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Systematic Review

Insights into association between urolithiasis and prostate cancer

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Abstract

Background and objective: Urolithiasis or renal stones form a major urinary tract infection with formation of calcifications in the bladder and uterus. With the lifestyle diseases burgeoning, the renal stones have become a common cause with an approximate 1 in 1000 people affected all over the world with a risk ratio of 3 : 1 in men and women. On the other hand, prostate or genitourinary cancers are well documented to be associated with urolithiasis.

Methods: A gene list was prepared from the published NCBI dataset, comprising all the genes related to urolithiasis primarily with mutations (both pathogenic and likely pathogenic Single nucleotide polymorphisms, SNP's) for every particular gene screened later from the published datasets. To see the interactions among all the potential genetic factors, PPI based tools were used and an interaction map was prepared. For the characterization of mutations, we have used gnomAD for verifying all the SNPs whether they are synonymous or nonsynonymous mutations.

Results: We outlined the list of genes and discussed the systems bioinformatics integrated approach associated with it.

Conclusion: We found a large number of genes common to them and their association is subtly known for immunomodulatory response.

Keywords

Urolithiasis; Genitourinary cancer; Prostate cancer; Renal/kidney stones; Hyperuricemia; Calcium homeostasis

1. Introduction

Urolithiasis also called urinary tract stone disease is the condition when stones are formed in any part of the renal system (urethra, urinary bladder or kidney) [1]. As the third most common urinary disease worldwide, its incidence varies across the nations [2]. In Asian countries, it is found to be 1% to 5%, whereas in Europe it is 5% to 9%, and 7% to 13% in North Americans [3]. The overall total incidence rate in the world was 62 per 100,000 per year while among men and women was 197 per 100,000 per year [4]. While a very high rate of frequency and reversion is observed, the classification of the risk factors has not yet been carried out [3]. A confirmed risk of familial inheritance in

increased chances of stone formation is equivalent to 2.57 times in men [3]. With the genetic tendencies to manifest urolithiasis not known, the intricate interactions between genetic and external environmental factors would perhaps allow us to have a deeper understanding of the disease [3, 4]. Approximately 50% of kidney stone patients are at risk of recurrence within the first 5 years after the first event [5]. On the other hand, prostate cancer (PCa) in recent times has reached the second most prevalent malignancy among men and the 5th most frequent type of cancer in the world to be diagnosed (Globocan, 2020; last accessed 3 February 2021). The same trend is being followed at present times because of its multifactorial nature and varied ethnic differences [6, 7]. Estimation of 2018 revealed that 1,276,106 fresh cases and 358,989 deaths were notified where the majority cases came from developed countries [7]. For example, the latest Population Based Cancer Registries (PBCR) statistics 2020 of India, a total number of prostate cancer cases are 41,532 with a crude rate of 5.7 among men [8].

The pathogenesis of urolithiasis is complex with the formation of small stones that usually remain asymptomatic, but if it is larger than 5 mm, it ends up being an impediment to the ureter and is intensely painful. The stone formed inside the kidneys passes out in the urine and leaves the body [1]. Some stones can also enter the pelvic region and begin to damage the kidneys, while bladder stones can form on their own or can be seeded into those that come from the kidneys in the urine stream [1]. Some microorganisms are also known to play a role in the stone formation like urea splitting (Proteus species) forms the struvite stones (infection stones) in the kidney. Not only urinary, but also intestinal microbes may also be responsible as a consequence of their associations with other diseases, such as hypertension, diabetes mellitus, obesity, and other metabolic syndromes [9]. Interestingly, 70% of calcium stones are composed of oxalate as gut microbiota like oxalate metabolizing bacterial species (OMBS) specifically *Oxalobacter formigenes* ingests oxalate and activates its secretion to form oxalate stones [9]. On comparing both (PCa and CaOx) types of calcium stones hardly a very small difference is seen in them, nevertheless, the expression patterns of different matrix proteins of both types are reported [10]. Furthermore, a correlation between increased body mass index (BMI) and formation of kidney stones was also seen. On the basis of some evident studies which has shown that there is more mineral excretion (Uric acid, Calcium, Sodium, Oxalate, Phosphorous, Sulphate, Magnesium, Cysteine and Citrate) and fall in pH of urine [11]. Although, the prevalence of calcium oxalate is higher irrespective of obesity. More specifically, in obese patients uric acid stones (63%) are common when compared to non-obese (11%) patients [11]. Since obesity along with age is more susceptible to stone formation, both these are associated risk factors for urolithiasis [11]. Low pH endures phosphate or calcium stones but high pH favors uric acid stones [11]. On the other hand inflammatory agents (eicosanoids) having poly fatty acids lower the excretion of calcium thereby further reducing the kidney stone formation and these fatty acids can change the vitamin D synthesis which controls the calcium excretion [12]. Stone formation is still an unclear process, however the mass spectrometric proteomic approach for matrix proteins might be helpful in more understanding of stone formation. Urolithiasis has posed itself as a universal health issue. This new era has already given approaches which are far less invasive but the rate of recurrence has proved the advancement inadequate for the urolithiasis prevention [13]. Despite other lifestyle reasons, it may be possible that some urolithiasis genes and their polymorphisms are associated in developing PCa also [1]. In the present bioinformatics study, we reviewed the role of urolithiasis and PCa in relation to genetic association and associated risk factors. While we have identified their pathogenic and likely pathogenic polymorphisms by co-relational studies.

