Molecular genetics of kidney stone disease

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ABSTRACT

Kidney stone disease (KSD) is a multifactorial disease caused by a complex interaction of genetic and environmental factors. It causes significant morbidity and medical care expenses worldwide, which can be found commonly in tropical territory including Thailand. A majority of kidney stones are composed of calcium and it is usually associated with a metabolic abnormality such as hypercalciuria, hyperoxaluria, hyperphosphaturia, hyperuricosuria, hypocitraturia, and a defect of urinary acidification. However, few defects associated with monogenic forms of KSD have been identified. To date, molecular genetic studies to investigate genetic contribution of multifactorial KSD have been extensively performed and a number of causative genes have been recognized, but they vary among populations. In Thailand, the highest prevalence of KSD was observed in the northeastern (NE) area. Its etiology and pathogenesis are still obscure and unique characteristics with no conditions of increased urinary solutes such as hypercalciuria, hyperoxaluria, and hyperuricosuria. These conditions are different from what have been reported in other ethnic groups. The study to identify causative genes will provide more understanding of pathogenesis underlying KSD and also the unique pathogenesis of KSD in NE Thai patients. These will lead to improved quality and efficiency of patient care, diagnosis, prevention and control of diseases and complications. The knowledge of reported monogenic and multifactorial KSD, and the update on molecular genetic studies to investigate genes responsible for the disease in NE Thai patients are reviewed in this article.

Keywords: Kidney stone disease; Nephrolithiasis; Genetic association study; Single nucleotide polymorphisms; Candidate gene

INTRODUCTION

Kidney stone disease (KSD) or nephrolithiasis is a formation of hard mass containing protein and crystalline materials within the kidney, ureter, or bladder. The patients with KSD suffer from colicky flank pain, abdominal pain and painful urination that are frequently attended by nausea, vomiting, hematuria, dysuria, and oliguria (Coe *et al*., 2005). The prevalence of KSD affects 5-15% of population worldwide with recurrence rate of 50% within 5–10 years and 75% in 20 years (Trinchieri *et al*., 1999; Moe, 2006). In Thailand, KSD is common in the northeastern (NE) part where its prevalence is 6.6% (Sritippayawan *et al*., 2009). Therefore, KSD is an important clinical problem

causing medical care expenses and public health burden. The etiology of KSD is heterogeneous, ranging from a monogenic defect to a complex interaction between genetic and environmental factors (Coe *et al*., 2005). Several scientific evidences have indicated the contribution of genetic component in the pathogenesis of KSD and a limited number of monogenic forms have been identified, for examples mutations of *calcium sensing receptor* (*CASR*) gene in autosomal-dominant hypoparathyroidism and mutations of the *claudin 16* (*CLDN16*) gene in familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (Attanasio, 2011; Vezzoli *et al*., 2011). In addition, by using many genetic approaches including the modern strategy of the genome-wide association study (GWAS) to identify genes responsible for the KSD, many genetic variations of several human genes have been described. However, these reported genes vary among ethnic groups and a frequent genetic abnormality causing the disease has not been elucidated.

KSD is endemic in the NE population of Thailand. The most recent investigation from our group demonstrated that it is prevalent in this population and the risk of having the disease is higher among members of affected families, compared to that of the normal control population, indicating an involvement of genetic factor (Sritippayawan *et al*., 2009). To further investigate genetic factor contributing to kidney stone formation in this population, we conducted association studies for eight candidate genes related to stone inhibitors. We then firstly reported the association between *prothrombin* (*F2*), encoding urinary prothrombin fragment 1 (UPTF1), and KSD in the NE Thai female patients (Rungroj *et al*., 2011). Subsequently, a specific *F2* variation associated with kidney stone risk was identified, highlighting the role of UPTF1 in the kidney stone formation (Rungroj *et al*., 2012).

The knowledge of the genetic influence in KSD has evolved significantly in the past century. Discovery of the causative genes and recognition of their variations has made molecular diagnostics possible and lead to improved quality and efficiency of patient care, identification of new therapeutic targets and treatment approaches. In this review, we describe genetic determinants underlying KSD and provide updates on molecular genetic studies of genes responsible for the disease in NE Thai patients.

