Urol Res (2009) 37:141–146
DOI 10.1007/s00240-009-0189-1

ORIGINAL PAPER

Evidence suggesting a genetic contribution to kidney stone in northeastern Thai population

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Received: 1 August 2008 / Accepted: 27 March 2009 / Published online: 22 April 2009

Abstract Genetic factor may play a role in the pathogenesis of kidney stone that is found in the northeastern (NE) Thai population. Herein, we report initial evidence suggesting genetic contribution to the disease in this population. We examined 1,034 subjects including 135 patients with kidney stone, 551 family members, and 348 villagers by radiography of kidney–ureter–bladder (KUB) and other methods, and also analyzed stones removed by surgical operations. One hundred and sixteen of 551 family members (21.05%) and 23 of the 348 villagers (6.61%) were affected with kidney stone. The relative risk (λ_R) of the disease among family members was 3.18. Calcium stones (whewellite, dahllite, and weddellite) were observed in about 88% of stones analyzed. Our data indicate familial aggregation of kidney stone in this population supporting that genetic factor should play some role in its pathogenesis. Genetic and genomic studies will be conducted to identify the genes associated with the disease.

Keywords Kidney stone · Nephrolithiasis · Genetic evidence · Genetic factor · Thailand · Thai · Northeastern Thai

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Introduction

Urinary tract stone has previously been recorded to be prevalent in Thailand [1–3]. However, in the past few decades, bladder stone in children has markedly declined as the result of the improvement of nutrition and living standard while kidney stone in adults remains to be a major health problem in the northeastern (NE) Thai population [4–6]. Although the etiology of kidney stone in the NE Thai population is unknown, it is possibly different from what was reported in the western and other ethnic groups because it does not seem to be associated with the conditions of increased urinary solutes such as hypercalciuria, hyperoxaluria, and hyperuricosuria [7]. Interestingly, the analysis of urinary constituents of normal adult villagers and individuals with the previous history of kidney stone showed that their daily urinary excretions of major electrolytes and solutes including sodium, potassium, oxalate, phosphate, and citrate were lower than those of the healthy city dwellers [7, 8]. The predominant abnormalities in these patients were hypocitraturia and potassium deficiency probably attributable to low dietary intake and loss through sweating [9, 10], but these abnormalities were not specific and found to be

associated with several disorders [11, 12]. Previously, the reported prevalence of kidney stone in the NE Thai population was greatly variable [6, 12, 13], which probably depended on the methods of studies and it is not clear whether the genetic factor will play a role in its pathogenesis. The aim of this study is thus to investigate evidence of genetic contribution to kidney stone in the NE Thai population. The result in this study showed that the prevalence of kidney stone among members of the affected families is higher than that of the villagers, implying that genetic factor should play some role in its pathogenesis.

Subjects and methods

The study was conducted in Khon Kaen Province (449 km from Bangkok) in the northeast of Thailand and this project was approved by the Ethics Committees of the Faculty of Medicine Siriraj Hospital and the Ministry of Public Health. A written informed consent was obtained from individual subject before enrolling into the project. The patients with kidney and/or ureteric stone were diagnosed and admitted for surgical intervention at Khon Kaen Regional Hospital during 2004–2006. The ages of all the recruited patients were more than 15 years. The patients' family members were included into the study without selection and enrolled without a prior knowledge whether they had kidney stone or not. Most of the patients and their families were of rural (village) origins. The rural control subjects were the villagers who resided in five villages within Khon Kaen Province but outside the city area; they were randomly chosen from a census registration by two-stage simple random sampling using SPSS 13.0 program for selection of only one individual from each family. The rural population who live in this region of the country is more homogeneous than those who live in other regions of the country [14], although the patients' families lived both inside and outside Khon Kaen Province while the villagers resided only within this province. The exclusion criteria of subjects were the presence of kidney stone secondary to all known causes (including renal tubular acidosis, primary hyperparathyroidism, inflammatory bowel disease, cushing disease, hyperthyroidism, and drug-induced kidney stone) diagnosed by clinical history and symptoms, physical and laboratory examinations, acute acid loading test, blood and urine biochemical and electrolyte analyses.