A systematic review was done with search for published literature using PubMed using the keywords, *viz.* "Urolithiasis" and "Prostate Cancer". A gene list is then prepared from the published National Centre of Biotechnology Information (NCBI) dataset, comprising all the genes related to urolithiasis primarily with mutations (both pathogenic and likely pathogenic Single nucleotide polymorphisms, SNP's) for every particular gene screened later from the published datasets. List of all the pathogenic variants and their associated protein changes in gene sequences are added in the supplementary file (**Supplementary Table 1**). To see the interactions among all the potential genetic factors, GeneMANIA and String databases were used and an interaction map was prepared. After which, determination of the cellular and subcellular location of all the potential genes was done by using target p2.0 and uniprot databases respectively. For the characterization of mutations representing the associations of urolithiasis and PCa, a correlational study is applied. For this purpose, we have used genomAD (Fig. 1) for verifying all the SNPs whether they are synonymous or nonsynonymous mutations.

Genemania analysis revealed 20 other associatory genes which are; *HRH1*, *A2M*, *FGA*, *NPL*, *ZBTB16*, *VKORC1L1*, *IL37*, *ORAI3*, *ORAI2*, *PROZ*, *PON2*, *HPRT1*, *PON3*, *IL1A*, *CAT*, *LCTL*, *IL18BP*, *KLB*, *APOA1* and *IL1RL2*. Based on several network studies till date, the identified urolithiasis genes are categorized on their functional grounds such as phosphate or calcium regulation *(VDR, KL,* Calcitonin receptor etc.), calcium sensing receptor related to calcium regulation (*CLDN14, ORAI1*), stone matrix (*OPN*), stone formation inhibitors (*SLC13A2, F2*), uric acid stone related (*CARD8*), for stones having atazanavir (*UGT1A1*) and also the anti-inflammatory and antioxidant stress (*IL-1, PON1*) related ones (Fig. 2). Many genome wide association studies have been performed to identify the other candidate genes and their SNPs causing nephrolithiasis (*SLC34A1, CLDN14, AQP1, DGKH* and *ALPL*) [3]. We also checked this from the gene database of NCBI by which 22 urolithiasis responsible genes were identified and enlisted and also their pathogenic and likely pathogenic SNPs were identified, *viz-VDR, IL6, IL1B, SPP1, PON1, SOD2, F2, IL1RN, IL18, CASR, PLAU, KL, VKORC1, ORAI1, CP, HSPG2, GGCX, CALCR, SLC26A1, APRT, ZNF365*

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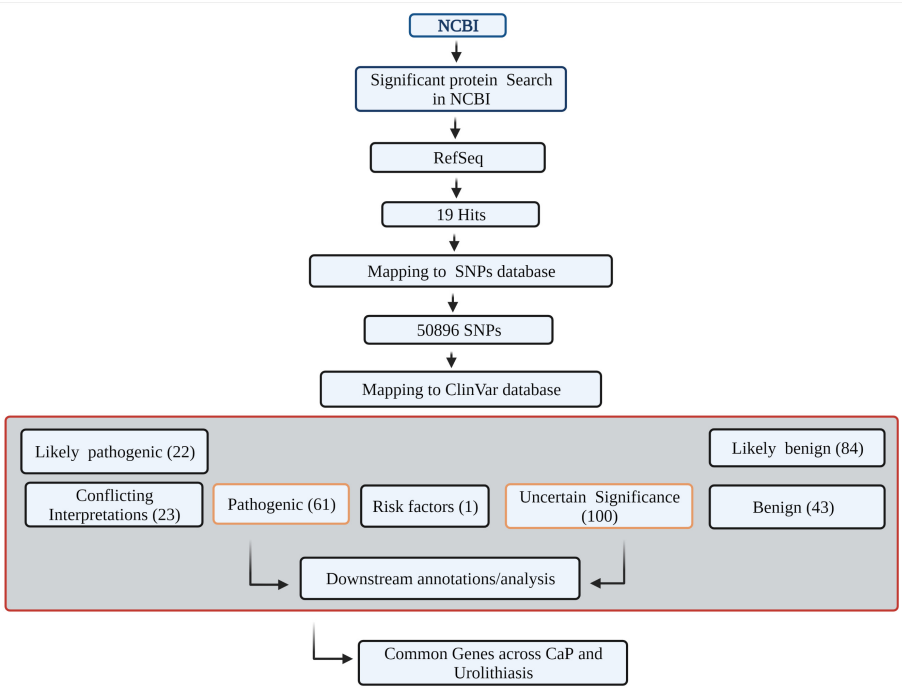

FIG. 1. A flowchart for the steps of gnomAD to identify the variant types and their rarity of Urolithiasis related genes. We mapped refseq proteins (19) of urolithiasis to the SNP database which resulted in the identification of 50896 different SNP's, which were subjected to ClinVar/dbVar. Later from the given categorized list (pathogenic, likely pathogenic, conflicting predictions, uncertain significant, benign and likely benign) we filtered out those genes which are pathogenic (61) and are having uncertain significance (100). These SNPs can be verified on the basis of type of variation (missense or nonsense) or can also be analysed for their associations with other diseases.

and *HOGA1*. Urolithiasis related roles of some of these genes are mentioned in a Table (**Supplementary Table 2**).