Genetic epidemiology of KSD

Genetic contribution to KSD has been documented long time ago. It has been recognized in the 19th century that patients with kidney stone were more likely than non-kidney stone formers to have other family members affected with KSD (Clubbe, 1872). Several studies showed that the disease risk was high in the members of family with history of KSD. The familial aggregation studies, which are commonly summarized in term of relative risk (λ_R), heritability (h^2), and twin study, which is often represented in term of concordance rate, indicated the contribution of genetic components to disease susceptibility. The first evidence of genetic influence to KSD was studied in 174 patients (including parents, siblings, and offspring) compared with 174 control subjects. The results showed the prevalence of KSD in patients group was significantly higher than in control group (McGeown, 1960). Subsequently, it has been reported that the relative risk of KSD in the affected families is approximately 2–4 folds when compared with general population (Resnick *et al*., 1968; Trinchieri *et al*., 1988). Furthermore, other studies investigated the influence of genetic factor by measuring the possibility of disease phenotype that can be transmitted to siblings and showed there was the high degree of heritability for KSD (Falconer and

Adams 1965; Loredo-Osti *et al*., 2005), suggesting the disease development could be transmitted from the parents. More recently, a large cohort study in Iceland revealed that the risk of KSD in the members of the affected families was significantly higher than in the general population (Edvardsson *et al*., 2009). These data suggested strong evidences of genetic factor contributed to KSD.

Several twin studies have shown higher concordance rate, defined as the proportion of identical twins that developed KSD, which is higher in monozygotic twins than dizygotic twins. In a Vietnamese study, the concordance rate of the probands in monozygotic twins was 32.4% whereas it was 17.3% in dizygotic twins and the degree of heritability was 56% (Goldfarb *et al*., 2005), suggesting genetic factor is a cause of KSD. In another twin study, the heritability of urinary stone risk markers (such as calcium, oxalate, citrate, and uric acid) in monozygotic twins was greater than in dizygotic twins (Hunter *et al*., 2002; Monga *et al*., 2006). The difference of the concordance rate and degree of heritability in monozygotic twins, whose genetics are identical, and dizygotic twins, who shared only some of their genetic background, imply the involvement of genetic factor in KSD.

Monogenic disorders cause KSD

Many studies described a number of KSD serve as a Mendelian fashion, a monogenic disease in which the defect of only one gene can trigger the onset of the disease such as Dent's disease, Bartter syndrome, hereditary distal renal tubular acidosis (dRTA), primary hyperoxaluria, mutations of calcium-sensing receptor, and primary hyperparathyroidism (Resnick *et al*., 1968; Vezzoli *et al*., 2011). Genetic defects associated with monogenic forms of KSD are summarized in Table 1 and some of them are described below.

Dent's disease

Dent's disease is a rare X-linked recessive renal tubular disorder characterized by proximal tubulopathy, low molecular weight proteinuria, hypercalciuria, nephrocalcinosis and progressive renal insufficiency, with or without bone disease (Wrong *et al*., 1994). It is caused by the mutations of *chloride channel voltage-sensitive 5* (*CLCN5*) encoding a voltage-gated chloride channel protein (CLC-5) (Lloyd *et al*., 1996). The CLC-5 has various functions comprising control of channel activation, ion selection, and regulation of cell volume (Jentsch *et al*., 2005). It is predominantly expressed in the proximal tubules of the kidney and has been reported to be involved in membrane recycling via endocytic pathway, accumulation of intravesicular acid, and membrane trafficking through receptor-mediated endocytosis (Devuyst *et al*., 2005; Hara-Chikum *et al*., 2005). The mutations of *CLCN5* gene result in impairment of chloride channel function. For examples, mutations in the CBS domain of CLC-5 lead to disruption of protein trafficking, accumulation of the mutated protein in the Golgi body, and impairment of chloride flow (Carr *et al*., 2003). Furthermore, the *CLCN5*-deficient mice developed Dent's disease (Gunther *et al*., 2003).