A total of 1,034 subjects including 135 patients with kidney and/or ureteric stone, 551 family members, and 348 villagers—representing control population, were recruited for the study. Clinical history of kidney stone, associated symptoms (i.e., back and abdominal pain, hematuria, and stone passage), treatments, surgical scars, findings in previous X-ray films, family history, and pedigree were recorded. All subjects were again investigated by roentgenography of kidney–ureter–bladder (KUB) and in some suspicious cases by additional ultrasonography. Urine and blood samples were collected for biochemical and electrolyte analyses. The cases with distal renal tubular acidosis, a known risk factor for kidney stone, were initially identified by spot urine pH > 5.5 and confirmed by short acid loading test [15], which were then excluded from the study. Stones were also collected from a group of 109 patients after removal by surgery for analyses using Nicolet™ 380 Fourier Transform Infrared Spectrometer. All statistical analyses were carried out by SPSS 13.0 program. The prevalence of kidney stone in family members and in villagers, a control population, was determined. The relative risk (λ_R) of kidney stone in family members was determined from the prevalence in family members compared with that of the control group.

Results

From the studies by KUB radiography, ultrasonography, surgical scar observation, and clinical history, we found that 116 of 551 family members (21.05%) and 23 of 348 villagers (6.61%), who were previously unknown for kidney stone status, were affected with kidney stone (Table 1). Thus, the relative risk (λ_R) of kidney stone among the family members, compared with the villagers, a control population, was found to be 3.18. Clinical symptoms were recorded in the patients and family members with kidney

Table 1 Number of studied patients, family members and villagers, methods for diagnosis, prevalence of kidney stone, and relative risk

	Patients	Family members	Villagers
Number (*N*)	135	551	348
Age (years)	48.9 ± 11.4	48.7 ± 12.8	45.9 ± 16.6
Males/females	35/100[a]	225/326	150/198
Diagnosis of kidney stone	135	116	23
By KUB radiography	133	58	13
By ultrasonography	–	1	4
By surgical scar	2	20	2
By clinical history[b]	–	37	4
Prevalence (%)	100	21.05	6.61
Relative risk	–	3.18[c]	–

[a] The female bias was due to that a majority of patients were recruited from female wards

[b] This group of subjects had negative results of KUB radiography or ultrasonography or no record of surgical scar but they had a strong clinical history as justified from the presence of several symptoms associated with kidney stone, especially hematuria and stone passage

[c] Relative risk in the family members was estimated from the prevalence in this group divided by the prevalence in the group of villagers representing a control population

stone ($n = 251$). A majority (~88%) of the patients and affected family members had combined clinical symptoms associated with kidney stone including abdominal and back pain, hematuria, and stone passage. Thirty affected individuals (~12%) had no associated symptoms although all of them had kidney stone as shown by positive KUB radiography and two also had surgical operations.

Figure 1 shows age distributions of the subjects in the groups of patients, affected family members, and affected villagers, respectively. Both patients and affected family members had similar age distributions with the peak ages between 40 and 59 years while the affected villagers had a broadly low distribution with a shift to older ages. The average ages in the first two groups (48.9 ± 11.4 and 50 ± 11.6 years) were significantly less than that in the last group (60.0 ± 13.6 years) with P values of 0.0001 and 0.0006, respectively.

The location and number of stones observed in 192 patients and affected family members were analyzed. Unilateral (either right or left side) and bilateral kidney stones were found in about 72 and 28% of the affected individuals, respectively. The locations of stones were in the kidney (~80%), kidney and ureter (~11%), ureter (~8%), and kidney or ureter and urinary bladder (1%). The percentages of affected individuals with one, two, more than two, and staghorn stones were about 22, 9, 34, and 35%, respectively. The analysis of chemical composition of kidney stones, which were removed by surgical operations from the patients showed that approximately 88% of the stones contained calcium salts (whewellite, dahllite, and weddellite) and the remaining (12%) comprised uric acid, struvite, and ammonium hydrogen urate (Table 2).

