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Kajian Artikel : Faktor Risiko Genetik Urolitiasis Idiopatik: Peran Penyebab Gen Dalam Pembentukan Batu Ginjal

Genetic Risk Factors For Idiopathic Urolithiasis:The Causative Role Of Genes In Stones Formation. A Review Article

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ABSTRAK

Latar Belakang: Faktor genetik urolitiasis memainkan peran penting dalam etiologi. Penjelasan gen yang bertanggung jawab dapat mengarah pada terapi dan pencegahan gen yang ditargetkan dengan lebih baik di masa depan. Artikel ini bertujuan untuk menjelaskan berbagai faktor genetik yang berperan dalam pembentukan batu ginjal. Metode: Sebuah tinjauan atikel tentang urolitiasis berdasarkan pendekatan genetika dilaporkan mendasari pembentukan batu. Sejumlah 41 abstrak dan artikel penelitian yang diterbitkan oleh jurnal yang bereputasi internasional dipilih berdasarkan kata kunci faktor genetik dan urolithiasis Simpulan: Pemahaman yang lebih dalam tentang faktor genetik yang berperan dalam mekanisme pembentukan batu serta kemajuan molekuler dan farmakogenomik telah merevolusi diagnosis dan pengobatan, dan membuka jalan untuk identifikasi target terapi baru dan pendekatan pengobatan berdasar rekayasa genetik.
Kata kunci : genetik, idiopatik, batu ginjal

ABSTRACT

Background: The genetic factor of urolithiasis plays an important role in the etiology. Elucidation of responsible genes can lead to better targeted gene therapy and prevention in the future. This article aims to explain various genetic factors that play a role in kidney stone formation Method: A review article on urolithiasis based on a genetic approach is reported to underlie stone formation. A total of 41 abstracts and research articles published by internationally reputed journals were selected based on the keywords genetic factors and urolithiasis. Summary: A deeper understanding of the genetic factors that play a role in the mechanisms of stone formation and advances in molecular and pharmacogenomics have revolutionized diagnosis and treatment, and paved the way for the identification of new therapeutic targets and treatment approaches based on genetic engineering.
Keywords: *Genestic, idiopathic, urolithiasis, kidney stone*

INTRODUCTION

The Urolithiasis is derived from the words Urolithiasis = ouron (urine, urine) and lithos (stone, stone, crystal), which is the formation of stones in the urinary system, Nephroliths (called renal calculi, ren, renes (Latin), kidney and calculi, pebbles in the language aesculapian, also called nephrolithiasis or urolithiasis, accumulation of minerals or other material forms forming minor stones in the kidneys, ureters or bladder (Smith *et al,*, 2010).

The prevalence of urolithiasis worldwide ranges from 7% to 13% in North America, 5-9% in Europe, and 1 - 5% in Asia (Sorokin *et al,* 2017). Because of the high recurrence rate of urolithiasis, the American Urological Association (Pearle *et al,* 2015) and the European Association of Urology (Türk *et al,* 2016) recommend to manage and prevent future

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recurrence by assessing dietary and medical treatment.

The increased prevalence of kidney stones is a global phenomenon. Data from five European countries, Japan, and the United States show that the incidence and prevalence of stone disease have increased over time throughout the world (Romero et al, 2010). Genetic factors have been postulated to play an important role in the risk of urolithiasis, such as a positive family history is a well-known risk factor for urolithiasis. The rate of disease association in monozygotic twins is higher than dizygotic twins (32.4% vs 17.3%) (Goldfarb et al, 2005).

Single gene mutation states such as cystinuria are known to cause nephrolithiasis in a small proportion of stone patients (Monico *et al,* 2011). *Genetic* factors that contribute to patients with idiopathic stone formation are little known, various studies have been attempted to explain the *pathology* of lithogenesis, but the exact mechanism associated with stone formation is still not fully understood. Several risk factors have been identified as causes of kidney stone formation, such as dietary, infections, low fluid intake, metabolic disorders and genetic factors. In this review, we identify genetic factors that play a role in the formation of kidney stones based on the results of the research conducted from 1999 to 2016.

METHOD

A review article on urolithiasis based on a genetic approach is reported to underlie stone formation. A total of 41 abstracts and research articles published by internationally reputed journals were selected based on the keywords genetic factors and urolithiasis.

