Genetic Heterogeneity of Kidney Stone Disease in Northeastern Thai Patients

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ABSTRACT

Kidney stone disease (KSD) is a health problem worldwide, with a reportedly increasing prevalence and incidence across the world. In Thailand, KSD is common in the north (N) and northeastern (NE) parts of the country, with the NE region accounting for more than 40% of total patients. Calcium stones comprise 80% of all kidney stones, making them the most prevalent globally, as well as in Thailand. Generally, KSD is often associated with metabolic abnormalities of the urinary solute concentration or decreased urinary solubility, including hypercalciuria, hyperoxaluria, hypocitraturia, hyperuricosuria, cystinuria, low urinary volume, and defects in urinary acidification. The etiology of KSD is poorly understood, but it is known that both genetic and environmental factors are involved and the disease is heterogeneous, ranging from monogenic defects to complex interactions between genetic and environmental factors. Reported studies of KSD using genetic and genomic approaches have revealed that ion transporters and channels, the calcium-sensing receptor signaling pathway, and the metabolic pathways of vitamin D, oxalate, cysteine, purines, and uric acid play important roles in causing KSD. In Thailand, studies of KSD employing different genetic and genomic approaches i.e. candidate gene analysis, genome-wide association studies (GWAS), linkage analysis, and next-generation sequencing, have identified genetic alterations in *F2*, *PAQR6*, *SLC13A2*, *ITLN1*, *SCN10A*, and *PBK* genes. These have provided insights into both the common and rare genetic variants and genetic heterogeneity of KSD in Thai patients. The identification of genetic defects and molecular pathways causing KSD in the Thai cohort contributes to the increase of our understanding of the pathogenesis of KSD.

Keywords: kidney stone disease; single nucleotide polymorphism; exome sequencing; genetic heterogeneity; Northeast Thailand

INTRODUCTION

Kidney stone disease (KSD) is a condition in which insoluble material is formed in the kidney from the crystallization of supersaturated substances in urine, which may adhere and deposit at the tubular epithelial cells in the kidney or pass through the urinary tract. Calcium stones are the most common stone type, comprising 80% of all stones, globally. However, other types of stones including uric acid, struvite, cystine, and xanthine have also been found (Coe *et al.*, 2005; Lieske *et al.*, 2014). Similar to the global trend, the main stone types found in Thai patients are calcium stones (Aegukkatajit *et al.*, 1994; Yanagawa *et al.*, 1997).

KSD is a major health problem with increasing prevalence and incidence across the world (Romero *et al.*, 2010). The prevalence of kidney stones is 5%–15% in the world populations, with a recurrence rate of 50% within 5–10 years, and 75% in 20 years (Johnson *et al.*, 1979; Trinchieri *et al.*, 1999). The high recurrence rates lead to higher costs of medical treatment, hospitalization, healthcare

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expenses, social costs, and indirect costs from time lost from work, thus creating an economic burden (Saigal *et al.*, 2005). In the United States, the male to female ratio of KSD prevalence was reported to be 10.6%:7.1% (Scales *et al.*, 2012). In Thailand, kidney stones are particularly common in the north (N) and northeastern (NE) parts of the country, where their prevalence is 6.6% (Sritippayawan *et al.*, 2009). The incidence rate in Thai population is higher than 85 per 100,000. Of these cases, more than 40% are from the NE region (National Statistical Office, 2021).

In the patients, KSD can be both asymptomatic and symptomatic. Usually, the first symptom of a kidney stone is extreme pain, which may begin suddenly when the stone attempts to pass through the urinary tract, blocking the flow of urine. Other symptoms associated with kidney stones are flank pain, hematuria, frequent painful urination, nausea, vomiting, and fever (Coe *et al.*, 2005). The etiology of kidney stones is unclear but both genetic and environmental factors are involved. Thus, KSD is heterogeneous and its etiology ranges from monogenic defects to complex interactions between genetic and environmental factors (Gambaro *et al.*, 2004). KSD is considered to be a systemic disorder associated with other non-communicable diseases, such as chronic kidney disease, renal failure, coronary artery disease, hypertension, type 2 diabetes mellitus, and metabolic syndrome (Madore *et al.*, 1998; Rule *et al.*, 2009; Rule *et al.*, 2010). It is often associated with metabolic abnormalities of the urinary solute concentration or decreased urinary solubility, including hypercalciuria, hyperoxaluria, and hyperuricosuria. Notably, the clinical characteristics of the disease in NE Thai patients were not similar to those previously reported in other ethnic groups, whereby hypocitraturia and potassium deficiency were observed predominantly in these patients (Sriboonlue *et al.*, 1991). Therefore, it was hypothesized that the mechanisms of stone formation in this population may differ from those previously reported in other ethnic groups.

