International Journal of Medicine and Medical Research
2021, Volume 7, Issue 1, p. 12-19


DOI 10.11603/ijmmr.2413-6077.2021.1.12468

# VITAMIN D AND UROLITHIASIS IN CHILDREN

***Sh.A. Yusupov[1], A.M. Shamsiev[2], J.A. Shamsiev[3], P.A. Pulotov[4]**
*1, 2, 3, 4 – SAMARKAND STATE MEDICAL INSTITUTE, SAMARKAND, REPUBLIC OF UZBEKISTAN*

**Background**. *Urolithiasis is currently one of the topical issues of contemporary urology and medicine in general. This is primarily due to the high prevalence of urolithiasis; according to several population studies it ranges from 3.5 to 9.6%. At the same time, there is a steady increase in its incidence. Therefore, the matter of urolithiasis is one of the most urgent in present-day medicine.*

**Objectives.** *The aim of the research was to study the content of a polymorphic genetic marker of the vitamin D receptor gene related to development and relapse of urolithiasis in children.*

**Methods.** *The content of a polymorphic genetic marker of the vitamin D receptor gene related to development and relapse of urolithiasis in 100 children was investigated.*

**Results.** *The results of the study prove that the vitamin D receptor gene assists in revealing disorders that promote urolithiasis development.*

**Conclusion.** *Comparative analysis of the frequency of distribution of Fok1 genotypes of the vitamin D receptor gene polymorphism showed that statistical significance of the association (p=0.02) of f allele according to the dominant inheritance model (total Ff+ff genotypes) was established in the group of patients with urolithiasis compare to the corresponding indicator of the control group (63%).*

**KEYWORDS: vitamin D, urolithiasis, VDR gene, gene polymorphism, dysuria.**

## Introduction

It is established that urolithiasis is polyetiological. The final step of stone formation is salts crystallization in a urine supersaturated solution. However, a variety of mechanisms take part in pathogenesis before this, i.e. disorders of renal circulation, disturbance of urinary tract urodynamics, and inflammation in them [2, 3].

Urolithiasis is defined as a metabolic disease that is caused by several endogenous and/or exogenous factors and is characterized by occurrence of stones in the urinary system [3]. It is clear that stones in the urinary tract are a clinical manifestation of the disease; removal of the stone does not stop its progression, and it develops further if the causes are not eliminated [19].

Calcium stones are the most common, that is more than 80% of cases. Correspondingly, most of the calcium stones (about 85-90%) are calcium oxalates, 1-10% – calcium phosphates [7]. Recently, a tendency to decrease in the incidence of phosphate stones in the world structure was noticed. Probably, this is caused by a decrease in the occurrence of infected stones because of advances of minimally invasive surgery for urolithiasis and use of the latest antibacterial therapy [1,14].

Thus, metabolic disorders are significant in the pathogenesis of urolithiasis. Ever more, there are uric acid stones (up to 10% of all urinary stones); they include uric acid and its salts, along with mixed stones (up to 5% of all calcium stones) that contain calcium salts together with uric acid and/or its salts [18].

Violation of calcium metabolism is one of the risk factors for occurrence and relapse of urolithiasis; its regulation in the human body is a complex process. Three major hormones: parathyroid hormone (PTH), calcitonin, and metabolite of vitamin D, 1,25-dihydroxycholecalciferol-1,25 – the most important, are involved in calcium homeostasis maintenance [12].

Vitamin (hormone) D is a controlling anabolic hormone having antioxidant properties and an exclusive systemic metabolic effect [12]. Then again, seasonal fluctuations in vitamin D rate (high levels in summer and autumn and low – in winter and spring, similarly to annual testosterone cycles) take place [19]. On the other hand, regulation of the expression of

**Corresponding author: Yusupov Shukhrat, PhD, DSc, Head of the Department of Paediatric Surgery, Samarkand State Medical Institute, Samarkand, Republic of Uzbekistan. E-mail: shuchrat_66@mail.ru*

hormone D metabolism genes variates according to the androgens level. Hence, androgen deficiency intensifies adverse health effects caused by vitamin D deficiency [10].

The receptor of vitamin D is encoded by the vitamin D receptor gene characterized by genetic polymorphism, i.e. different allelic variations of this gene in humans [4]. Bsm I, Fok I, Taq I are the most important polymorphisms of the vitamin D receptor gene involved in progress of diseases [18, 19]. Several studies associate VDR gene polymorphism with urolithiasis. Some publications prove the significance of occurrence of the ApalAA genotype that determines sensitivity to vitamin D in the formation of calcium stones in the urinary organs [7, 14]. It is also established that in patients with urolithiasis the HLA B13, B22 and B35 genes are more common than in healthy individuals [2].