Family data analysis showed that 67 of the 135 families (~50%) consisted of two or more affected members while the remaining 68 families (~50%) had only one affected member. Twenty-nine families (~21%) contained three or more affected members in the family. The examples of pedigrees with four or more affected members are shown in Fig. 2.

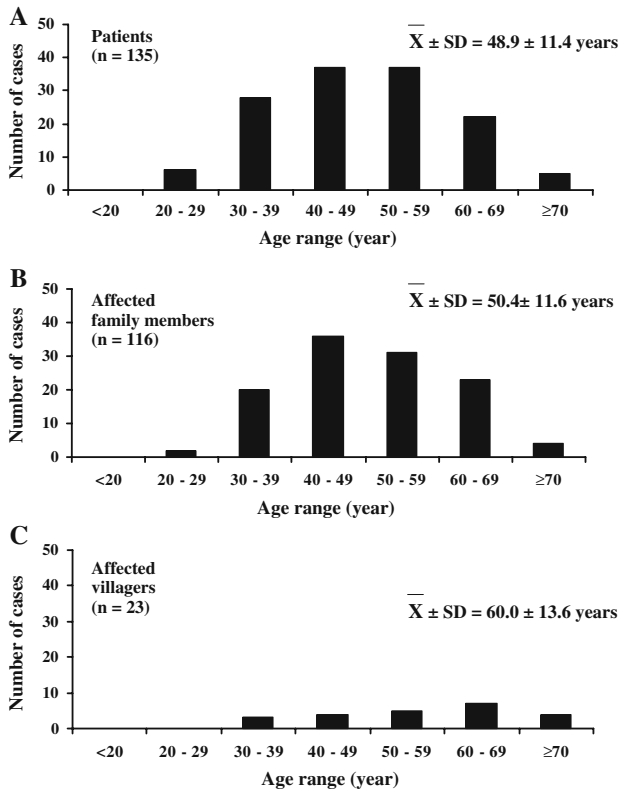

Fig. 1 Age distributions and average ages of three subject groups including patients, affected family members, and affected villagers. The peak ages in the first two groups were between 40 and 59 years while that in the last group were between 50 and 69 years. The average ages (mean ± standard deviation) in the first two groups (48.9 ± 11.4 and 50 ± 11.6 years) were significantly younger than that in the last group (60.0 ± 13.6 years)

Discussion

Kidney stone is a major heath problem in the NE Thai population [4–6]. A large number of kidney stone patients were hospitalized [4, 5]. From our own experience and available data, each year several thousands of new kidney stone cases were admitted to our and other regional hospitals for extracorporeal shockwave lithotripsy and surgery. The cause of kidney stone in this population is unknown but may be unique as it is not obviously associated with increased urinary solutes [7, 8], which are known to be stone promoters. To examine the evidence of genetic contribution to kidney stone in this population, we studied the prevalence of kidney stone in members of the affected families to compare with that of villagers representing the rural control population. While the prevalence of the disease in the villagers was 6.6%, comparable to that was previously reported 8.4%

Table 2 Chemical compositions of kidney stones removed from the patients by surgeries

Chemical composition	Number	Percentage
Whewellite or calcium oxalate monohydrate ($CaC_2O_4 \cdot H_2O$)	48	44.04
Dahllite or carbonate–hydroxylappatite [$Ca_5(PO_4,CO_3)_3(OH)$]	43	39.45
Uric acid ($C_5H_4N_4O_3$)	10	9.17
Weddellite or calcium oxalate dihydrate ($CaC_2O_4 \cdot 2H_2O$)	5	4.59
Struvite or magnesium–ammonium phosphate–hexahydrate [$(NH_4)MgPO_4 \cdot 6(H_2O)$]	2	1.83
Ammonium hydrogen urate ($NH_4C_5H_3N_4O_3$)	1	0.92
Total	109	100