The mechanisms involving in stone formation are the interaction of crystals in supersaturated urine with some intra-renal structure, crystal growth, and crystal aggregation, consequently leading to stone formation (Aggarwal *et al.*, 2013). The risk factors for stone formation include genetic and environmental factors. The most common types of stones are calcium oxalate stones. The conditions that increase urinary calcium and oxalate excretion enhance calcium oxalate supersaturation will therefore increase the risk of KSD. Additionally, factors such as calcium and oxalate intake, gastrointestinal tract (GI) absorption, bone turnover, and renal reabsorption influence the calcium and oxalate levels in both serum and urine. These processes are controlled by the parathyroid hormone, 1,25 dihydroxy vitamin D, and calcium-sensing receptor (CaSR) signaling, whose alterations can act as risk factors of KSD (Howles *et al.*, 2019). There is evidence suggesting that *vitamin D receptor* (*VDR*) polymorphism is associated with the hypercalciuria phenotype and a higher risk of stone formation (Mossetti *et al.*, 2004; Bid *et al.*, 2005). Moreover, several variations in the *CaSR* gene cause a decrease in *CaSR* expression and kidney stone development (Vezzoli *et al.*, 2011). Food intake of oxalate and its intestinal absorption as well as oxalate metabolism in the liver or kidney also contribute to the underlying hyperoxaluria and KSD. Primary hyperoxaluria is a severe metabolic disorder, characterized by a deficiency or mistargeting of specific enzyme in the glyoxalate metabolic pathway, resulting in excessive oxalate production (Danpure and Rumsby, 2004; Cellini *et al.*, 2012; Beck *et al.*, 2013). Patients with digestive diseases, such as inflammatory bowel disease, can develop secondary hyperoxaluria, leading to kidney stone formation (Torricelli *et al.*, 2021). Moreover, *Oxalobacter formigenes* in humans have been proposed to participate in intestinal oxalate metabolism (Allison *et al.*, 1986; Stewart *et al.*, 2004). Other calcium oxalate stone promoters are high sodium, high urate, low urine pH, and low urine volume, while the inhibitors include organic substances such as nephrocalcin, urinary prothrombin fragment-1, and osteopontin and inorganic substances such as citrate and magnesium (Aggarwal *et al.*, 2013). The mechanism of kidney stone formation includes calcium oxalate monohydrate (COM) crystals adhesion or endocytosis on to renal tubular epithelial cells (Bigelow *et al.*, 1996; Lieske *et al.*, 1999; Evan *et al.*, 2005). The oxalate, COM, and CaP exposure to renal tubular cells increases the production of reactive oxygen species (ROS) and oxidative stress, leading to cell injury and inflammation. This accelerates crystal aggregation and growth, which ultimately leads to stone formation (Khaskhali *et al.*, 2009; Khan, 2013).

In this review, we focus on the genetic and genomic studies of KSD in the NE Thai population, including case-control and family-based studies, to provide an update on the genes associated with KSD and the related mechanisms of stone formation. The accumulative data gathered from our studies indicate the genetic heterogeneity of KSD in the NE Thai patients.

Epidemiology and genetic studies of KSD

Many studies have demonstrated that individuals with family history of KSD have a higher risk of developing the disease than those without family history. Approximately 40% of the patients with KSD have a positive family history, in which the onset of the disease is earlier than that without the family history (Koyuncu *et al.*, 2010). Twin studies have estimated the heritability of the risk for KSD to be 56%–57% in men, and 46% in women (Goldfarb *et al.*, 2005; Halbritter *et al.*, 2015); thus, suggesting the role of genetic factor involving in KSD. Furthermore, epidemiological studies have estimated the relative risk (λ_R) in family members to range from 2–4-fold up to 16-fold higher than that of the general population, depending on the degree of relatedness (Griffin, 2004). In Thailand, KSD is prevalent in the N and NE regions of the country. The reported prevalence of KSD in this population is considerably varied among previous studies (Sriboonlue *et al.*, 1992; Nimmannit *et al.*, 1996; Yanagawa *et al.*, 1997), which is probably related to the method conducted in the different studies. According to the Office of the Permanent Secretary, Ministry of Public Health there are more than 50,000 urolithiasis patients /year in Thailand and the incidence rate in the population is more than 85 per 100,000. Of these cases, more than 40% are from the NE region (Figure 1A and 1B) (National Statistical Office, 2021). The reason for such higher susceptibility in the NE region of Thailand is still unknown. However, there are evidence suggesting low potassium and low citrate status in the rural dwellers of NE, due to low daily dietary intake and loss through sweat, as risk factors (Sriboonlue *et al.*, 1998; Tosukhowong *et al.*, 2002). In addition, genetic factors play some roles in the pathogenesis of KSD in the region. A study conducted in Khon Kaen province showed the relative risk (λ_R) among family members to be 3.18 (Sritippayawan *et al.*, 2009).