2. Disease-gene interactions

While analyzing the gene-disease (gene-phenotype) interaction networks (Fig. 3), 5 keywords (disease names) were given, viz. urolithiasis, hyperuricemia, hyperoxaluria, prostate cancer and renal diseases against the searches. In the resultant image, we found an approximate 2000 genes, among which *CREBBP* was found to be interacting most.

3. Vitamins and calcium response play an important role in lieu of urolithiasis

From our annotations, we found association of vitamins and calcium in lieu of urolithiasis. We give a gist of those genes here under.

ORAI 1 (*calcium release-activated calcium modulator 1*): Cancerous cells exploit the *ORAI 1* dependent calcium channels for supporting its hallmarks like proliferation, apoptosis inhibition, migration and angiogenesis in different cancer types [14]. *ORAI 1* protein is the main endogenously store operated Ca^{2+} entry (SOCE) of human FPCa cells and also forms its main source of calcium influx to stimulate apoptosis. But its downregulation inhibits apoptosis which confirms its requirement in pro apoptosis. Its transfection analysis has shown a pro apoptotic property rescuing in PCa cells [15]. The ROS (hydrogen peroxide) dependent Ca^{2+} channels stimulate the PCa cell sensitivities to apoptosis and are called ROS induced cell death [16].

VDR (*Vitamin D (1, 25- dihydroxyvitamin D3) receptor*): PCa is explored as polygenic with a broader level of ethnic differences [17]. A positive association of polymorphism rs2238135 (G allele) is displayed in Mexican men with a Gleason score of $\geq$7 [17]. Almost 90% of circulating vitamin D is because of sun exposure. In a study of six polymorphisms of *VDR* along with sunlight tanning effect in increasing PCa susceptibility showed the result of *VDR* involvement depends on ultra violet (UV) exposure and concentration of serum vitamin D. There is an inverse relation between exposure and PCa risk where increasing exposure results in decrease of PCa risk. It clears that if vitamin D level is not limiting it proves its protective side. A study was done in African Americans where SNP1 and SNP4 in interaction with sun tanning showed 2 and 4 times increased chances of PCa cases respectively whereas SNP5 showed protective outcome by reducing the risk by 5%. Interestingly, among the reported SNPs, SNP2 and SNP6 showed no associations [18]. A genotype study found homologous loci for *VDR* rs2107301 and rs2238135 showed 2–2.5 times increased chance of risk for PCa [19]. On the other hand, the SNP7 (rs7975232) or Apa 1 and SNP4 (907175 C >T) can be better predictors with high specificity of 92.4% and sensitivity 74.7% [20].

VKORC1 (vitamin K epoxide reductase complex subunit 1): Prolonged usage of anticoagulants like warfarin are known to lower the PCa. Its target *VKOR* has shown its high expression in benign cells of the prostate only whereas in cancerous cells expression is found insignificant. *VKORC* is associated with