Bartter syndrome

Bartter syndrome is a group of autosomal recessive hereditary disorders that is characterized by defects of salt transport in the thick ascending limb of Henle's loop (TAL) (Hebert, 2003). Most patients with Bartter syndrome have renal salt wasting that may lead to lowered blood pressure (hypotension), hypokalemic alkalosis, and hypercalciuria with nephrocalcinosis (Thakker, 2000; Hebert, 2003). Mutations of six genes that are expressed in the TAL have been associated with six types of Bartter syndrome. Bartter syndrome type I is due to mutations of gene encoding *sodium-*

Table 1 Some of the Mendelian inherited forms of KSD (modified from Attanasio, 2011; Vezzoli *et al*., 2011).

Gene	Protein	Phenotype	Mode[a]	Disease	References
CLCN5	Chloride channel-5 (CLC-5)	Multiple reabsorption defects in the proximal tubule. Stones, nephrocalcinosis and possible end-stage renal failure.	X-linked	Dent's syndrome	Cho *et al*., 2008; Scheinman *et al*., 2000
OCRL1	Phosphatidylinositol 4,5-bisphosphate 5-phosphatase	Multiple reabsorption defects in the proximal tubule. Stones, nephrocalcinosis and possible end-stage renal failure. Hydrophthalmia and cataract.	X-linked	Dent's syndrome 2 Lowe syndrome	Cho *et al*., 2008
SLC12A1	Na-K-2Cl cotransporter	Renal hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism and nephrocalcinosis.	AR	Bartter syndrome type I	Simon *et al*., 1996a
KCNJ1	Potassium channel	Renal hypokalemia, alkalosis, hypercalciuria, secondary aldosteronism and nephrocalcinosis.	AR	Bartter syndrome type II	Simon *et al*., 1996b
ClCNKB	Basolateral chloride channel	Hypokalemic alkalosis, hypercalciuria	AR	Bartter syndrome type III	Simon *et al*., 1997
CASR	Calcium sensing receptor	Hypokalemic alkalosis, hypomagnesemia, hypercaliuria, hypocalcemia	AD	Bartter syndrome type V Autosomal-dominant hypoparathyroidism	Pearce *et al*., 1996
SLC4A1	Anion exchanger	Hypokalemic hyperchloremic acidosis, nephrocalcinosis and kidney stones.	AD	Distal renal tubular acidosis (dRTA)	Bruce *et al*., 1997
ATP6V1B1	H^+-ATPase, subunit B1	Hypokalemic hyperchloremic acidosis with nephrocalcinosis and kidney stones. Neural deafness.	AR	dRTA with progressive neural deafness	Karet *et al*., 1999
ATP6V0A4	H^+-ATPase, subunit a4	Hypokalemic hyperchloremic acidosis with nephrocalcinosis and kidney stones.	AR	dRTA without progressive neural deafness	Smith *et al*., 2000
CLDN16	Claudin 16	Urinary loss of magnesium and calcium, nephrocalcinosis, and progressive kidney failure in homozygotes. Heterozygotes may produce kidney stones.	AD	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	Müller *et al*., 2003
CLDN19	Claudin 19	Renal wasting of magnesium and calcium, nephrocalcinosis and progressive kidney failure in homozygotes. Macular colobomata and nystagmus.	AD	Familial hypomagnesemia with hypercalciuria and nephrocalcinosis with ocular impairment	Konrad *et al*., 2006
SLC34A3	Sodium-phosphate cotransporter	Severe rickets and kidney stones caused by renal loss of phosphate, hypophosphatemia, and hypercalciuria.	AR	Hypophosphatemic rickets with hypercalciuria	Bergwitz *et al*., 2006
AGXT	Alanine-glyoxylate aminotransferase	Hyperoxaluria, chronic renal failure, oxalosis	AR	Primary hyperoxaluria type I	Nishiyama *et al*., 1991
GRHPR	Glyoxylate reductase/ hydroxypyruvate reductase	Hyperoxaluria, chronic renal failure, oxalosis	AR	Primary hyperoxaluria type II	Cramer *et al*., 1999