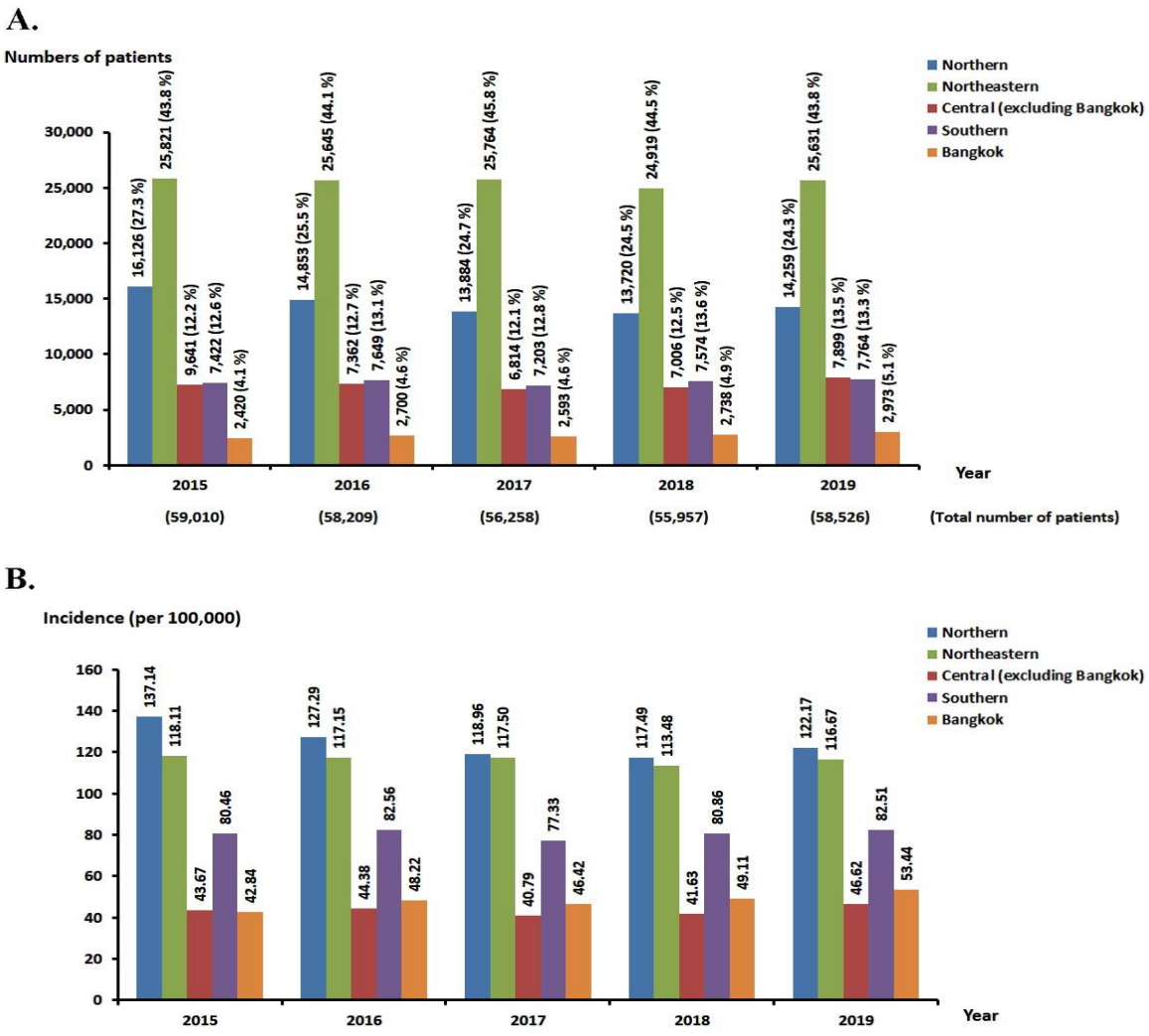

Figure 1 Number of patients (A) and incidence of kidney stone disease (KSD) in Thailand (B). The data in four regions were collected between 2015–2019.

The previous studies suggested that the probable mode of inheritance of KSD is autosomal dominance with variable or incomplete penetrance (Coe *et al.*, 1979; Nicolaidou *et al.*, 1996; Reed *et al.*, 1999; Wolf *et al.*, 2005) or the mixture of co-dominant and polygenic transmission (Loredo-Osti *et al.*, 2005). Regarding to the mode of inheritance, KSD could be inherited as a rare monogenic disorder or complex polygenic transmission. This implies that many genes may contribute to the disease causation. The monogenic causes of KSD are very heterogeneous. Genes responsible for hypercalciuria, hyperoxaluria, and other risk phenotypes have been reported. For example, mutations in *CLDN16*, *CLCN5*, *SLC34A3*, *CaSR*, *SLC12A1*, *KCNJ1*, *ClCNKB*, and *ADCY10* genes cause KSD related to hypercalciuria (Sayer, 2017; Halbritter, 2021), whereas mutations in *AGXT*, *GRHPR*, and *HOGA1* genes can cause KSD associated with primary hyperoxaluria (Danpure and Rumsby, 2004; Cellini *et al.*, 2012; Beck *et al.*, 2013). Mutations in at least 30 genes have been identified as monogenic genes of KSD and/or nephrocalcinosis. Recent reports of KSD in European and European American cohorts suggested that monogenic disorders account for 16.8%–20.8% of the cases in children and 11.4% of the cases in adults (Halbritter *et al.*, 2015; Braun *et al.*, 2016). Recessive monogenic mutations occur more commonly in children, especially in the infantile subgroup. In contrast, dominant monogenic mutations are found more frequently in patients with late-onset KSD (Halbritter *et al.*, 2015; Daga *et al.*, 2018). Interestingly, mutations in the cystinuria gene *SLC7A9* were most frequently found in an American cohort, with median age of stone manifestation at 26 years (Halbritter *et al.*, 2015). Moreover, clinical data showed possible cystinuria and some patients exhibited calcium-containing kidney stones (Cupisti *et al.*, 2012; Halbritter *et al.*, 2015). The contributions of polygenic influences from multiple loci have been investigated by candidate gene and genome-wide association studies in various populations, which have indicated that multiple genes and molecular pathways contribute to the risk of kidney stone formation. Polymorphisms in multiple loci have been reported to be associated with KSD: *VDR*, *ALPL*, *SLC34A1*, *SLC34A4*, *CLDN14*, *TRPV5*, *CYP24A1*, and *CaSR* genes encoding proteins for the renal handling of phosphate and calcium; *F2*, *MGP*, *OPN*, *HSPG2*, *PLAU*, and *UMOD* genes encoding proteins for preventing calcium salt precipitation or inhibiting stone formation; *AQP1* gene encoding protein for a water-specific channel in the kidney proximal tubule (Taguchi *et al.*, 2017; Halbritter, 2021).