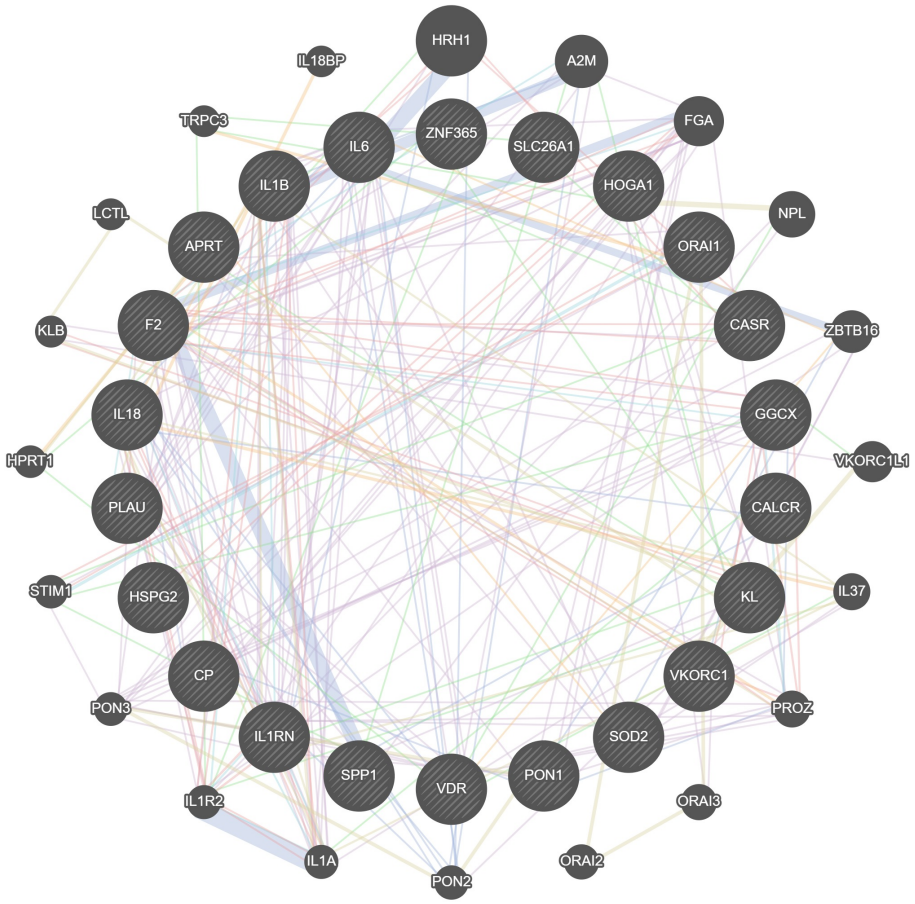

FIG. 2. A schematic representation of an interaction map of all the 22 urolithiasis and other 20 associated genes using GeneMania, forming a network of urolithiasis causal genes with other genes. The purple edges show that those genes are coexpressed for example *IL-18* and *VDR; CALCR* and *ZNF365.* The blue edges show that they are localized to the same organelle (blue edges connected by nodes, viz. *HRH1* and I*L-6; F2-SPP1*).

many processes that can enhance the invasion and metastasis like angiogenesis and cell migration. These anticoagulants target its subunit C1. Therefore, the SNPs are expected in C subunit to be involved in increasing PCa susceptibility. The mechanism is not known but it is assumed that either it might be hampering the formation of new lesions or the growth of already formed ones. Their associations can't be confirmed at this point with available literature and work done but the expression of VKOR in benign indicates its potential of increasing PCa risk and chemoprotective capability of warfarin [21].

ORAI 2 and ORAI 3 (*calcium release-activated calcium modulator*): Calcium stone formation takes place after its internalization in the form of crystals (PCa, CaOx or mix of both) through proximal tubular cells into the terminal fluid and causes oxidative stress. Internalization of these crystals show stimulatory effect on GPCR mediated persistent rise of intracellular concentration of calcium through Store-operated calcium entry (SOCE) channels where its component STIM 1, 2 (calcium sensors) and *ORAI 1, 2, 3* (pore forming subunits) were upregulated. Suppression of these component channels or SOCE genes might play a translational role in causing lithiasis (nephrolithiasis) by reversing calcium internalization signaling [22].

FGA (*fibrinogen alpha chain*): *FGA* is one of the stone matrix proteins (SMP) [23] but in lower abundance [24]. Matrix of both types has some inflammatory proteins within them [10]. Human stones are known to have both kinds of organic and inorganic mineral components in which the inorganic part is 2–3% lower by weight and it acts like a template initially as rest is formed by proteins (64%), glycolipids, carbohydrates and GAGs [22]. It is highly secreted (with uniquely glycosylated fragments at c-terminal) into the urine in response to an infection and serves as an indicator of lithiasis [25].

HRH1 (histamine receptor H1): Osteoporosis is seen as a very frequent sign of mastocytosis due to which it is also considered as an associated complication of systemic mastocytosis. To treat this, H1 and H2 histamine receptor antagonists are given [26]. A very common symptom of stone formation is pain which can be of two types depending upon the location and movement of the stone. It can be a flank pain when it is located in the upper region of the ureter or it can be like groin pain when moved down to the lower ureter [27]. Histamine 1 receptors are frequently found inside the ureter and their antagonist (dimenhydrinate) are found helpful in relieving pain caused due to stones (renal colic) and ease the natural elimination of stones by inhibiting renal vasodilators and urethral contractions [27].

PROZ1 (*protein Z, vitamin K dependent plasma glycoprotein*) *is* a stone matrix protein but in higher abundance [24, 28].