The huge range of biological effects of vitamin D, its involvement in carbohydrate, fat, purine metabolism, as well as its anabolic, antiproliferative, immunomodulatory effects, the investigation of cases of its deficiency is essential.

**Methods**

To perform the tasks set, a clinical examination of 100 children with urolithiasis and 100 practically healthy children was conducted, as well as the collection and analysis of statistical data on urolithiasis in children of different age groups to identify the gender, age-related and family frequency of urolithiasis, nutrition and lifestyle features, as well as the seasonality of this pathological process. Ultrasound and X-ray examinations of the urinary organs of patients were performed.

The selection of patients was carried out on the basis of the diagnosis established in the clinic with the written consents of the probands. Blood samples were collected from the patients with urolithiasis (100 samples) and a control group of practically healthy children (100 samples). Venous blood (1 ml) was kept in 0.5 ml of sodium citrate solution at -20 °C.

The material for the research was provided by the Republican Specialized Scientific and Practical Medical Center of Pediatric Surgery of Samarkand.

Table 1 presents data on distribution of the patients according to age in the groups under consideration.

Table 1 shows that among the patients, school-age children prevailed – 69 (69%). The reason is the fact that it is the age when metabolic disorders are the most often manifested; it is associated with the transition of children to a general diet, violation of drinking regime, etc., and in the younger group – the diet is quite rational and metabolic changes are less pronounced.

The distribution of patients in both groups depending on gender is presented in Table 2.

The data presented in Table 2 shows that according to the gender distribution of patients, incidence of urolithiasis is higher among boys – 68 (68%) children than girls – 32 (32%).

The most common complaints of patients with urolithiasis were pain in the lumbar region, fever, hematuria, turbidity of urine, increased or decreased urination. Acute urinary retention and spontaneous discharge of concretions were noted in some cases. In dislocation of concretions in the ureter n/w the pain was present in the iliac region on the same side. The patients with renal insufficiency had charac-

**Table 2. Division of patients depending on gender**

| Gender | Control group (n=100) | | Main group (n=100) | | Total (n=200) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| Girls | 35 | 35 | 32 | 32 | 35 | 17.5 |
| Boys | 65 | 65 | 68 | 68 | 165 | 82.5 |

**Table 1. Age-related division of patients with urolithiasis and healthy children**

| Age of patients (years) | Control group (n=100) | | Main group (n=100) | | Total (n=200) | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| 0-3 | 17 | 17 | 31 | 31 | 48 | 24 |
| 4-11 | 43 | 43 | 43 | 43 | 86 | 43 |
| 12-17 | 46 | 46 | 26 | 26 | 72 | 36 |

teristic symptoms, i.e. headache, drowsiness, poor appetite.

At admission pain syndrome was evidenced in 89 (89%) patients. Also, a severe pain syndrome of renal colic was present in 15 (15%) patients. The nature and localization of the pain syndrome depended on the child's age, presence of concomitant concretions in the urinary tract. In the patients of a younger age group, abdominal pain was typical. Older patients complained for lumbar pain more often, sometimes complained of irradiation of pain along the ureter.

In 3 (3%) children suffering from concretion in the lower third of the right ureter, pain syndrome led to unjustified appendectomy performed at the place of residence. In these patients ureterolithotomy was associated with some technical difficulties due to an adhesive process.

Dysuric manifestations were evidenced in 28 (28%) patients and mostly characterized by frequent and painful urination. Acute urinary retention was present in 5 (5%) patients. Dysuric manifestations were nearly 2 times more common in younger patients than other. Acute urinary retention in all patients was managed by inserting an Ad'mer catheter; in 3 (3%) patients, after the catheter was removed, spontaneous discharge of the concretion was evidenced.

According to the localization of the concretions, the following were identified: renal calculi in 43 patients (left-13, right – 21, on both sides – 9); ureter stones in 12 patients (c/3 ureter – 1, b/3 ureter – 1, n/3 ureter – 10); bladder stones in 9 patients (recurrent bladder stone in 1 of them); stones of the proximal urethra in 4 patients; multiple urolithiasis in 10 patients. Combined urolithiasis with urinary disorders were revealed in 22 children.