Genetic and genomic approaches for the identification of genes associated with KSD

To date, several approaches have been applied for the identification of disease-causing or disease-associated genes in Mendelian disorders or complex diseases. Each approach provides both advantages and limitations (Table 1), which researchers can appropriately select for their work depending on their study design, sample collection, disease knowledge, budget, and application. To identify genes responsible for KSD, genetic approaches based on genetic association study, linkage study, and exome sequencing are employed. In contrast to the traditional association study and linkage study approach, genome-wide association study (GWAS) and genome-wide linkage analysis were developed as rapid, high-throughput, and cost-effective alternative approaches. In addition, these are hypothesis-free approaches to identify the disease locus in a single run. By using single nucleotide polymorphisms (SNPs) as genetic markers, the functional SNPs can be further defined. Usually, the identified disease locus is too large for conventional Sanger sequencing, making it unable to reduce the number of candidate genes sufficiently (Botstein and Risch, 2003). This problem can now be solved by the development of recent exome sequencing technologies, i.e., the next-generation sequencing, to sequence the DNA region of interest. Moreover, exome sequencing can be used to identify all kinds of genetic variations at base-pair resolution throughout the coding sequences of the human genome (Gilissen *et al.*, 2011).

Association study

Genetic association study is a powerful method used to identify the susceptible genes or genome regions that contribute to common and complex diseases. This approach is based on the principle of linkage disequilibrium (LD), in which common variations are selected for genotyping (Table 1). Genetic association studies generally aim to identify the genetic variation that occurs more often in individuals with the disease (case group) than in individuals without the disease (control group). To investigate the correlation between disease status and genetic variation, a higher frequency of the genetic markers in the case group can be interpreted as an increased risk of a disease. Genetic association study findings have been used to explain a small effect of the causes in complex non-Mendelian diseases

(Farber and Lusis, 2009) or the sum of the phenotypic effect of multiple genes. The availability of SNP microarray allows researchers to perform an association study at a genome scale and to exponentially increases the ability to identify phenotype–genotype associations (MacArthur *et al.*, 2017). Using this approach, a number of genetic variations have been reported to be associated with KSD. Here, we summarize genetic etiology of KSD in some Asian populations, identified by association studies (Table 2).

Linkage analysis

Linkage analysis is another powerful method for identifying potential pathogenic variants, and is applicable to both monogenic diseases (parametric linkage) and complex diseases (model-free or non-parametric linkage) (Dawn Teare and Barrett, 2005). The principle of this approach is based on the law of segregation, which states that allele pairs segregate randomly from each other during gamete formation (Table 1). Using common variants as genetic markers, linkage analysis can be used to trace the gene that co-segregates with a disease trait without actually knowing mutation. Known mutations can also be selected for genotyping in family members by linkage analysis. Identification of potential genetic contributions with small effects can be accomplished, owing to recent genotyping technology and statistical strategies (Bodmer and Bonilla, 2008). Mutations that segregate with KSD have been identified by linkage analysis, including mutations in the *SCN10A* (Nettuwakul *et al.*, 2018), *SLC34A3* (Tencza *et al.*, 2009), and *OCRL1* (Hoopes *et al.*, 2005) genes.

Table 1 The features and characteristics of association study, linkage analysis, and next generation sequencing for the identification of genes associated with the disease.

Features	**Association Study**	**Linkage Analysis**	**Next Generation Sequencing**
Biological Basis	Linkage disequilibrium (LD) and recombination events in past generations of a population	Segregation and recombination of genetic markers in pedigree data	Massively parallel DNA sequencing to determine variants
Hypothesis for disease causing	Hypothesis based for candidate gene study and hypothesis free for genome-wide study	Same as association study	Both hypothesis based and hypothesis free approach possible
Subjects	Population studies in affected subjects (assumed unrelated cases and controls)	Pedigree analysis among family members	Related or unrelated individuals
Benefits	- Large scale genotyping to detect common variants in a population - Do not need familial or relationship information - Can identify multiple genes each with minimal effects	- Good for monogenic Mendelian diseases - Can identify rare alleles that are present in small numbers of families - Can be applied to multifactorial disease locus mapping	- Better coverage and resolution to identify direct causal genes - Detection of rare causal variants - Applicable to both pedigree and population studies
Limitations	- Requires large sample to establish significant association in genes with small effect - Prone to false positives - Population stratification influences results of analysis - Low power in detecting allelic heterogeneity	- Cannot detect rare variants with low penetrance alleles - May fail to replicate/ reproduce results in different families - Usually have poor genetic resolution in the centimorgan range	- High rate of discovery and need validation - Storage and processing of large data sets - Lack of proper standards across different NGS platform.

Table 2 Genetic etiology of KSD in some Asian populations identified by association studies.

Country	Gene	Variation of interest	Sample size (case/control)	Odds Ratio	P-Value	Reference
China	*IL-18*	rs549908	272/104	3.10	<0.0010	Lai *et al.*, 2010
	VDR	rs7975232	464/450	2.04	0.0060	Wang *et al.*, 2012
	Klotho	rs3752472	426/282	1.51	0.0430	Xu *et al.*, 2013
	SLC26A6	rs184187143	225/201	6.10	0.0070	Lu *et al.*, 2016
	CaSR	rs1042636	615/315	1.45	0.0210	Ding *et al.*, 2017
	ALPL	rs1256328	331/553	1.52	0.0009	Li *et al.*, 2018b
	CaSR	rs7652589	624/470	1.68	0.0030	Li *et al.*, 2018a
Japan	*MGP*	rs4236	122/125	0.55	0.0470	Gao *et al.*, 2007b
	OPN	SNP10 (Novel SNP in promoter)	126/214	1.64	0.0260	Gao *et al.*, 2007a
	OPN	SNP11 (Novel SNP in promoter)	126/214	1.76	0.0113	
	RGS14	rs12654812	601/201	1.43	0.0031	Yasui *et al.*, 2013
	DGKH	rs7981733	601/201	1.41	0.0050	
	FAM188	rs12669187	601/201	1.57	0.0064	
Thailand	*F2*	rs5896	132/126	0.49	0.0030	Rungroj *et al*., 2012
	PAQR6	rs759330	216/216	2.02	0.0001	Rungroj *et al*., 2014
	SLC13A2	rs11567842	145/115	8.34	<0.001	Udomsilp *et al*., 2018
	ITLN1	rs2274907	216/216	1.54	0.0021	Pungsrinont *et al*., 2021