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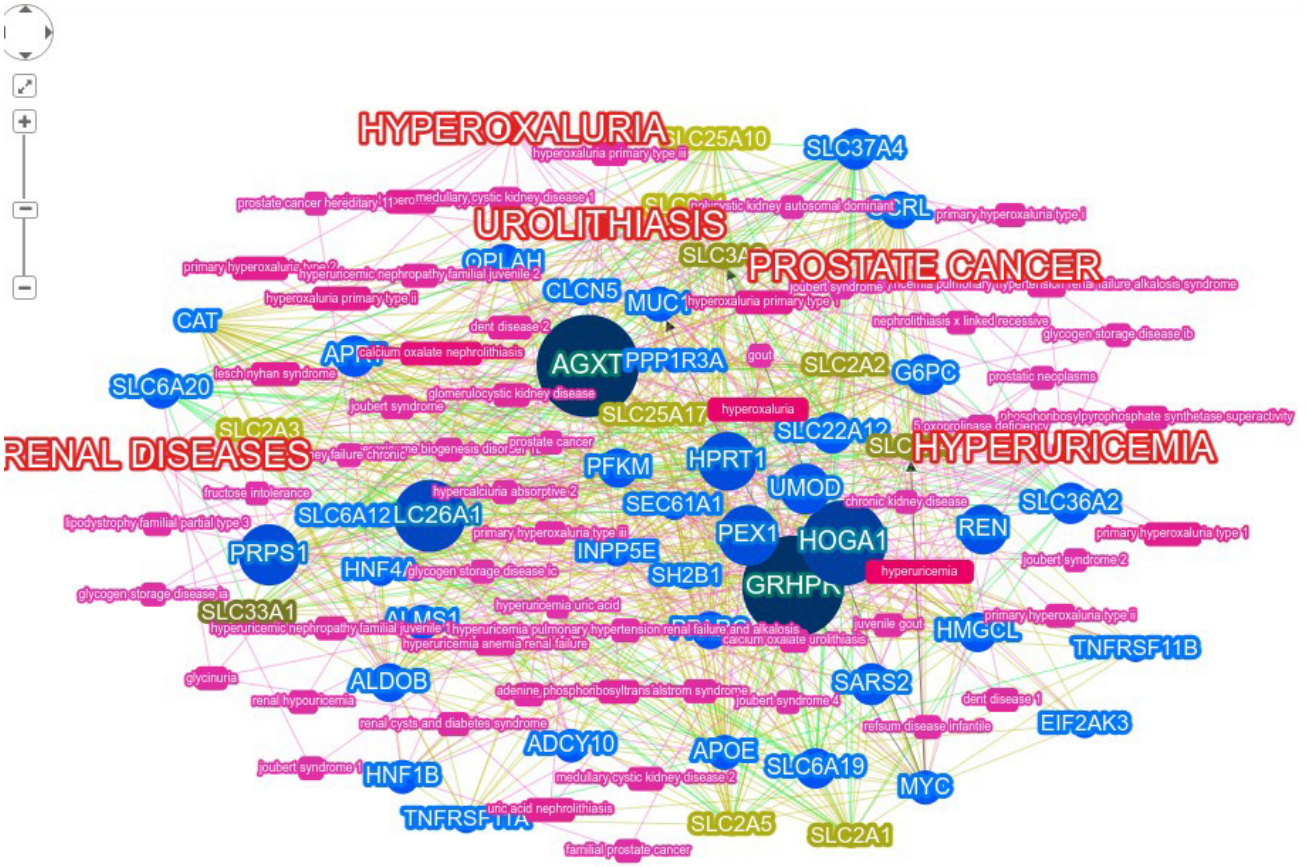

FIG. 3. Disease gene based network analysis using phenolyzer. All the edges indicate the propensity of interactions. By turning off gene annotation, interactions of all specific diseases and input terms; by turning off disease annotation, network of all the genes; Protein-protein interaction network of genes from the same gene family; and all genes of same family can be analyzed.

HPRT1 (*hypoxanthine phosphoribosyltransferase 1*): *HPRT* related hyperuricemia can be found in both the cases whether it is partial or complete deficiency of *HPRT* (Lesch-Nyhan Syndrome, OMIM 300322) which causes excess of uric acid resulting into hyperuricemia, gout and urolithiasis. A recent study on a 22 year old man having gout has shown serum urate level of 12.2 mg/dL where the normal range is 3.8–7.0 [29]. *HPRT* deficiency also causes overproduction of purine [30]. In a X-linked disorder of *HPRT* deficiency, metabolism of purine gets affected, ending into hyperuricemia with the females not showing these symptoms [31]. As a consequence of *HPRT* deficiency, the amount of uric acid which is an end product of purine degradation is increased. Such excess of uric acid precipitates and crystallizes inside the renal reaction to form stones [32]. On the other hand, increased uric acid excretion can also encourage the CaOx stones. Depending upon the type of enzyme involved in metabolism of purine, other types of stones could also be formed inside the kidney [4].

APOA1 (apolipoprotein A1): A SDS-PAGE and immunoblotting based analysis has been done with intent to understand the stone matrix and has verified that out of 13, 9 proteins reside in all forms of urinary stones. These 9 proteins are human serum albumin (HAS), α 1-acid glycoprotein (α1-GP), alpha l-microglobulin (α 1-M), immunoglobulins (Igs), apolipoprotein A1 (apo-A1), transferrin (Tr), α l-antitrypsin (α 1-T), retinol-binding protein (RBP) and renal lithostathine (RL). Rest of them include β 2-microglobulin (found in CaOx and UA stones only) while ceruloplasmin, haptoglobin and Tamm-Horsfall protein (THP) are not present in any of them. Not all but some of them are only found in matrix and in fact present in all stone types but their amount can vary stone to stone type wherein these proteins are found attached to albumin [13, 33].