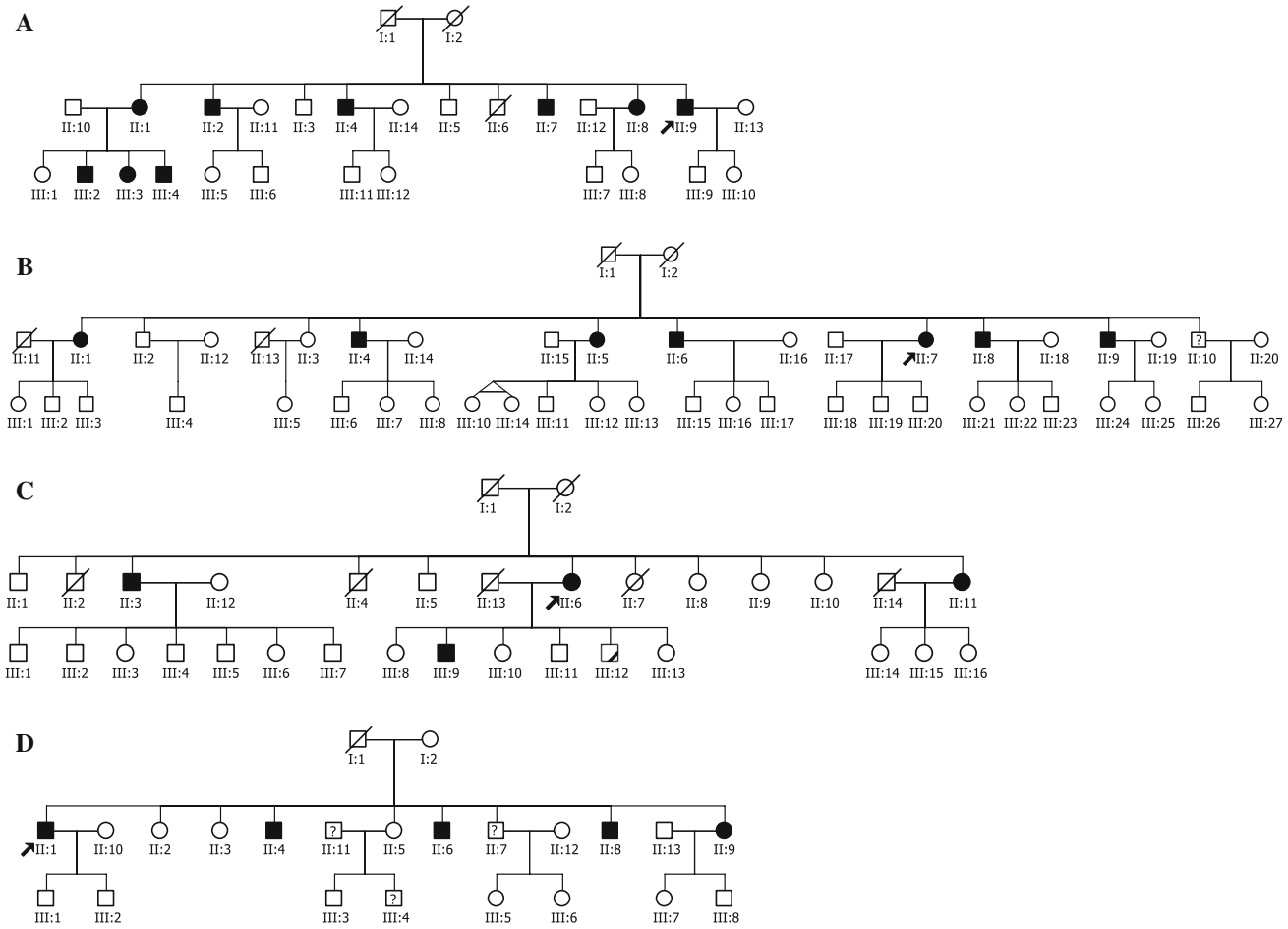

Fig. 2 The examples of pedigrees with four or more members affected with kidney stone. *Symbols* used in the figure are as follows: *open square* unaffected male, *open circle* unaffected female, *filled square* affected male, *filled circle* affected female, *slash* deceased, *arrow* proband