Next-generation sequencing (NGS)

Next-generation sequencing (NGS) is an evolution of sequencing technology. It provides massively parallel, high-throughput DNA or RNA sequencing. In contrast to the first-generation sequencing, NGS yields massive sequence data and minimizes the need for multi-steps in Sanger sequencing, such as a sample preparation step, DNA template, and sequence read length (Table 1). Most of the next-generation sequencing platforms rely on sequencing-by-synthesis technique, and conduct sequencing and detection simultaneously. Raw data received from NGS are shorter than those received from Sanger sequencing as they are determined by a function of the signal-to-noise ratio. NGS can be used for sequencing of whole genomes (genome sequencing) and targeted regions of interest (targeted sequencing or gene panel sequencing), including all coding gene sequences (exome sequencing). Using whole exome sequencing and gene panel sequencing, a number of novel and known mutations in *AGXT*, *ATP6V1B1*, *CLDN16*, *CLDN19*, *GRHPR*, *SLC3A1*, *SLC12A1*, *SLC9A3R1*,*SLC34A1*, *SCN10A*, and *PBK* genes have been identified as monogenic causes of KSD (Halbritter *et al.*, 2015; Braun *et al.*, 2016; Daga *et al.*, 2018; Nettuwakul *et al.*, 2020).

Genetic and genomic studies of KSD in Thailand

As mentioned earlier, almost half of the patients with KSD in Thailand can be found in the NE region of the country; therefore, many studies have recruited case subjects for clinical and genetic studies from this region. For genetic and genomic studies, several approaches have been applied to identify the genes responsible for KSD in the NE Thai population, especially candidate gene and genome-wide association studies. Moreover, most recent strategies with the NGS technology have been applied to search for the causative genes in affected families using exome sequencing.

Association studies

An overview of the genetic association studies on KSD in the NE Thai populations is provided in Table 3. The first study on the genetics of urinary stone-inhibitors in the NE Thai population was carried out by our group (Rungroj *et al.*, 2011). Urinary stone-inhibitor proteins defects including F2 (prothrombin) were proposed to be involved in kidney stone formation. The case subjects (164 cases) were patients (aged 20–80 years old) diagnosed with KSD in Khon Kaen Regional Hospital during 2004–2006. The healthy control subjects (216 controls) were people without a history of KSD and

were recruited from the same area as the cases. We genotyped 67 SNPs in 8 candidate genes by dHPLC and found that 8 of 10 SNPs distributed within the *F2* gene, including 2 haplotypes, were associated with KSD risk (Figure 2). The functional SNP in the *F2* gene was further determined by Sanger sequencing. Later, an association between an *F2* variant (rs5896, p.T165M) and KSD in the NE Thai female patients (132 cases vs. 126 controls) was reported (Table 3) (Rungroj *et al.*, 2012). The significant differences in the genotype and allele frequencies were maintained only in the female group (p = 0.033 and 0.003; OR = 0.49 and 0.59, respectively), suggesting a potential protective role of *F2* against stone formation.

In addition, another study investigated the association of *SLC13A2* (*sodium dicarboxylate cotransporter-1*) polymorphism with the hypocitraturic phenotype in Thai patients with KSD (Udomsilp *et al.*, 2018). Citrate is a stone inhibitor that forms complexes with calcium (Chow et al., 2004). This study showed that SNP rs11567842 in the *SLC13A2* gene is not likely to be a direct genetic risk factor for kidney stone formation. However, it was strongly associated with the hypocitraturic phenotype in KSD patients (Table 3 and Figure 2). The patients with the AA genotype had significantly lower urinary citrate levels than those with the GG genotype. The AA genotype was susceptible to the hypocitraturic trait, whereas GG was a protective genotype for hypocitraturia. Patients with AA had a higher expression level of *SLC13A2* mRNA in their affected kidneys than those with GG.

For whole genome SNP genotyping, our group analyzed a set of 104 reported candidate genes involved in KSD, and found that rs759330 is a potential candidate associated with KSD in the NE Thai patients (Rungroj *et al.*, 2014). The SNP rs759330 is located 144 bp downstream of *BGLAP*, at a predicted microRNA binding site at 3′UTR of the *PAQR6* gene. The SNP rs759330 was genotyped in 216 patients and 216 control subjects and significant differences were found in its genotype and allele frequencies (p = 0.0007 and 0.0001, OR = 2.02 and 2.02, respectively) (Table 3 and Figure 2). In the study by Pungsrinont *et al.*, whole genome SNP genotyping was performed. SNPs were analyzed as clusters based on the concept of linkage disequilibrium (LD) and haplotypes, to identify the candidate gene associated with KSD in the NE Thai patients (Pungsrinont *et al.*, 2021). Moreover, SNP rs2274907 in the *ITLN1* gene was significantly different between the case and control subjects, in both the genotype frequencies and allele frequencies (p = 0.001 and 0.0021; OR = 2.44 and 1.54, respectively) (Table 3 and Figure 2).