[a]Mode of inheritance, AD: Autosomal dominant; AR: Autosomal recessive

potassium-chloride cotransport (*SLC12A1*), type II is due to mutations of the *ROMK potassium ion channel* gene (*KCNJ1*), and type III is due to mutations of the *voltage-gated chloride channel* (*CLC-Kb*). Functional defects of these genes involves in decreasing of salt transport by TAL (Hebert, 2003; Langman, 2004). Bartter syndrome type IV is caused by mutations of the *barttin* (*BSND*) gene, a β-subunit of chloride channel that is required for trafficking of CLC protein and type V is due to gain-of-function mutations of the *calcium sensing receptor* (*CASR*) gene. Functional defects of these two genes are involved in regulation of salt transport (Waldegger *et al*., 2002; Watanabe *et al*., 2002). Lastly, Bartter syndrome type VI is due to mutations of the *CLCN5* gene (Besbas *et al*., 2005).

Hereditary distal renal tubular acidosis (dRTA)

Hereditary distal renal tubular acidosis (dRTA) is a metabolic acidosis disorder that is characterized by the deficiency of hydrogen ions secretion in the distal nephron (Laing *et al*., 2005). dRTA is also associated with other diseases such as hypokalemia, hypercalciuria with nephrocalcinosis, nephrolithiasis, and often metabolic bone disease (Laing *et al*., 2005). dRTA is a group of autosomal dominant and/or autosomal recessive inheritance based on type of genes mutation (Batlle *et al*., 2001). Autosomal dominant dRTA is due to mutations of the gene encoded *solute carrier family 4 anion exchanger member 1* (*SLC4A1* or *AE1*) (Bruce *et al*., 1997; Karet *et al*., 1998). However, mutations of this gene also cause autosomal recessive dRTA in Thai patients (Yenchitsomanus *et al*., 2002). The major function of AE1 protein is involved in chloride and bicarbonate ions transport across the cell (Laing *et al*., 2005). The mutations of *AE1* gene can cause several abnormalities function, including reduction of chloride transport and defective AE1 protein trafficking (Quilty *et al*., 2002; Devonald *et al*., 2003; Rungroj *et al*., 2004). Autosomal recessive dRTA is caused by mutations of gene encoding H^+-ATPase (Karet *et al*., 1999). It is associated with or without progressive nerve deafness caused by mutations of *ATP6V1B1* or *ATP6V0A4* genes, respectively (Smith *et al*., 2000; Stover *et al*., 2002). Moreover, in some patients with autosomal recessive dRTA, *ATP6V1B1* or *ATP6V0A4* genes mutations were not found, indicating mutations in other genes may be a cause of autosomal recessive dRTA (Stover *et al*., 2002).

Primary hyperoxaluria

Primary hyperoxaluria is a severe rare autosomal recessive metabolic disorder, which is characterized by the deficiency of specific enzyme in the glyoxalate metabolic pathway, leading to excessive production of oxalate. Primary hyperoxaluria type I is caused by *alanine-glyoxylate aminotransferase* (*AGXT*) gene mutations (Danpure *et al*., 2003). More than 150 mutations of *AGXT* gene have been reported, most of them are missense mutations (Cellini *et al*., 2012). Many *AGXT* mutations have impact on structure and function of AGXT protein. For examples, S206P and G41R mutations causing enzyme inactivation by increased degradation in the peroxisome and mutation of G161R (common mutation) induced the cytosolic aggregation and enzyme degradation (Langman, 2004; Oppici *et al*., 2013). Primary hyperoxaluria type II is caused by the mutations of the *glyoxylate reductase/hydroxypyruvate reductase* (*GRHPR*) gene resulting in inactivation of both glyoxylate reductase and hydroxypyruvate reductase (Danpure and Rumsby 2004). The effect of these mutations could enhance urinary oxalate excretion, which can promote calcium oxalate stone formation.