Genomic DNA was separated from the whole blood of patients diagnosed for urolithiasis and almost healthy individuals of the control group. It was performed by means of reagents kit Diatom DNA Prep 200 (IsoGen Laboratory LLC) according to a standard protocol. This kit comprised a lysing agent with guanidine thiocyanate, which was designed to destroy cells, solubilize cell debris and denature cell nucleases. With a lysing reagent the DNA was absorbed on the NucleoS™ sorbent, then washed from salts and proteins with an alcohol solution. The DNA, which was eluted from the Extra-Genome sorbent, was used for further analysis.

PCR was performed by means of special oligonucleotide primers and a reagents kit for PCR amplification of DNA GenePak™ PCR Core (IsoGen Laboratory LLC). We used Master Mix tubes ready for amplification, which comprised a lyophilized state Taq DNA polymerase, deoxynucleose triphosphates, and magnesium chloride with final concentrations of 1 u, 200 microns, and 2.5 mM, respectively, and an optimized buffer system intended for PCR amplification. 5 µl of a primers mixture, a final concentration of 0.5 µm, 10 µl of diluent PCR, and 5 µl of the test DNA were added to the Master Mix tubes. For PCR, the GeneAmp ® PCR system 9700 with a 96-cell block (Applied Biosystems) was used. The amplification program for the VDR gene involved 5 minutes of predenaturation at 95 °C, 34 cycles: 94 °C – 30 sec, 66 °C – 30 sec, 72 °C – 30 sec, and a final elongation for 7 minutes at 72 °C. The temperature-time mode of amplification for the Urokinase gene was: 5 minutes of preliminary denaturation at 95 °C, 40 cycles: 95 °C – 30 sec, 56 °C – 30 sec, 72 °C – 30 sec; as well as final elongation at 72 °C for 7 minutes.

**Results**

Bioinformatic search for the nucleotide sequences of these genes was carried out in the Ensemble Genome Browser genomic database. After PCR amplification of the VDR gene fragment, the PCR-derived products were subjected to PCR analysis using Fok I endonuclease (manufactured by NPO Sibenzyme) (Fig. 1, Table 3).

The genotypes of the VDR gene polymorphisms were interpreted on the basis of different band patterns on the electrophoregram (Fig. 2).

After photodocumentation, the subsequent restriction fragments were genotyped according to the presence of corresponding fragments.

**Table 3. Chromosomal structure and localization of the studied gene**

| Gene, polymorphism | Primers | Nucleotide sequence | Restrictases |
|---|---|---|---|
| Vitamin D receptor Fok-I polymorphism | Pr_VDR_F | AGCTGGCCCTGGCACTGACTCTGCTCT | Fok-I |
| | Pr_VDR_R | ATGGAAACACCTTGCTTCTTCTCCCTC | |