[6], it was as high as 21.0% among members of the affected families (Table 1). Thus, the relative risk (λ_R) of the disease among members of the affected family who were largely first-degree relatives was 3.18-fold higher than that in the villagers, indicating a family clustering of the disease. The relative risk in the second-degree relatives could not be calculated because the number of second-degree relatives was too small for the calculation. Although the family members were recruited without selection and prior knowledge of kidney stone status, it is still possible that there might be some recruitment bias whereby the members with kidney stones could have been preferentially included because they might have clinical symptoms that brought them to be investigated in the project. This would make a relative risk (λ_R) lower than the estimated 3.18. It is not known how large this possible recruitment bias is. However, a majority of the family members were free of the disease and its related clinical symptoms. In addition, the evidence that 30 family members (~12%) who had no clinical symptoms were affected by kidney stones indicates that at least in this group of affected members their recruitments were not attributable to the associated clinical symptoms. This relative risk is the evidence suggesting a genetic contribution to the disease and the high incidence of hospitalized kidney stone cases in this NE Thailand region may be at least partly due to the high prevalence of familial cases.

The findings that average ages of the patients and affected family members (48.9 ± 11.4 and 50 ± 11.6 years) were significantly less than that of the villagers (60.0 ± 13.6 years) may indicate that although the population was homogeneous, they might carry different types of kidney stones. However, based on the available data, these groups of subjects are likely to carry a similar type of kidney stone because most of them carried opaque stone as detected by KUB radiography indicating calcium-containing stones, although it was not possible for us to obtain the stones from the villagers for the analysis of their compositions. Even though, there are many possible genetic causes for calcium-containing stones (e.g., calcium oxalate stone) resulting from different pathophysiologies.

About a half of the recruited families had one affected member and the other half had more than one affected members. This may indicate the presences of both sporadic and familial cases of kidney stone in this population, which is normally observed for many well-established genetic diseases with monogenic and polygenic causes such as thalassemia, diabetes, etc., especially when the families were small. There were, however, many families with several affected members and the examples are shown in Fig. 2. The presence of several affected members in the same families suggests the role of genetic factor for the disease. Nevertheless, the familial clustering could also be caused by environmental factors such as diet although in our previous study we could not demonstrate the relationship of nutrient intake and kidney stone in this population (unpublished data). Even though there were many families with several affected members, it was difficult to establish the definite mode of inheritance for the disease. One reason is that the onset of the disease was at about midlife and thus before this age the family members who were genetically affected might not have the disease. From our data, we found that there were both autosomal dominant (AD) and autosomal recessive (AR) modes of inheritance with a more prevalence of the families with the AR pattern. All forms of inheritance (AD, AR and X-linked) could be found in the reported monogenic hypercalciuric stone-forming diseases [16]. The development of disease in adulthood indicates that, in addition to the genetic component, environmental factors may also play some role in pathogenesis of the disease.

To further investigate into the role of genetic factor in pathogenesis of kidney stone in the NE Thai population, we will employ genetic or genomic approach, such as candidate-gene and genome-wide association and linkage analyses, to identify the disease or susceptible genes in this group of patients and family members. For example, a case–control association study may be conducted by the analysis of single-nucleotide polymorphisms in candidate genes encoding urinary stone-inhibitor proteins. The result of this genetic or genomic study may lead to the elucidation of molecular pathogenic mechanism of kidney stone in this population.

In conclusion, genetic factor should play some role in the pathogenesis of kidney stone in the NE Thai population as the disease has characteristics of familial aggregation and a high relative risk among members of the affected families. The gene responsible for the disease should be identified by the current genetic or genomic approach.

Acknowledgments This work was financially supported by grants from the Faculty of Medicine Siriraj Hospital (to S. S.), the National Center for Genetic Engineering and Biotechnology (BIOTEC), National Science and Technology Development Agency (NSTDA) (to P. Y.), and Mahidol University (to P. Y.). We thank the patients and their families for participation in this project, the staff members of the Department of Medicine, Khon Kaen Hospital for their helps in logistics and field studies, the staff members of the Division of Nephrology, Department of Medicine Siriraj Hospital, Mahidol University for their assistances in laboratory works, and Ms. Ratree Tavichakorntrakool for her helps in parts of clinical studies and sample collection. P. Y. is a Senior Research Scholar of Thailand Research Fund (TRF).

Conflict of interest statement The authors declare no conflicts of interest.

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