Mutation of calcium sensing receptor (CASR)

CASR gene encodes a 1,078 amino acid of calcium sensing receptor (CASR) protein (Thakker, 2004). It is predominantly expressed in the parathyroid glands and renal tubules, and is a member of the G protein-coupled receptors (Stechman *et al*., 2009). It regulates the parathyroid hormone (PTH) secretion and calcium reabsorption in the renal tubules (Thakker, 2004). Several studies indicated that the autosomal dominant hypercalciuria and hypoparathyroidism are caused by many activating or inactivating mutations of this gene, which can promote calcium stone formation (Vezzoli *et al*., 2011).

Studies of KSD susceptibility genes

Study of KSD susceptibility gene is useful for improvement of disease prevention, disease management, and lead to better understanding of the molecular mechanisms underlying pathogenesis. However, since the majority of kidney stones are calcium-containing (Herring, 1962) and hyper-calciuria is the most commonly identified metabolic risk factor for KSD, the examination for susceptibility loci has logically focused on genes involved in calcium metabolism. To date, several genetic approaches including a single candidate gene association study, genome-wide association study (GWAS), and linkage analysis have been performed to investigate genes that responsible for KSD (Attanasio, 2011; Tore *et al*., 2011). The association study is based on principle of linkage disequilibrium (LD), which is a statistical observation of the relationship between frequency of alleles and phenotypes, according to population-based studies; while linkage analysis is based on the principle of linkage, which describes genetic relationship between chromosome regions and phenotypes, according to family-based studies (Strachan and Read, 1999). From these approaches, a number of genetic variations of several human genes have been reported to be associated with KSD. For examples, *osteopontin (OPN)* (Gao *et al*., 2007; Liu *et al*,. 2010), *calcitonin receptor (CTR)* (Chen *et al*., 2001a), *vitamin D receptor (VDR)* (Chen *et al*., 2001b), *urokinase* (Tsai *et al*., 2002), *interleukin (IL-1β and IL-Ra)* (Chen *et al*., 2001c; Mittal *et al*., 2007), *E-cadherin* (*CDH1*) (Tsai *et al*., 2003; Tan *et al*., 2013), *androgen-oestrogen receptors (AR and ER)* (Chen *et al*., 2001d), *vascular endothelial receptor growth factor (VEGF)* (Chen *et al*., 2003), *fetuin-A* (*AHSG*) (Aksoy *et al.*, 2010), *matrix Gla protein* (*MGP*) (Lu *et al*., 2012) and *calcium sensing receptor (CASR)* (Vezzoli *et al*., 2007; Chou *et al*., 2011) have been reported to be associated with KSD with a predominantly hypercalciuria and calcium oxalate kidney stones. However, these reported genes had little effect on clarifying the contribution to KSD and a frequent genetic abnormality causing the disease has not been elucidated.

More recently, by genome-wide association studies (GWAS) examined the whole genomic DNA with many thousands of SNPs, genes that associated with KSD were reported. The first GWAS in the population from Iceland and the Netherlands with KSD was published in 2009, and identified a member of the claudin gene family (*CLDN14*) as a risk locus. In detail, a synonymous variant (rs219780) in the *CLDN14* has been associated with KSD and bone mineral density (Thorleifsson *et al*., 2009). Subsequently, *uromodulin (UMOD)* variant affected risk of chronic kidney disease by providing protection against KSD was reported by the same research group (Gudbjartsson *et al*., 2010). By using this GWAS method, new loci for uric acid KSD in Sardinia population have been investigated and the minor A allele of SNP rs10946741 in the flanking

5'UTR of *LRRC16A* gene showed a statistically significant increase in patients with uric acid KSD (Tore *et al*., 2011). Another GWAS study of susceptibility gene for KSD has been carried out in Japanese population. Novel susceptible loci at 5q35.3, 7p14.3, and 13q14.1 were identified and SNP rs11746443 located in the upstream of the *SLC34A1* and *AQP1* genes that may increase the risk of KSD was reported (Urabe *et al*., 2012). Later, a replication study for these loci reported that three SNPs including rs12654812, rs12669187, and rs7981733 located on the *RGS14*, *FAM188B*, and *DGKH* genes, respectively, were also associated with KSD in Japanese population (Yasui *et al*., 2013).