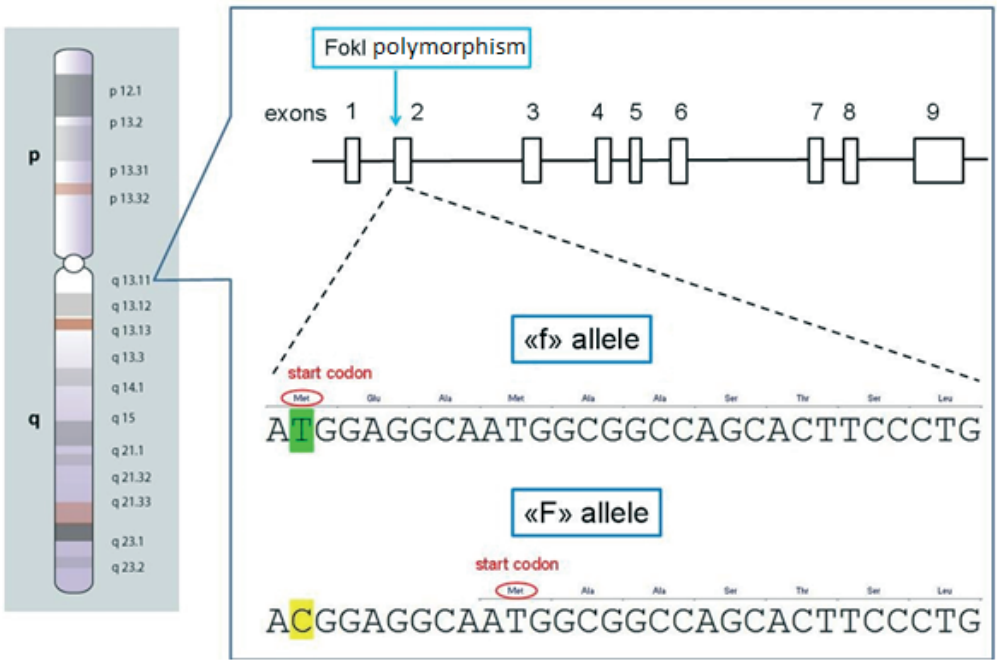


**Fig. 1.** *VDR gene Fok-I polymorphism.*

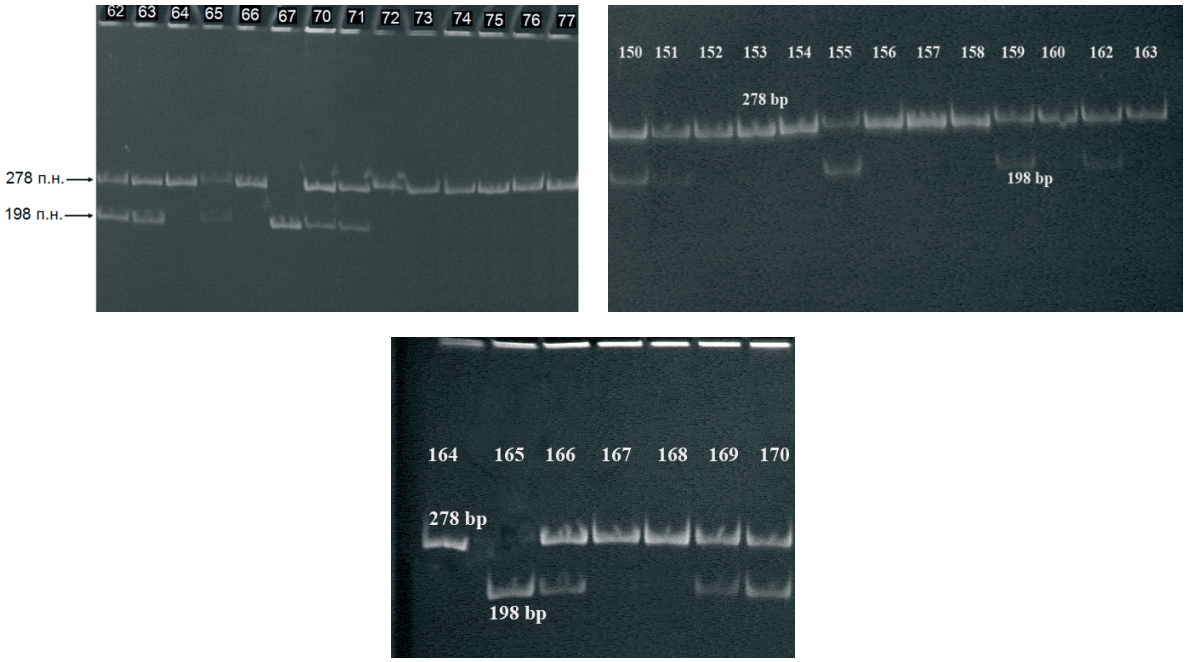


**Fig. 2.** *FDRF analysis of the Fok1 polymorphism of the VDR gene.*

Genotyping analysis of VDR gene PDRF products (restriction products) was performed.

One fragment weighing 278 bp indicated that this sample was a carrier of the homozygous genotype WT (Wild Type), and three fragments weighing 278 bp, 198 bp and 80 bp – a carrier of the heterozygous genotype WT/MUT, the presence of two fragments weighing 198 bp and 80 bp – a carrier of the homozygous genotype MUT (Mutant) (Fig.3).

The frequency distribution of the VDR gene polymorphism Fok1 genotypes in the control group corresponded to the Hardy-Weinberg distributions.

A comparative analysis of the frequency distribution of the VDR gene polymorphism

