency (AC + CC) found in cases aggregated to 45% as compared to 30% in controls and this difference shows a significant association with kidney stone predisposition ($P < 0.03$). Though this finding is in agreement with Kuang et al. (2010),²⁴ but their report shows comparatively higher odds ratio (3.1 v/s 1.9 in our study). Previously published studies on the genetics of kidney stone disease have included research on genes that code for the vitamin D receptor, androgen and oestrogen receptors, calcitonin receptor, IL-1 β and IL-1 receptor antagonist, urokinase, vascular endothelial growth factor, E-cadherin and heparan sulfate.^{28, 29} Some of these genetic polymorphisms, such as Vitamin D or calcitonin receptors, IL-1 and urokinase, have been replicated in cohorts of patients with nephrolithiasis or urolithiasis.³⁰ In this study, cytokine IL-18 was selected as a candidate gene because it may be an important component in the pathogenesis of many diseases. The positive results encourage the authors to seek other cytokine network genes for potential associations with kidney stone disease. Nevertheless, in addition to this candidate gene, whole cytokine genes should be studied as a network in future investigations.

Furthermore, higher number of rare alleles (AC + CC) were found in male patients as compared to females ($P = 0.04$). Moreover, patients with <45 years of age were more significantly associated with combined (AC + CC) as against AA ($P < 0.002$).

Further, group of patients with hydronephrosis were observed to carry more variant genotypes in comparison to those without hydronephrosis. The possibility may be due to the more inflammation owing to the presence of variant genotype in this group.

This study clearly demonstrated that IL-18+105 A>C SNP is associated with nephrolithiasis in the sample of ethnic Kashmiri population. Furthermore, on the basis of the significance found from statistical analysis, it may be concluded that patients with allele C in IL-18+105 A/C homozygote has a higher risk of developing nephrolithiasis. Further studies need to be conducted to authenticate the results.

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