CAT catalase: Amongst urinary tract problems, urinary calculi is phenomenally observed among many and is the third most frequent problem. Lipid peroxidation is known to produce continuous reactive oxygen free radicals which develop oxygen stress inside the renal cells. This causes renal inflammation and injured epithelium and acts as a seed bed for stone formation in case of hyperoxaluria. Both inflammation and renal injuries play a significant role in urolithiasis. Catalase (*CAT*) of serum level is formed very low in urolithiasis patients. Role of the peroxidation and its oxidative stress function were suspected in the urolithiasis mechanism. Calcium and phosphate stone formation begins at the distal part of the distal tubule or loop of henle. Catalase and peroxidase act as antioxidants by shrinking the role of chain initiation of free radicals. Here in urolithiasis patients, catalase activity is inhibited and peroxidation increases. Also the peroxidation and antioxidant enzymes both play a role in pathogenesis of

urolithiasis [34].

Role of the remaining associated genes; *PON2, PON3, LCTL* (*lactase like*), *IL18BP* (*interleukin 18 binding protein*), *IL1RL2* (*interleukin 1 receptor like 2*), *NPL* (*N-acetylneuraminate pyruvate lyase*), *ZBTB16* (*zinc finger and BTB domain containing 16*), *VKORC1L1* (*vitamin K epoxide reductase complex subunit 1 like 1*), *IL37* (*interleukin 37*), *A2M* (*alpha-2-macroglobulin*) *and KLB* (*klotho beta*) is not clear yet.

4. Urolithiasis and PCa

Urolithiasis and PCa could be seen at the same time and are treated simultaneously in many cases [35]. By applying conditional logistic regression, a case control study has confirmed the associations of PCa with previous urinary calculi (kidney, bladder and other unspecified sites) [36]. For example, Urinary calculi can be classified into two subcategories; primarily because of metabolic issues and secondary as a result of several diseases (comorbidity), medicines, dietary habits (fat intake), anatomy, infections or more likely in those patients having diabetes or glucose intolerance. Thus, dietary changes like more fat consumption on one side promotes stone formation and on the other side through the hormonal imbalance (by Androgen Receptors), ultimately leading to PCa progression [36]. While treating a PCa patient with luteinizing hormone-releasing hormone analogs, they produce androgen deficiency along with osteoporosis through certain cytokines mainly IL-1, 6, 10 and TGF-1. This state of bone loss also increases calcium and phosphorus minerals in the serum and urine resulting in renal calcium deposition in kidneys (nephrolithiasis) [37]. Androgen therapy also lowers the ammonium excretion resulting in an increase of free ions inside tubular lumen which increases risk of uric acid lithiasis. Therefore, oxidative stress and decreased urinary pH because of androgen deprivation therapy (ADT) also causes urolithiasis [37]. According to some follow up cases, people undergoing testosterone replacement therapy have also shown association by inhibiting an active calcium transporter (TRPV5) and increasing calcium excretion and oxalate levels in urine [38]. A study says doing brachytherapy for PCa has higher chances of lithiasis because of iodine seeds acting as nidus [39]. Also a next generation sequencing (NGS) based exome analysis of common genes between Asians and Caucasians' for PCa found 9 genes and *UGT1A*1 was one of them [40]. However, *UGT1A*1, already mentioned, is responsible for urolithiasis by forming atvanizer related kidney stones.

4.1 UGTIA1

Protease inhibitors like atazanavir are also well known to be associated with kidney stones. A case study of 74 years old HIV patients reported kidney stones with composition of atazanavir and renal colic. Atazanavir linked lithiasis holds a prevalence rate of 7% [41]. This type of nephrolithiasis is considered rare in comparison to other types of lithiasis. Genotype TC of rs10929303, GC of rs1042640 and rs8330 allele of UGT1A-30-UTR independently contributing to risk in these HIV patients [42]. Depending upon the types of protease inhibitor drugs, composition of stone will change accordingly (emtricitabine, lenofovir, ritonavir, indinavir, nelfinavir) [43]. Therefore urolithiasis has shown its impact in PCa through calcium homeostasis, ROS or androgen receptors. A table showing a plausible relationship of the urolithic genetic risk factor with PCa susceptibility altogether indicates there are a host of other genes that regulate the functions.

4.2 CASR (calcium sensing receptor)

A transmembrane receptor, whose homologous expression doesn't happen in those cells that are involved in calcium homeostasis or prostate tissue but still they play an important role in homeostasis and PCa progression. In an immunohistochemistry analysis, to check calcium sensing receptor (*CASR*) expression in prostate tumors, with an increasing risk of metastasis in PCa patients. Because the fact that PCa usually metastasizes particularly to skeletal sites only, causes bone remodeling and increases extracellular calcium [44], suggesting that the bones are providing an appropriate niche for the PCa cells to proliferate and get localized [44]. The localization of PCa mostly takes place at the site of high turnover (increased rate of bone formation and bone loss) region of bones. This process of continuous turnover releases a lot of extracellular calcium as inorganic bioactive products and this level goes up from 2.5 to 7.5 mmol/L. Here it clears its role as a candidate mediator of PCa skeletal metastasis [44]. This increased calcium stimulates the *CASR* and metastasis through *PI3K/Akt/mTOR* signaling. Gene variations of *CASR* are commonly seen linked and are overexpressed in PCa cells. These PCa tumor cells with hyper expressions have more tendencies to metastasis. *CASR* increases only in those patients with PCa who have decreased *VDR* whereas increased *VDR* is supposed to suppress the tumor development, but the mechanism is still not clear. It is not a proliferation or apoptosis with which *CASR* is related to in fact more chances are related to vascular growth in PCa [45]. Lately, collected reports has also represented *CASR* overexpression causes increase in metastasis and mortality of PCa patients, but it's expression, localization and functional study using LNPCa cell lines by protein silencing approach (anti *CASR* siRNA) suggested that the difference is not in the expression but the cellular localization which can be responsible for the rise in extracellular $Ca^{2+}$and progression of PCa [46]. Increased *CASR* can be a marker of NE differentiation in PCa patients. It is a well-established fact that any change in cytosolic calcium level can stimulate many important events inside cancerous cells like invasion, proliferation or apoptosis resistance [47]. In a study on African American men identified a *CASR* polymorphism; CASR Q1011E which might have associations with less aggressiveness of PCa [48].