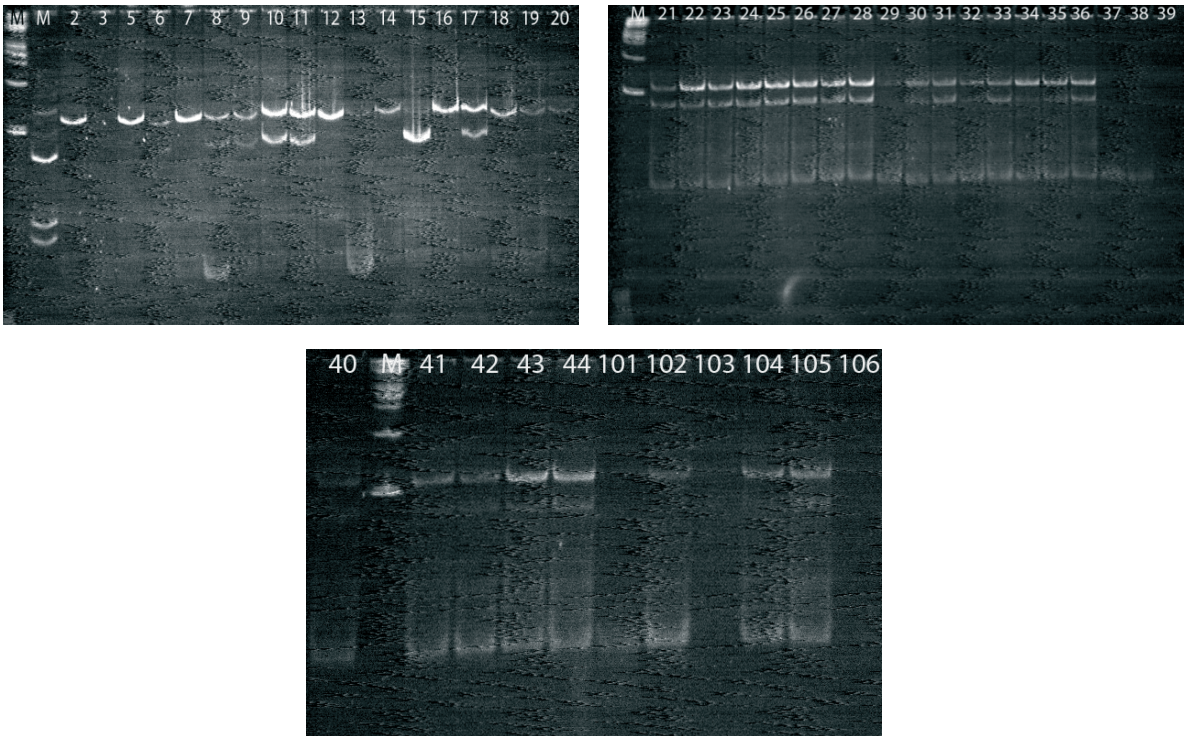


**Fig. 3.** *PDRF analysis of the Fok1 polymorphism of the VDR gene.*

Fok1 genotypes showed a statistically significant association (p=0.02) of the f allele regarding the dominant inheritance model (Ff +ff genotypes) in the group of urolithiasis patients compare to the corresponding indicators in the control group (Fig. 4).

As shown on the diagram, the genotype of heterozygotes F/F of the Fok1 polymorphism of the VDR gene was the most often recorded in the control group (53%), and in the group of urolithiasis children, a decrease tendency was established, no confidence between the indicators (47%) (p>0.05) was evidenced. The F/f+f/f polymorphism Fok1 of the VDR gene was the most informative genotype in urolithiasis, which occured almost 2 times more often compare to the control group (p<0.01).

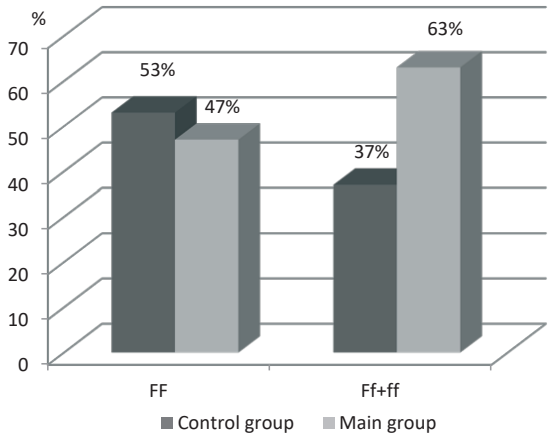


**Fig. 4.** *Frequency distribution of Fok1 polymorphism genotypes of the VDR gene in the control group and in patients with urolithiasis.*

The frequency distribution of the heterozygotes F / F genotype was 44.4%; in the control group – 15%, respectively ($\chi^2$=0.47; p=0.24; OR=1.35; 95% CI 0.57-3.17; df=1). f allele detection increased the risk of urolithiasis in children in 2.4 times compare to the F allele (95% CI=0.68-2.93, df=1).

Allele determines the vitamin D receptor synthesis (427 amino acids); it is defined as *f, and the shorter form (424 amino acids) of the receptor is VDR*F. The study of the patient samples proved that the ff-normal genotype was revealed in 83 patients; a homozygous variant of the mutant Ff genotype – in one case, a heterozygous FF genotype – in 127 cases by the VDR gene polymorphic marker FokI (3663T>C).

The allelic form of VDR*F*f was associated with a frequency of 74% and urolithiasis manifestations in the studied group of patients; the *f allele occurrence was 93 compare to the *F allele – 89.