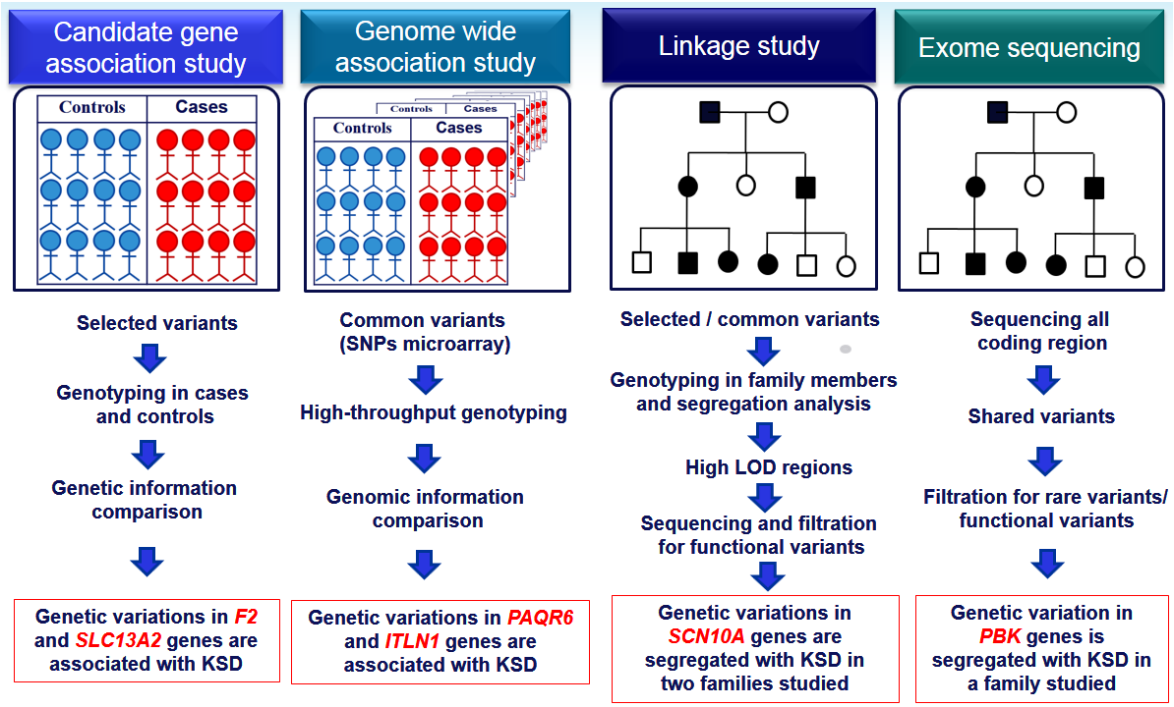

Figure 2 Genetic and genomic approaches for identification of genes associated with kidney stone disease in the northeastern (NE) Thai patients.

Family-based study

Genome-wide linkage analysis and/or exome sequencing were employed to identify disease-causing genes in KSD families by our group (Table 4). We recruited 256 patients with KSD and their family members from Sappasithiprasong Hospital in Ubon Ratchathani province. An extended family (Family 1) with a maximal estimated LOD score (ELOD) of 3.31, comprising 17 family members (7 affected and 10 unaffected), was selected for whole genome linkage analysis and exome sequencing. Two variations (c.2727C>A; p.N909K and c.5426A>G; p.K1809R) in the *SCN10A* gene were found to be segregated with KSD in Family 1 and an additional variation (c.3445G>A; p.V1149M) was identified by gene scanning in another affected family (Family 2) (Figure 2 and 3) (Nettuwakul *et al.*, 2018). More recently, we discovered a novel loss-of-function alteration (c.127G>A; p.G43R) in the *PBK* gene, which segregated in another affected family (Family 3), via exome sequencing (Nettuwakul *et al.*, 2020). This family comprised 8 affected members, including a twin pair and 20 unaffected members (Figure 2 and 3) with a maximal ELOD of 2.66.

Table 3 Genetic variations identified by case/control studies.

Genes	Variations	SNP ID	Frequency (1000genome)	No. of case/ control	p-value (odd ratio)	Gene functions	Proposed KSD mechanisms	References
F2	p.T165M (c.494 C>T)	rs5896	0.2192	132/126	0.0030 (0.49)	Coagulation factor	Stone inhibitor	Rungroj *et al*., 2012
PAQR6	c.*395C>G	rs759330	0.2270	216/216	0.0001 (2.02)	Receptors for progesterone	Ca^{2+} reabsorption	Rungroj *et al*., 2014
SLC13A2	p.I550V (c.1795A>G)	rs11567842	0.4734	145/115	<0.001 (8.34)	Sodium dicarboxylate cotransporter, citrate reabsorption	Citrate reabsorption, urinary inhibitors of stone formation	Udomsilp *et al*., 2018
ITLN1	V109D (c.326T>A)	rs2274907	0.4187	216/216	0.0021 (1.54)	Binding to oxalate degrading bacteria	Oxalate absorption	Pungsrinont *et al*., 2021

Table 4. Genetic variations identified by family-based studies.

Genes	Variations	SNP ID	Frequency (ExAC)	Segregation In family	Function Predictions*	Gene functions	Proposed KSD mechanisms	References
SCN10A	p.N909K (c.2727C>A)	rs567269429	0.00009	Family 1	3	Voltage-gated sodium channel	Ion imbalance	Nettuwakul *et al.*, 2018
SCN10A	p.K1809R (c.5426A>G)	rs561166361	0.000008	Family 1	6	Voltage-gated sodium channel	Ion imbalance	Nettuwakul *et al.*, 2018
SCN10A	p.V1149M (c.3445G>A)	rs560631745	0.00007	Family 2	6	Voltage-gated sodium channel	Ion imbalance	Nettuwakul *et al.*, 2018
PBK	p.G43R (c.127G>A)	-	-	Family 3	5	Phosphorylation of p38 MAPK	Response to ROS	Nettuwakul *et al.*, 2020

* Prediction of the impacts of amino acid changes on the protein structures and functions by 6 web-based programs. The results show the number of programs that predict as “Pathogenic”, “Damaging”, “Probably damaging”, “Possibly damaging”, “Disease causing”, or “Deleterious”.