The following genes are reported to have a possible causative role in urolithiasis: (1) Stone molecule matrix (Osteopontin, OPN), (2) Genes related to calcium regulation (eg: calcium sensing receptor (CASR); claudin 14 (CLDN14); calcium active-release calcium modulator 1 (ORAI1); (3) Genes related to calcium regulation/phosphate (eg: vitamin D (VDR); klotho (KL); sodium hydrogen antiporter 3 regulator 1 (NHERF1); fibroblast growth factor 23 (FGF23); and calcitonin receptor (CALCR), (4) Genes Related to Urinary Inhibitors of Stone Formation (e.g. Solute carrier family 13 member 2; Prothrombin); (5) Genes Related to anti-inflammatory and antioxidative stress (e.g. Interleukin 1 receptor antagonist, Paraoxonase-1, Genes for uric acid stones), (6) Other Genes (eg. Phosphate carrier NPT2a, Aquaporin-1, Diacyl glycerol kinase, Alkaline phosphatase, and Transient receptor potential cation channel subfamily V member 5) and (7) Monogenic urolithiasis

RESULT AND DISCUSSION

1. Stone Macromolecule Matrix.

Several macromolecules, such as Tamm-Horsfall glycoprotein, osteopontin, bikunin, and nephrocalcin have been detected in patients with calcium oxalate kidney stones. The role of single nucleotide polymorphisms in genes that encode these substances and the risk of idiopathic calcium oxalate stone formation has been examined.

A strong association of several SNPs in Osteopontin genes (T-593A, C6982T, rs1126616, -156delG) with urinary stone formation in populations of Turkey, Japan and Taiwan has been demonstrated. (Xiao *et al,* 2016). Likewise, polymorphism (I550V) in the gene coding for cotransporter Na + / dicarboxylate (hNaDC-1), the main regulator of urinary citrate excretion has been shown to be associated with the risk of repeated calcium-containing stones. (Okamoto *et al,* 2007). Urinary citrate is a powerful inhibitor of calcium oxalate crystal formation in human urine. Homozygous patients for this variant show significantly lower urinary citrate.

Osteopontin (OPN) is a highly phosphorylated glycoprotein that was initially identified in bone that functions as a protein adhesion motif to integrins and CD44, also identified as one of the organic components (matrix) of calcium-based urinary stones. The OPN Knock Out rat research report produces Calcium oxalate (CaOx) crystals (Tzou *et al,* 2016), whereas other studies show that the OPN facilitates the development of crystals by the process of mineralization and inflammation mediated by other cytokines and immune cells including macrophages (Joshi *et al,* 2017).

There is a controversial function, OPN is a constituent of the stone matrix, also known as a specific monocyte chemoattractant in the kidney interstitium, plays a role in suppressing nucleation and aggregation of CaOx crystals in vitro; conversely OPN knockdown in hyperoxaluric mice can cause a reduction in CaOx crystal deposition (Tsuji *et al,* 2014), several reports of OPN produce CaOx crystals (Tzou *et al,* 2016)

Extracellular OPN functions through interactions with cell surface receptors, including integrins (avb1, avb3, avb5, avb6, a4b1, a5b1, a5b1, a8b1, and a9b1) and CD44 which regulate cellular processes such as bio-mineralization, tissue remodeling and immune regulation

OPN can directly bind the surface of certain apatite crystals so that it regulates its function as an inhibitor of mineralization. OPN is not only important for bone mineralization, but is also regulated in ectopic sites, pathological phytochemicals such as vascular calculus, valvular circulation, renal crystal formation, and gallstone formation (Kahles *et al,* 2014).

2. **Calcium Regulation Genes**

2.1. Calcium-sensing receptor (CASR)

CASR is a protein G paired receptor that modulates cell activity, according to extracellular calcium concentration. This protein is expressed in the parathyroid gland and the thick ascending limb loop of Henle. Its activation encourages increased calcium excretion in the kidneys through regulation of parathyroid hormone production (PTH) and renal tubular calcium reabsorption (Vezzoli *et al,* 2013).

Studies from Italy have suggested a relationship between a single functional nucleotide polymorphism (R990G) which is rare from the CaSR gene (chromosome 3q13.3–21.1), which causes an increase in receptor function, and hypercalciuria in 124 women recruited from outpatient osteoporosis. (Vezzoli *et al,* 2007), But the nonparametric relationship and quantitative nature analysis in 64 Canadian siblings of calcium oxalate and kidney stone phosphate with varying degrees of calciuria did not reveal an association with microsatellite markers in the CaSR gene region.