It is established that calcium urolithiasis is associated with the VDR*F*F genotype; in the individuals with this genotype the manifestations of urolithiasis at an early age are significantly more frequent; in the carriers of the VDR*f*f genotype the association with the development of urolithiasis is significantly lower; and in the individuals homozygous for the VDR*F*f genotype – intermediate.

The analysis of the VDR gene genotype frequencies proved that the analysed genotypes distribution in our population corresponded to the Hardy-Weinberg distribution (RHB) ($\chi^2$=5.14; p=0.03) (Table 4).

Thus, the attained results prove that the VDR gene is significant in revealing the disorders that contribute to urolithiasis development.

**Table 4. Statistical analysis of the genetic association of the VDR gene genotypes with urolithiasis according to the dominant inheritance model (test $\chi^2$, df=2)**

| Genotypes | Cases | Control | $\chi^2$ | p | OR | |
|---|---|---|---|---|---|---|
| | n=100 | n=94 | | | Case | 95% CI |
| Genotype F/F | 0.370 | 0.532 | 5.14 | 0.02 | 0.52 | 0.29-0.92 |
| Genotype F/f+f/f | 0.630 | 0.468 | | | 1.93 | 1.09-3.43 |

**Discussion**

Many scientists have proved that a violation of the metabolism of vitamin D leads to an imbalance in the phosphorus-calcium metabolism, which is a direct risk factor for the development of urolithiasis. A decrease in the level of vitamin D leads to a deterioration of health due to a range of physiological processes. However, many guidelines on urolithiasis provide recommendations on the limited administration of vitamin D due to the fear of development of increased lithogenesis. Some researchers proved that 1.25 (OH)2D3 has a direct effect on calcium excretion [8]. Currently, the relationship between the level of vitamin D and nephrolithiasis is debatable; the data obtained are contradictory, especially in paediatrics.

Schlingmann and co-authors stated that in children with urolithiasis, significant nephrocalcinosis and hypercalcemia had conditions of suppressed serum PTH and a significant increase in the level of 1.25-dihydroxyvitamin D3 due to CYP24A1 mutations [13].

Consequently, VDRs are encoded by the VDR gene with genetic polymorphism, i.e. the presence of various allelic variants of this gene in the population [5]. Bsm I, Folc I, Taq I were the most significant polymorphisms of the VDR gene involved in disease development. The prevalence of VDR gene polymorphism has racial and ethnic differences. In one population, one genotype of a polymorphic marker prevails, in another population – another genotype of a polymorphic marker [11, 15, 17]. In this regard, it is relevant to study the distribution of genotypes of the polymorphic marker Fok I of the VDR gene in the Uzbek population in children with urolithiasis.

The Fok I locus is characterized by a T / C transition in the start codon (ATG) of the second exon of the VDR gene, in which the length of the protein molecule of the receptor decreases due to the displacement of the start codon by three triplets. In the case of thymine (T) or the "f" allele, the M1 form of a molecule of 427 amino acids is synthesized; in the case of cytosine (C) or the "F" allele, a shorter and, accordingly, more active M4 form of the receptor with a length of 424 amino acids is synthesized [9]. According to the US researchers, in children with the FF genotype, bone mineral density was on average by 8.2% higher than in those with the recessive homozygous genotype (ff) and by 4.8% higher than in children with the Ff genotype [16].

A group of scientists guided by S. Azab conducted a study of the association of BsmI polymorphism of the VDR gene with the risk of development of nephropathy in patients with systemic lupus erythematosus; it showed that the BB (AA) genotype is a risk factor for this complication. However, there was no significant association of VDR gene variants with other clinical manifestations, laboratory profiles of systemic lupus erythematosus, the disease activity index or the level of 25-hydroxyvitamin D in the blood serum of patients [6].

According to the results of out study, it was established that in the Uzbek population the genetic markers of predisposition to urolithiasis are: genotypes Ff+ff of the VDR gene. A comparative analysis of the frequency distribution of the VDR gene polymorphism Fok1 genotypes proved a statistically significant association (p=0.02) of the f allele regarding the dominant inheritance model (Ff+ff genotypes) in the

group of urolithiasis patients compare to the corresponding indicators in the control group. The genotype distribution frequencies of F/F heterozygotes were 44.4%, and 15% – in the control group, respectively ($\chi^2$ =0.47; p=0.24; OR=1.35; 95% CI 0.57-3.17; df=1). Revealing of the f allele increased the urolithiasis risk in children in 2.4 times, compare to the F allele (95%) (CI = 0.68-2.93, df=1).