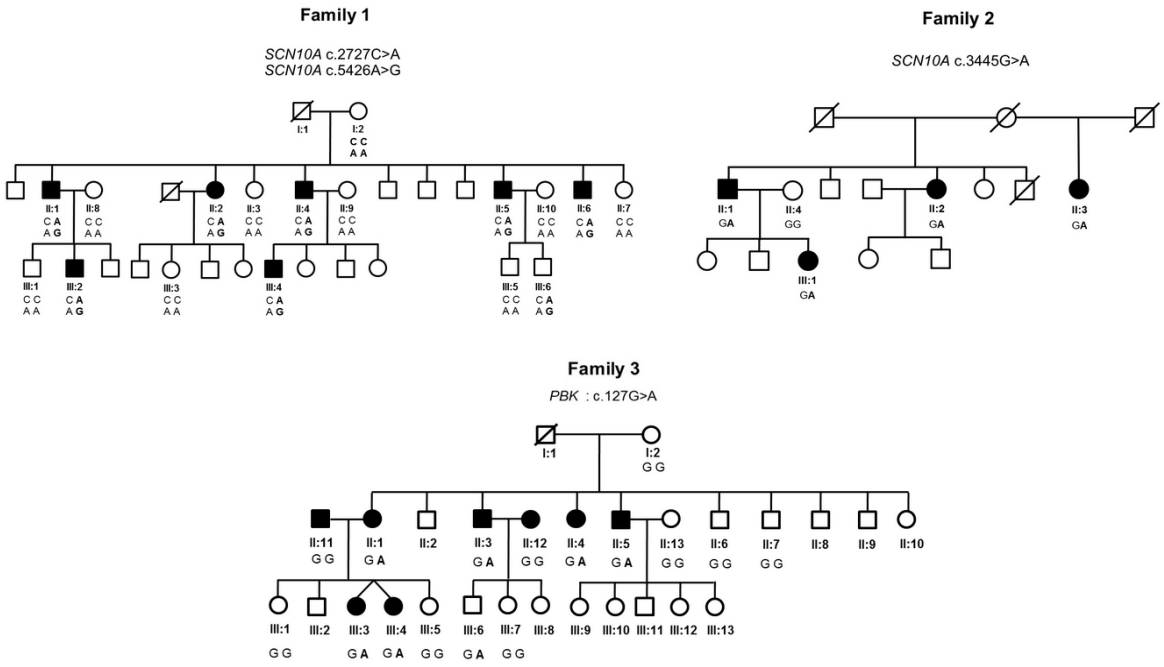

Figure 3 Segregation analyses of genetic variations in three families affected with kidney stone disease (KSD).

Functions of the genes and encoded proteins associated with KSD in Thai population

The current evidence of the potential causative genes and their mutations and polymorphisms associated with KSD in Thai population, especially in the NE Thai patients, have been collected and the results demonstrate the genetic heterogeneity of KSD in the NE Thai population. The identified genes are involved in various mechanisms of stone formation, including stone inhibition, ion imbalance, oxidative stress, and oxalate degrading bacteria as described in Figure 4 and summarized below.

F2

Prothrombin (coagulation factor II) is encoded by the *F2* gene. Urinary prothrombin fragment 1 (UPTF1), the product of prothrombin, was initially described as a crystal matrix protein within calcium oxalate crystals, and is considered to be a potent inhibitor of calcium oxalate growth and aggregation in urine (Suzuki *et al.*, 1994; Stapleton and Ryall, 1995) (Figure 4). The association study of *F2* variant (rs5896 or T165M) showed that C allele was the protective allele only in the female group. The reason why rs5896 plays a role only in the female group is still unclear. However, the prevalence of KSD in the NE Thai population has been shown to be predominant in the male group, with male to female ratio of about 2:1 (Sritippayawan *et al.*, 2009). Gender and sex hormones are known to have some influence on the prevalence of KSD. Thus, it is possible that different modifiers might differently influence males and females, or this might be the result of a complex interaction between F2 and specific sex hormones in either group. Furthermore, the UPTF1 level was high in the urine samples from female subjects carrying homozygous-CC. This could explain the protective effect of C allele in the female group with a lower risk of developing KSD (Rungroj *et al.*, 2018).

PAQR6

PAQR6 is the gene encoding progestin and adipoQ receptor family member 6, which belong to the progestin and AdipoQ receptor family (PAQR) that can be activated by progesterone or by some of its metabolites such as dihydroprogesterone and allopregnanolone. These receptors are involved in reproduction, development, immunological, and neuroendocrine responses (Fernandes *et al.*, 2005; Dressing and Thomas, 2007; Mesiano *et al.*, 2011; Pang *et al.*, 2013). However, *PAQR6* has never previously been described to be associated with KSD. It was hypothesized that *PAQR6* may be regulated by progesterone and may simulate Ca^{2+} reabsorption at the distal part of the nephron (Shughrue *et al.*, 1988; Brunette and Leclerc, 2002; Tang *et al.*, 2005). The SNP rs759330 that is located at a predicted microRNA binding site at 3′ UTR of the *PAQR6* gene (Rungroj *et al.*, 2014) might affect the level of gene expression and is correlated with Ca^{2+} reabsorption in the kidney (Figure 4).

SLC13A2

SLC13A2, encoding a sodium-coupled citrate transporter, was reported to play a role in the formation of kidney stones. Citrate inhibits calcium oxalate crystallization by forming complexes with calcium (Chow *et al.*, 2004) (Figure 4). The patients with AA genotype of SNP rs11567842 had a high expression of *SLC13A2* mRNA in their affected kidneys (Udomsilp *et al.*, 2018). A higher expression level of the *SLC13A2* gene in renal tubular cells can lead to an increased reabsorption of citrate, as well as a risk of hypocitraturia. Persistent and long-standing hypocitraturia may gradually promote the development of KSD.