2.2. Claudin 14 (CLDN14)

CLDN14 is a member of the claudin protein membrane family that regulates parts of paracellular ions and small solutes in tight junctions of the epithelium. CLDN14 is expressed in the kidneys, both in the Henle loop and in the proximal tubules, as well as in the epithelium of several other organs, and has been selectively observed to reduce the permeability of Ca^{2+} (41_TD $ DIF) through tight junctions.(Thorleifsson *et al,* 2009)

Studies have shown that CLDN14 expression is highly regulated by CASR activation, and disregulation of the kidney CASR. CLDN14 pathway can contribute to the development of kidney stones (Guha *et al,* 2015).

2.3. Calcium release-activated calcium modulator-1.

ORAI-1 is a membrane calcium channel subunit that is activated when calcium deposits run out. These gene

mutations produce deficiencies in signaling pathways that depend on the calcium reserves that are operated, which leads to immune system dysfunction. (Chou *et al,* 2011).

3. Calcium/Phosphate Regulation genes

3.1. Vitamin D receptor.

This gene codes for the nuclear hormone receptor for vitamin D3. It plays a central role in mineral metabolism, including intestinal calcium absorption and renal calcium absorption.(Lin *et al,* 2011).

3.2. Klotho.

Klotho is a type-I transmembrane protein associated with β-glucosidase, a new regulator of calcium and phosphate homeostasis. Klotho is expressed in tissues responsible for calcium homeostasis, including the kidneys, parathyroid glands, and choroidal plexus epithelium in the brain. Klotho also plays an important role in increased calcium uptake in the kidneys via TRPV5 phosphate homeostasis via FGF23. (Telci *et al,* 2011; Xu *et al,* 2013).

3.3. Sodium hydrogen antiporter 3 regulator-1.

NHERF1, also known as SLC9A3R1, binds renal tubular transporters including the Na^+ (37_TD$DIF) phosphate co-transporter 2a (NPT2a) and the PTH type 1 receptor. NHERF1 knockout mice demonstrate increased urinary calcium, phosphate, and uric acid excretion, with resultant renal calcium phosphate crystal deposits (Tzou *et al*, 2016).

3.4. Fibroblast growth factor 23.

The recently identified growth factor (FGF-23) regulates renal phosphate homeostasis by reducing renal reabsorption and intestinal absorption. FGF23 reduces phosphate by downregulating NPT2 co-transporters, resulting in urinary phosphate wasting. It also acts to decrease serum phosphorus levels by reducing the bioavailability of vitamin D3 (Telci *et al,* 2011; Rendina *et al*, 2013).

3.5. Calcitonin receptor.

Calcitonin, a 32 amino acid protein, binds to the CALCR receptor in bone osteoclasts as well as in kidney tubular cells. Calcitonin acts as a renal calcium-conserving hormone by increasing Ca2+ and Mg^{2+} reabsorption and decreasing phosphate reabsorption in the kidneys. CALCR polymorphisms are reported to be associated with changes in bone mineral density in different populations, several studies have established an association of SNP with urolithiasis (Atmoko *et al*, 2021).

4. Urinary Inhibitors of Stone Formation genes

4.1. Solute carrier family 13 member 2.

SLC13A2 is located on chromosome 17q11.2, consists of 14 exons, and encodes Na + / dicarboxylate cotransporter-1 (NaDC-1). NaDC-1 plays an important role in citrate reabsorption in the apical membrane of the proximal tubule; this protein is the main determinant of urinary citrate excretion. Genetic predisposition rather than metabolic abnormality may thus be a major cause for idiopathic hypocitraturia generating interest in NaDC-1 (Okamoto *et al,* 2007).

4.2. Prothrombin.

Prothrombin is also known as coagulation factor II, a serin-protease coagulation protein in the bloodstream that converts soluble fibrinogen into insoluble fibrin strands and catalyzes many other coagulation-related reactions. Prothrombin synthesis is controlled by F2. Urinary prothrombin fragment 1 (UPTF1), was initially detected as a crystal matrix protein within calcium oxalate crystals, and it is considered to be a potent inhibitor of calcium oxalate growth and aggregation in urine (Rungroj *et al,* 2012).

5. Antiinflammatory and antioxidative stress genes

5.1. Interleukin 1 receptor antagonist.

Interleukin (IL) -1 is one of the main proinflammatory cytokines that facilitate tissue inflammation. Its receptor, IL-1 receptor antagonist, is encoded by IL-RN and exhibits anti-inflammatory function by binding to the same receptor as IL-1a and IL-1b. (Çoker Gurkan *et al,* 2013).