The heterozygosity of F/F mutations may predispose to formation of stones; therefore, screening should be carried out to determine the level of 25(OH)D in serum (which will be high) and levels of 24, 25(OH) vitamin D (which will be low), before prescribing vitamin D supplements to the patients with kidney stones to prevent exacerbation of calciuria. Those to be screened and genetically tested are the patients with high or above average serum calcium levels and reduced PTH levels.

The molecular genetic method of prediction of urolithiasis occurrence allows identifying a disease predisposition at any age: just about from the birth of a person, since the genotype of an individual does not change throughout life. Moreover, disease predisposition can be established by means of this method if no clinical or biochemical manifestations are present, specifically at the earliest preclinical stage of the pathology development. So, the earlier the genetic marker is detected, the more reliable and timely measures can be taken to prevent the disease.

**Conclusions**

A comparative analysis of the frequency distribution of VDR gene polymorphism Fok-1 genotypes showed a statistically significant association (p=0.02) of the f allele regarding the dominant inheritance model (Ff +ff genotypes in total) in the group of urolithiasis patients compare to this indicator in the control group that was 63%. In the Uzbek population, the genetic markers of predisposition to urolithiasis are: genotypes Ff+ff of the VDR gene. It is appropriate to test this genotype as a comprehensive program of urolithiasis prevention in Uzbekistan.

**Conflict of Interests**

Authors declare no conflict of interest.

**Author's Contributions**

*Yusupov Shukhrat Abdurasulovich, Shamsiev Azamat Mukhitdinovich* – conceptualization, methodology, formal analysis, writing – original draft, writing – reviewing and editing; *Shamsiev Jamshed Azamatovich*, *Pulotov Parviz Amridinovich* – data curation, writing – reviewing and editing, investigation, formal analysis.

## ВІТАМІН Д І СЕЧОКАМ'ЯНА ХВОРОБА В ДИТЯЧОМУ ВІЦІ

**Ш.А. Юсупов[1], А.М. Шамсиев[2], Ж.А. Шамсиев[3], П.А. Пулотов[4]**

*1, 2, 3, 4 – САМАРКАНДСЬКИЙ ДЕРЖАВНИЙ МЕДИЧНИЙ ІНСТИТУТ, САМАРКАНД, РЕСПУБЛІКА УЗБЕКИСТАН*

**Вступ.** *Сечокам'яна хвороба одна з найбільш актуальних проблем сучасної урології та медицини в цілому. Це пов'язано в першу чергу з високою поширеністю сечокам'яної хвороби, яка, за даними декількох популяційних досліджень, становить від 3,5 до 9,6%. При цьому відзначається неухильне зростання захворюваності.*

**Мета.** *Вивчити вміст поліморфного генетичного маркера гена рецептора вітаміну Д асоційованого з розвитком і рецидивуванням сечокам'яної хвороби у дітей.*

**Методи.** *Методом ПЛР проведено генетичне дослідження поліморфного генетичного маркера гена рецептора вітаміну Д асоційованого з розвитком і рецидивуванням сечокам'яної хвороби у 100 дітей.*

**Результати.** *результати, отримані в цьому дослідженні, вказують на те, що ген VDR сприяє визначенню порушень, що сприяють розвитку сечокам'яної хвороби*

**Висновки.** *В результаті проведеного порівняльного аналізу розподілу частот генотипів fok1 поліморфізму гена VDR встановлена статистично значуща асоціація (p=0.02) алеля f за домінантною моделлю спадкування (сумарно генотипи Ff+ff) в групі хворих з уролітіазом порівняно з відповідним показником в групі контролю, який склав 63%.*

**КЛЮЧОВІ СЛОВА: вітамін Д, сечокам'яна хвороба, ген VDR, поліморфізм генів, дизурія**

**Information about the authors**

**Yusupov Shukhrat Abdurasulovich**, PhD, DcS, Head of the Department of Pediatric Surgery, Samarkand State Medical Institute, Samarkand, Republic of Uzbekistan.

ORCID 0000-0001-7259-028X, E-mail: shuchrat_66@mail.ru

**Shamsiev Azamat Mukhitdinovich,** PhD, DcS, Professor of the Department of Pediatric Surgery, Samarkand State Medical Institute, Samarkand, Republic of Uzbekistan.

ORCID 0000-0001-8482-7037, E-mail: prof.ashamsiev@mail.ru

**Shamsiev Jamshed Azamatovich,** PhD, DcS, Professor of the Department of Pediatric Surgery, Samarkand State Medical Institute, Samarkand, Republic of Uzbekistan.