Genetic studies of KSD in Thailand

KSD is a major health problem in the northeastern (NE) Thai population (Yanakawa *et al*., 1997; Aegukkatajit *et al*., 1999). Its cause is unknown but may be unique because hypercalciuria, hyperoxaluria, and hyperuricosuria that are common in the western and other ethnic groups were not demonstrated in the most of these patients (Sriboonlue *et al*., 1991). Previously, the reported prevalence of KSD in this population was considerably variable (Sriboonlue *et al*., 1992; Nimmannit *et al*., 1996; Yanakawa *et al*., 1997), which probably depended on the methods of studies and it is not clear whether the genetic factor plays a role in its pathogenesis. The most recent investigation, conducted in Khon Kaen with 1,034 subjects including 135 patients, 551 family members, and 348 villagers of control population, reported that the prevalence of KSD in the members of the affected families (21.05%) was higher than in the villagers (6.61%). Thus, the relative risk of the disease among family members was 3.18, indicating a genetic factor plays a role in the pathogenesis of KSD in this population (Sritippayawan *et al*., 2009).

To further investigate the role of genetic factor in pathogenesis of KSD in this population, our group employed various genetics approaches such as candidate-gene and genome-wide association studies and linkage analysis, to identify the disease or susceptible genes. Our first attempt was to perform a candidate-gene association study by genotyping 67 SNPs in 8 candidate genes, comprising *TFF1*, *S100A8*, *S100A9*, *S100A12*, *AMBP*, *SPP1*, *UMOD*, and *F2*, that encode stone inhibitor proteins including trefoil factor 1, calgranulins (A, B, and C), bikunin, osteopontin, Tamm-Horsfall protein, and urinary prothrombin fragment 1 (UPTF1), respectively, in patient and control subjects. We found that minor allele and homozygous genotype frequencies of 8 from 10 analyzed SNPs distributed within the *F2* gene were significantly higher in the control group than those in the patient group. In addition, two *F2* haplotypes were found to be dually associated with kidney stone (one with decreased risk and the other with increased risk) in the female group, indicating that *F2* variations influence the risk of KSD in the NE Thai female patients (Rungroj *et al*., 2011). Subsequently, the specific variation of *F2* gene associated with KSD in these patients was identified by sequencing of *F2* promoter and all coding regions (Rungroj *et al*., 2012). One exonic non-synonymous SNP rs5896 (c.494C>T) located in exon 6 results in a substitution of threonine by methionine at the position 165 (T165M) was found. The SNP rs5896 was then genotyped in 209 patients and 216 control subjects and the statistical analysis showed that C allele and homozygous CC genotype of the rs5896 in the patient group were significantly lower than in control group. However, the significant differences of genotype and allele frequencies were maintained only in the female group. The effect of amino-acid change on the structure of protein product of *F2* gene (UPTF1) was

also examined by homologous modeling and *in silico* mutagenesis. T165 is conserved and T165M substitution will affect hydrogen bond formation with E180. These results indicated that *F2* variant (T165M) is associated with KSD risk in the NE Thai female patients and emphasized the role of UPTF1 in the kidney stone formation. Further study to examine the link between genetic variation and biological function of the variant protein is in progress.

Recently, the next-generation sequencing techniques that are feasible to sequence all exons or the whole genomes are likely to become the commonly used tool to identify disease gene (Gilissen *et al*., 2012). Our group is employing a combination method of genome-wide linkage analysis and exome sequencing for identification of disease-causing genes and mutations underlying KSD in the NE Thai families.

CONCLUSIONS

Genetic contribution to monogenic and complex forms of KSD has been extensively investigated and recognized during the past few decades. A number of variations of certain genes involved in KSD have been widely reported. However, the contribution and pathogenic weight of these genes remain unclear. Further molecular genetic studies to identify causative genes of KSD are still required. An advance of high-powered sequencing techniques like whole genome or exome sequencing will undoubtedly enhance the potential to identify additional risk loci and this knowledge will provide a better understanding of pathogenesis underlying stone forming and will improve quality and efficiency of patient care, diagnosis, prevention and control of diseases and complications.

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