5.2. Paraoxonase-1 (PON 1)

PON1 is a serum enzyme bound to high density lipoprotein that functions as an antioxidant. Its activity is reduced in an environment of high oxidative stress and is associated with increased lipid peroxidation, which is a factor in determining the tendency for stone formation. (Atar *et al,* 2016).

5.3. Genes for uric acid stones.

A study reports the possible relationship of SNP in caspase activation and domain 8 gene (CARD8) in the formation of stones with gout (uric acid) (Chen *et al,* 2015). CARD8 is an innate immune component involved in suppressing NF-kB activation. CARD8 suppresses the immune response and inflammatory activity. CARD8, also known as NDPP; DACAR; DAKAR; NDPP1; TUCAN; CARDINAL is an innate immune component involved in the suppression of activation of the core factor KB. CARD8 suppresses the immune response and inflammatory activity, which is located on chromosome 19q13.33 and consists of 22 exons. (Chen *et al,* 2015)

6. Genes in hyperoxaluria

6.1. Pimary hyperoxaluria-1 (OMIM259900)

Persistent and marked hyperoxaluria is proven from infancy, although the level of hyperglycolic aciduria varies. More than 100 mutations in the gene coding for AGT (AGXT, 2q37.2) have been described. Molecular diagnosis is possible in most patients (Williams *et al,* 2009). About a third of patients experience a significant reduction in urinary oxalate excretion when receiving a pharmacological dose of vitamin B6, a response that has been associated with the most common mutations (c.508 G> A, G170R), which causes a unique peroxisome - a defect in mitochondrial trade. (Monico *et al,* 2005).

6.2. Pimary hyperoxaluria-2 (OMIM260000)

Lack of cytosolic activity of liver glyxylate / hydroxyprovatase reductase (GRHPR) causes PH2 (Giafi, & Rumsby, 1998). GRHPR has multiple enzymatic activity, catalyzes the reduction of glycylates to glycolic and hydroxypyronate to D-glycerate in the human heart.

6.3. Pimary hyperoxaluria-3

Primary hyperoxaluria (PH3) has been clinically recognized for some time in patients with early onset nephrolithiasis and is characterized by hyperoxaluria that cannot be distinguished from PH1 and PH2 but the liver's AGT and GRHPR activity is normal. (Monico *et al,* 2002)

Mutations in the HOGA1 gene have been determined to be responsible.(Belostotsky *et al,* 2010) This disease appears to be autosomal recessive, although its inheritance is not yet fully understood. (Monico *et al,* 2011). Hyperoxaluria is believed to be the result of a deficiency of the 4-hydroxy-2-oxoglutarate aldolase liver mitochondrial enzyme. Early experience shows that the prevalence of PH3 is similar to PH2. (Monico *et al,* 2011).

7. Other Genes

7.1. Phosphate carrier NPT2a.

SLC34A1, a member of the type IIa sodium phosphate cotransporter family. NPT2a is responsible for phosphate absorption at the apical membrane of renal proximal tubular cells. (Yasui *et al,* 2013) NPT2a knockout mice demonstrate hypercalciuria and renal calcium phosphate

crystal deposits (Tzou *et al,* 2016). Mutations of SLC34A1 appear to be associated with hypophosphatemic nephrolithiasis and osteoporosis in humans.(Yasui *et al,* 2013).

7.2. Aquaporin-1

Aquaporin-1 is a family of small integral membrane proteins associated with the main intrinsic protein (MIP or AQP0). This gene encodes an aquaporin which functions as both a molecular water channel protein and as a non-selective cation channel gated by cyclic guanosine monophosphate (cGMP).(Boassa, & Yool, 2003) Aquaporin-1 is widely expressed in the kidneys, especially in the proximal tubule, and has a function as a water channel. Aqp1 knockout mice exhibit reduced osmotic permeability and developed hydration after lack of water

7.3. Diacyl glycerol kinase, (DGKH)

DGKH is is a family of enzimes taht catalyzes the conversion of Diacylglycerol (DAG) to phosphatidic acid, utilizing ATP as a source of the phosphate. expressed in the brain and has been known to be associated with psychiatric disorders such as bipolar disorder and major depression. DGKH is a DGK family, which is involved in the entry of transplasmalemmal calcium ions. (Xu *et al,* 2014).