ORCID 0000-0002-4193-7372, E-mail: jamshedshamsiev@mail.ru

**Pulotov Parviz Amridinovich,** Assistant Professor of the Department of Pediatric Surgery, Samarkand State Medical Institute, Samarkand, Republic of Uzbekistan.

ORCID 0000-0003-1338-6873, E-mail: parviz8787@icloud.com

**References**

1. Apolikhin OI, Sivkov AV, Konstantinova OV, Slominsky PA, Tupitsyna TV, Kalinichenko DN. Association of urolithiasis in patients with various family history of urolithiasis with polymorphisms of its candidate genes in the Russian population. Experimental and Clinical Urology 2014; (3): 50-52.

2. Apolikhin OI, Sivkov AV, Konstantinova OV, Slominsky PA, Tupitsyna TV, Kalinichenko DN. The connection of unilateral and bilateral urolithiasis with genetic factors. Experimental and clinical urology 2015;(2):68-70.

3. Zhilenko MI, Gusakova DA, Tyuzikov IA. Prevalence of vitamin D deficiency/insufficiency in routine clinical practice. Questions of dietology. 2017. Vol. 7. No. 1. pp. 10-15.

4. Kaprin AD, Apolikhin OI, Sivkov AV, etc. Analysis of uronephrological morbidity and mortality in the Russian Federation for 2003-2013. Experimental and clinical urology. 2015. No. 2. pp. 3-7.

5. Alagol F, Shihadeh Y, Boztepe H, Tanakol R, Yarman S, Azizlerli H, Sandakci O. 2000. Sunlight exposure and vitamin D deficiency in Turkish women. J. Endocrinol. Invest. 23, 173-177.

6. Azab SF, Ali YF, Farghaly MA, Hamed ME, Allah MA, Emam AA. Vitamin D receptor gene BsmI polymorphisms in Egyptian children and adolescents with systemic lupus erythematosus: A case-control study. Medicine (Baltimore) 2016; 95 (46): e5233. DOI: 10.1097/MD.0000000000005233

7. Blomberg JM. Vitamin D metabolism, sex hormones, and male reproductive function. Reproduction. 2012. Vol. 144. № 2. P. 135–152.

8. Ferraro PM, Taylor EN, Gambaro G, et al. Vitamin D intake and the risk of incident kidney stones. 2017; 197(2):405-410.

9. Genetics and biology of vitamin D receptor polymorphisms / A.G. Uitterlinden [et al.] // Gene. 2004. 338. 143–156.

10. Girgis CM, Baldock PA, Downes M. Vitamin D, muscle and bone: integrating effects in development, aging and injury. Mol. Cell. Endocrinol. 2015. Vol. 410. P. 10–13.

11. Holick MF. Vitamin D: Photobiology, Metabolism, etc., In "Primer on the Metabolic bone Diseases and Disorders of Mineral Metabolism. American Society for Bone and Mineral Research. 1996, Philadelphia. 74-81.

12. Holick MF, Binkley NC, Bischoff-Ferrari HA et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J. Clin. Endocrinol. Metab. 2011. Vol. 96. № 7. P. 1911–1930.

13. Schlingmann KP, Kaufmann M, Weber S, et al. Mutations in CYP24A1 and idiopathic infantile hypercalcemia. N Engl J Med 2011; 365(5):410-21.

14. Skolarikos A, Straub M, Knoll T et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines // Eur. Urol. 2015. Vol. 67. № 4. P. 750–763.

15. Timms PM, Mannan N, Hitman GA et al: Circulating MMP9, vitamin D and variation in the TIMP-1 response with VDR genotype: mechanisms for inflammatory damage in chronic disorders? QJM. 2002. 95. 787-796.

16. Vitamin D receptor gene Fok1 polymorphism predicts calcium absorption and bone mineral density in children / SK Ames [et al.] // Bone Miner Res. 1999. 14, N. 5. 740–746.

17. Wang TJ, Pencina MJ, Booth SL, Jacques PF et al. Vitamin D Deficiency and Risk of Cardiovascular Disease. Circulation. – 2008. - №117. – C.503-511.

18. Wehr E, Pilz S, Boehm BO et al. Association of vitamin D status with serum androgen levels in men. Clin. Endocrinol. (Oxf.). 2010. Vol. 73. № 2. P. 243–248.

19. Xu H, Zisman AL, Coe FL, Worcester EM Kidney stones: an update on current pharmacological management and future directions. Expert Opin. Pharmacother. 2013. Vol. 14. № 4. P. 435–447.