CP (*Ceruloplasmin*) an antioxidant (glycoprotein) binds to copper in oxidative stress is known to increase in Indian females. Copper level increases in serum therefore can be used as an indicator of PCa [49].

GGCX (*Gamma-glutamyl carboxylase*): A South Asian pop-

ulation study showed 194 genes as potential risk factors in which *GGCX* is one of them and could be a novel finding if confirmed by experimental validation [50].

5. Interleukin families are associated with regulation of immune response in urolithiasis

The interleukins are a group of cytokines expressed in white blood cells and we review that at least 3 interleukins are known to play an important role in causing urolithiasis and regulating the immune response.

IL1A (*interleukin 1 alpha*): In the pediatric nephrolithiasis, the role of *CTR* and *VDR* polymorphism among the north Indian population was noticed. *IL1A* is among that cluster of genes which codes for the *IL1* protein family. The cytokine coding *IL1* has already established its association with the urolithiasis [51].

IL6 (*interleukin 6*): *IL6* has varying functions in regulating immune responses, cell growth, differentiations and *VEGF* expressions. It can even inhibit proliferation or support cell survival. Expression of *IL6* and its receptors are known to increase in either benign or malignant PCa where it plays an important role as a positive growth factor for many prostate cells [52]. *IL6* concentration increases to near about 18 times in localized PCa in comparison to normal prostate cells whereas its receptors increase by 8 times. The immunohistochemistry approach has verified its role in increasing net proliferation through stat3 phosphorylation and further signaling which supports its autocrine growth factor nature in AR dependent PCa's and lymph node carcinoma of prostate (LNCaP) cell lines. Activation of *IL6* receptors may cause anti-apoptotic activity also [53]. This autocrine activity is mediated by the *JAK-STAT* pathway [54, 55]. A study suggested *IL6* as a potential biomarker of aggressive PCa where CD44 is associated with aggressiveness by inducing stemness related characters and results in greater tumor burden [56].

IL18 (*interleukin 18*): Findings have revealed that to escape immune surveillance in prostate cell lines, a cytokine *IL18* receptor (*IL18* binding protein, isoforms only) expression increases and acts as an inhibitor in cell lines DU145 and PC3. Chronic inflammation is frequently observed in the prostate gland [14]. It is already a well-known fact that inflammatory genes somehow contribute to increasing risk of PCa by inflammation associated with DNA damage, angiogenesis, proliferation, invasion and metastasis. Two polymorphisms (–607 and +105) were mainly stressed in a study performed on Slovak population. According to the results the –607 polymorphism in the promoter region (heterozygous) with genotype AC and CC known to be with more PCa risk. *IL18* being a proinflamatory cytokine enhances both development and progression. It can also stimulate cytotoxic effects of NK cells and increase Th1 immune response to finish tumor cells. So, a definite mechanism of IL18 role in PCa development is not explained well. It can be said like its end impact is dependent on which specific effect is going to dominate. Its polymorphism is suspected to modulate its activity, productivity and susceptibility for PCa [15]. An immunohistochemistry based analysis confirmed that 75% of PCa cells produce *IL18* done on cell lines: prostate cancer cell line 3 (PC3), DU145 and LNCaP and acts as an autocrine or paracrine factor for tumor. Its secretion is increased by interferon gamma [16]. *IL18* haplotypes vary among the variety of ethnic groups. A hypothesis was made that polymorphism in promoter regions of IL18 plays a role in PCa and found SNP –137 GC and CC are more significantly linked. Haplotypes –137 G/C (rs187238) and –607 C/A (rs1946518) are more linked in Chinese population [57, 58].

IL1RN (*interleukin 1 receptor antagonist*): It is an anti-inflammatory cytokine that inhibits the proinflamatory cytokines *IL1*α and *IL1*β and supports the hypothesis that inflammation plays a significant role in PCa development. A Swedish study shows the risk of *IL1RN* polymorphisms (SNPs) in causing advanced PCa (both homozygous cancers and non-cancers) suggested positive associations of *IL1RN* haplotypes (ATGC) [59, 60]. In a genetic characterization by single nucleotide tagging results didn't agree with influences of these variations [61].