ITLN1

ITLN1, encoding the intelectin-1, can specifically bind to microbial carbohydrate chains in a calcium-dependent manner, as in the case of innate immune lectins (Tsuji *et al.*, 2001; Wesener *et al.*, 2015). *ITLN1* functions which associate with KSD are still unknown. It was hypothesized that intelectin-1 may recognize bacteria in the intestinal tract. Since human intelectin-1 is highly expressed in the intestinal tract, it might be associated with a Gram-negative anaerobic bacterium like *Oxalobacter formigenes*, which plays an important role in degrading oxalate in the intestinal tract.

SCN10A

SCN10A, encoding the $Na_V1.8$ α subunit of the voltage-gated sodium channel, was initially reported to be preferentially expressed in peripheral sensory neurons and heart tissue. Gain-of-function alterations of the *SCN10A* cause painful peripheral neuropathy (Garrison *et al.*, 2014), whereas its loss-of-function alterations result in prolonged cardiac conduction disease and Brugada syndrome (Chambers *et al.*, 2010; Hu *et al.*, 2014). The $Na_V1.8$ α subunit protein was also found to be expressed in proximal tubules and in the collecting ducts of the nephron in the human kidney. The variant protein (p.N909K and p.K1809R in the same polypeptide chain) expressed in cultured cells was unstable, which reduces the current density, as studied by the whole-cell patch clamp technique (Nettuwakul *et al.*, 2018). These analyses showed that loss-of-function alterations of *SCN10A* might reduce Na^+ reabsorption, resulting in a high Na^+ filtration, and decreased Ca^{2+} reabsorption (Figure 4).

PBK

The *PBK* gene, encoding the PDZ binding kinase, is a member of the mitogen-activated protein kinase (MAPKK) family, and its activated form phosphorylated p38 MAPK (Abe *et al.*, 2000; Gaudet *et al.*, 2000; Matsumoto *et al.*, 2004; Ayllon and O'Connor, 2007). The p.G43R substitution results in the instability of PBK and reduces the phosphorylation of p38 MAPK (Nettuwakul *et al.*, 2020), thereby regulating the downstream signaling pathway, including cell viability and apoptosis. This phenomenon might affect cell survival from oxidative stress, resulting in renal epithelial injury and kidney stone formation (Figure 4).

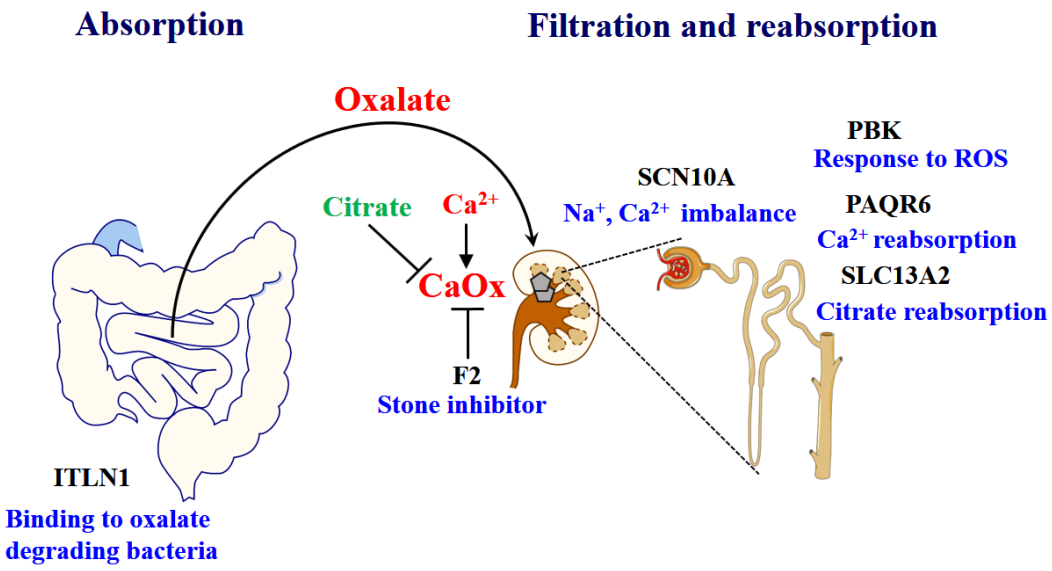

Figure 4 Genes responsible for kidney stone disease (KSD) in the NE Thai patients and their related mechanisms.

CONCLUSION

Several approaches can be applied to identify the genes responsible for KSD in Thai populations. The use of common SNPs for candidate-gene or genome-wide association approaches require further analysis to identify the causative mutations or functional SNPs. The advent of NGS technology has greatly assisted the identification of genes and mutations responsible for KSD. In this review, we presented the current evidence of the potential causative genes and mutations for KSD in the NE Thai patients. At least 4 common SNPs in *F2*, *PAQR6*, *SLC13A2* and *ITLN1* genes were identified by genetic association studies. Four mutations or non-synonymous alterations in *SCN10A* and *PBK* genes were identified by exome sequencing and gene scanning in the families affected with KSD. These results illustrate the genetic heterogeneity of KSD in the population in the NE region of Thailand. The identified genes are involved in various mechanisms of stone formation, such as stone inhibition, ion imbalance, oxidative stress, and oxalate degrading bacteria (Figure 4). The genes or loci identified in Thai patients with KSD provide insights into the pathogenesis of this disorder. However, additional studies are required to completely understand genetic alterations and mechanisms of KSD in the NE Thai population so that the more effective methods for prevention, treatment, and control of KSD in this population will be developed and applied.

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