7.4. Alkaline phosphatase.

Alkaline phosphatase (ALP), one kind enzyime found in the body, a member of the alkaline phosphatase family as a tissue nonspecific form and a membrane-bound glycosylated enzyme. ALP is expressed in the proximal tubules of the kidney and hydrolyzes pyrophosphate to free phosphate, suggesting its facilitating role in kidney stone formation

7.5. Transient receptor potential cation channel subfamily V member 5.

TRPV5 is a highly selective epithelial calcium channel expressed at the apical membrane of the distal renal tubule epithelial cells, which mediates calcium transport in the kidney and constitutes the rate-limiting step of active calcium reabsorption.

TRPV5 (- / -) mice showed significant impairment in calcium homeostasis similar to human patients with idiopathic hypercalciuria,(Hoenderop et al, 1999) including marked hypercalciuria, increased absorption of dietary calcium, increased levels of vitamin D, and disorders of the bone (reduced trabecular and cortical mass), suggesting a major regulatory role for TRPV5. The encoding of the human gene for TRPV5 is located on chromosome 7q35.43. Screening of the TRPV5 molecule in 20 patients with renal hypercalciuria revealed 8 changes in a single nucleotide base, but functional characterization of this variant failed to show differences from wild type TRPV5.(Renkema *et al*, 2009).

7.6. Cystinuria (OMIM 220100)

Cystinuria is an autosomal recessive trait, caused by renal reabsorption and proximal gastrointestinal damage from cystine and dibasic amino acids due to mutations in genes (SLC3A1 and SLC7A9) that encode these amino acid carriers. (Feliubadaló *et al*, 1999)

7.7. Xanthinuria / Hypoxanthinuria (lack of XDH) (OMIM 278300)

Lack of xanthine dehydrogenase (XDH) due to mutations in the XDH gene (2p22) also results in impaired purine degradation, in this case characterized by an increase in xanthine and hypoxanthine in the urine but with hypouricemia and hypouricosuria. This disease is more common in the Mediterranean and Middle East regions of the world and is inherited as an autosomal recessive trait. (Torres, & Puig, 2007).

7.8. Lack of HPRT (HPRT, EC 2.4.2.8) (MIM300322)

The important physiological role of

hypoxanthine-guanine phosphorybosil-transferase (HPRT) activity in the human purine metabolism (emphasized by its absence, which results in Lesch-Nyhan syndrome (MIM300322), is characterized by hyperuricemia, hyperikicosuria, urolithiasis of early uric acid (most common) in the year of the first life) and neurological complications (mental retardation and self-mutilation).

In the case of partial HPRT enzyme deficiency, which is referred to as Kelley-Seegmiller syndrome, less severe phenotypic manifestations are observed (e.g. hyperuricemia, gout), partially correlated with the rest of the HPRT enzymatic activity. Both syndromes result from personal or de novo mutations in the X-linked HPRT1 gene (Xq26-q27.2), with> 300 mutations described so far (Torres *et al,* 2007).

7.9. Genes for atazanavir-containing stones (OMIM UGT1A1)

Nephrolithiasis induced by atazanavir is a rare condition among all uroliths, and the exact mechanism for stone formation is not fully understood. UDP glucuronosyl transferase family 1 member A1 (UGT1A1) is expressed mainly in the liver and digestive tract, and plays a role in the elimination of bilirubin. Given that UGT1A1 is known for its association with atazanavir unconjugated hyper-bilirubinemia, this is also thought to be involved in atazanavir metabolism.

8. Monogenic urolithiasis

Dent disease, primary hyperoxaluria, deficiency of adenine phosphorybosyltransferase (APRT), hypoxanthine-guanine phosphorus-transferase deficiency (HPRT) and family hypomagnesemia deficiency with hypercalciuria and nephrocalcinosis (FHHNC) in particular, are associated with kidney failure. The formation of crystals in the kidney tubules in this condition results in an adverse inflammatory response that causes interstitial fibrosis and the development of end-stage renal disease (ESRD). Major genetic defects, classified based on metabolic risk factors for stone formation (Relan *et al,* 2004)

CONCLUTION

Urolithiasis is a common urology problem. In most cases, this multifactorial pathology develops due to a combination of inherited low-gene variants and environmental factors. The influence of genes on polygenic and monogenic urolithiasis has developed rapidly, giving rise to an appreciation for the participatory role of various proteins, including enzymes, transporters, channels and receptor proteins in the kidneys and other system organs.

A deeper understanding of the genetic factors that play a role in the mechanisms of stone formation and advances in molecular and pharmacogenomics have revolutionized diagnosis and treatment, and paved the way for the identification of new therapeutic targets and treatment approaches based on genetic engineering.

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