KL (*klotho*): *KL* is an anti-ageing gene which codes transmembrane proteins in renal tubes called Klotho. Its overexpression extends survival and also acts as antitumor [62]. It controls survival of cancerous cells through different pathways for example Insulin/insulin growth factor (IGF), tumor growth factor (TGF β1) and Wnt signaling [62, 63]. In prostate cancer it is downregulated or silenced [62]. It acts as a tumor suppressor gene (TSG) with Wnt signaling. Methylation analysis suggested a significant inverse relation between promoter methylation in PCa cell lines and Klotho expression. The 22Rv1 PCa cell line expresses *KL* mRNA but not in DU145 and PC3 because of methylation (hypermethylation). However, the 22v1 segment remains unmethylated (hypomethylation) from (CpGs –593 to –406bp) in the promoter region. This confirms an inverse relationship between *KL* mRNA expression and DNA methylation [64]. Down-regulation promotes its proliferation and fall in apoptosis in cancerous cells. It can be a normal biomarker of many cancers [65].

PLAU (*plasminogen activator, urokinase*): Relative expression of some genes in PCa showed that expression of *PLAU* decreases in PCa cells [20].

PON1 (*paraoxonase 1*): Oxidative stress is a well-known reason to induce risk but when there is SNP in varying regions of *PON1* causing this enzyme to alter its functional expression or might get inactivated. As a consequence the inflammatory oxidants will show modulated metabolism increasing its progression towards PCa development. It is found that polymorphisms of 3 genes show traits in combination that might increase PCa risk. These include CYP17A2A2/GSTP1Ilelle/PON192RR/PON55LL [66]. A SNP in the coding region of *PON1* I102Vallele is also found to decrease the enzyme and develop PCa. It is more likely to run in familial PCa [67]. Serum lipids (HDL-cholesterol) and HDL cholesterol associated antioxidant

enzymes (paraoxonase 1 and aryl esterase) are also studied for their assumed function in PCa promotion where *PON1* is noticed as an increasing factor [68]. Results clearly indicated that *PON1* levels might increase PCa risk. Based on this result it can also be assumed that *PON1* activity can limit the damage done by endotoxins of bacteria, stops lipid oxidation and ultimately lowers the chances of inflammation induced cancers [69]. Human paraoxonase 1 forms in the liver and is linked to HDL. A polymorphism (Q192R) with genotype QR was analyzed in Egyptian population by PSA level testing in association with PCa. Outcomes of molecular analysis raised expectations for its association in growth with QR genotype (192 codons having mutations) and Q is substituted by R allele at its codons. Homologous genotypes QQ and RR have reported non risky for PCa instead of QR with double risk. Therefore, their heterozygous polymorphism increases more susceptibility for PCa [68].

SOD2 (*superoxide dismutase 2, mitochondrial*): Neuroendocrine cell count increases with PCa progression and takes up the regulatory function in many processes. LNPCa cell lines were stimulated to differentiate into neuroendocrine (NE) cells. Analysis of these cells shows higher expression of mitochondrial *SOD2* with NE markers. This overexpression of *SOD2* is seen in advanced PCa. Immunofluorescence analysis suggested its essentiality in critical NE transdifferentiation and differentiation processes [70]. Another pooled analysis with the help of OR's, *in silico* tools, ELISA and immunohistochemical staining for *V16A* variant in *SOD2* showed more susceptibility for PCa and *SOD2* is downregulated in advanced ion and PCa's in contrast to initial stages [71]. It might be for migration and invasion causing more aggressiveness, therefore, level could be taken as a biomarker of growth progression to metastasis [72].

SPP1: *SPP1* is mainly linked with both metastasis and drug resistance in PCa. Its expression level of both mRNA and protein are noted to be significantly upregulated in metastasis castration resistant PCa (mCPRC). This validation declares *SPP1* as an extracellular matrix signature hub of mCPRC [73].

For the genes like *F2, IL1B, CALCR, SLC26A1, APRT, ZNF365* and *HOGA1* no particular links with PCa were found.

6. Conclusions

Urolithiasis is a complex multifactorial disease that results from interactions between genetic and environmental factors. Many studies have correlated urolithiasis with different other diseases such as diabetes, cardiovascular diseases, hypertension to name a few. We review the association of urolithiasis and PCa genes and provide insights using bioinformatics approaches. We found a large number of genes common to them and their association is subtly known for immunomodulatory response.

Abbreviations

BMI, Body Mass Index; NGS, Next generation sequencing; PCa, Prostate Cancer; SNP, Single Nucleotide polymorphisms.

Author contributions

BDK and XS have collected the data and involved in manuscript preparation, XW and XH have done proof reading, YW, SV are involved in proof reading and editing of the manuscript.

Ethics approval and consent to participate

All analyses were based on previous published studies; therefore no ethical approval and patient consent are required.

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Conflict of interest

The authors declare no conflict of interest.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at https://oss.jomh.org/jomh/article/1415208868009394176/attachment/JOMH2021012401_Supplementary_File.docx.

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