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The Role Of Genetic Factors In The Pathogenesis Of Urolithiasis Development

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Abstract

This study assesses the prognostic significance of polymorphisms in the uromodulin (UMOD) and vitamin D receptor (VDR) genes in the pathogenesis of urolithiasis (ICD) in the Uzbek population. Genotyping of UMOD rs429639 and VDR BsmI (c.IVS7 G>A) single nucleotide polymorphisms was performed by polymerase chain reaction (PCR) with allele-specific primers in 82 patients with urolithiasis and a control group. Results showed that the T allele and TT genotype of UMOD rs429639 (OR = 1.85, 95% CI: 1.05–3.29, p = 0.0337) and the G allele and GG genotype of VDR BsmI (OR = 2.18, 95% CI: 1.05–4.55, p = 0.0347) are significantly associated with increased risk of urolithiasis. Conversely, the C allele/CT genotype of UMOD and the A allele/GA genotype of VDR demonstrate protective effects. The UMOD locus deviated significantly from Hardy–Weinberg equilibrium in both groups, while the VDR locus was in equilibrium. These findings confirm the role of uromodulin and vitamin D receptor in sodium reabsorption, calcium-phosphorus homeostasis, and lithogenesis, and may be useful for developing genetic risk panels for urolithiasis in the Uzbek population.

Keywords: Urolithiasis, nephrolithiasis, genetic polymorphism, UMOD gene, VDR gene, rs429639, BsmI, Uzbek population, Hardy-Weinberg equilibrium, calcium metabolism, lithogenesis, SNP.

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1. Introduction

Urolithiasis (UL), also known as kidney stone disease, is one of the most widespread and common diseases worldwide (5–10%) and occurs most frequently in patients of working age. The term “urolithiasis” refers to a metabolic disorder caused by various endogenous and/or exogenous factors (including hereditary predisposition) and is characterized by the presence of stone(s) in the kidneys and urinary tract. The disease tends to recur and often follows a severe and persistent course. According to WHO data, it is diagnosed in 15% of the population.

The prevalence of urolithiasis varies greatly depending on the region of residence and climatic conditions. The problem of urolithiasis is becoming increasingly relevant. Its development is influenced by water quality and nutrition, as well as heredity. The risk of developing urolithiasis is significantly higher in individuals whose

close relatives have had this disease.

Despite advances achieved in the treatment of urolithiasis, recurrences may occur within five years in up to 50% of patients. Global experience accumulated from studying this problem across various fields of knowledge indicates that urolithiasis is probably the most polyetiological disease, with a very complex pathogenesis.

Over the past ten years, according to data from international literature, numerous studies have been conducted to investigate the association between specific gene polymorphisms and urolithiasis (UL). Some studies demonstrate the presence of a relationship between the gene under investigation and UL, whereas a number of publications report no such associations. The greatest interest worldwide has focused on studying associations between UL and different alleles of genes involved in the regulation of vitamin D metabolism [12, 13]. Among the most extensively studied candidate genes in UL are UMOD, which regulates the excretory function of the nephron, and VDR, which is involved in vitamin D and calcium metabolism. However, data on the distribution of UMOD rs429639 and VDR BsmI polymorphisms in different ethnic groups remain contradictory. Studying these markers in the Uzbek population is of great importance for clarifying the structure of genetic predisposition to UL and identifying associated alleles and genotypes that influence disease risk. The present study is aimed at a comparative analysis of the frequencies of SNP variants of UMOD and VDR in patients with UL and in a control group, as well as at assessing their compliance with Hardy–Weinberg equilibrium.

Studies of recent decades have shown that urolithiasis (UL) has a complex multifactorial nature, in which genetic mechanisms play a significant role alongside biochemical and environmental factors [1, 2]. Genes involved in the regulation of water–electrolyte balance and calcium metabolism are of particular interest. One such gene is UMOD, which encodes uromodulin, a protein involved in sodium reabsorption, modulation of ion transport, and protection of the nephron epithelium [3]. Several studies indicate that polymorphic variants of UMOD may alter protein expression and affect the risk of stone formation; however, the obtained results differ among populations and require further clarification [4]. Equally important is the VDR gene, which encodes the vitamin D receptor responsible for regulating calcium–phosphate homeostasis. Changes in receptor activity due to various SNP variants, such as BsmI, may influence calcium excretion, bone resorption, and lithogenic processes [5]. The literature reports that associations between VDR polymorphisms and the risk of UL are heterogeneous: some studies have identified a relationship between the GG or AA variants and an increased likelihood of nephrolithiasis, whereas others have found no significant differences [6, 7]. Most authors emphasize that variability in results can be explained by ethnic differences, variations in sample size, differences in genotyping methods, and phenotypic stratification of the studied groups [2, 6, 8, 9, 10, 11]. In this regard, conducting studies in individual populations, including the Uzbek population, appears important for clarifying the actual role of UMOD and VDR in the pathogenesis of urolithiasis (UL). A combined analysis of two loci makes it possible to comprehensively assess the contribution of different genetic systems involved in ion reabsorption, regulation of calcium metabolism, and the formation of a lithogenic environment.

There is a considerable number of studies devoted to the distribution of UMOD rs429639 and VDR BsmI polymorphisms in patients with urolithiasis, demonstrating a complex and sometimes contradictory picture. Although several studies have examined the association of VDR polymorphisms with the risk of urolithiasis and biochemical parameters, the results remain inconsistent across different populations, and methodological differences persist. Data on the frequency of polymorphic variants of the UMOD gene are less extensively studied; however, genomic research provides new perspectives on this issue. Methodological heterogeneity, population stratification, and limited sample sizes in some studies contribute to the variability of results. Overall, these studies emphasize the multifactorial nature of urolithiasis and the need for integrated approaches combining genetic, biochemical, and clinical data.

The aim of the study

Was to assess the prognostic significance of uromodulin and VDR gene polymorphisms in the pathogenesis of urolithiasis in the Uzbek population.

2. Methods

Genotyping of polymorphic regions of the immune response genes was performed using the polymerase chain reaction (PCR) with allele-specific primers (NPF

"Litekh", Moscow) and electrophoretic detection of PCR products in agarose gel. The distribution of genotypes at the studied polymorphic loci was analyzed using logistic regression analysis and tested for compliance with Hardy–Weinberg equilibrium using Fisher's exact test. Differences were considered statistically significant at $p < 0.05$.

3. Results

This study presents a comparative analysis of allele and genotype frequencies of polymorphic variants of the UMOD rs429639 and VDR BsmI c.IVS7 G>A genes in 82 patients with urolithiasis from the Uzbek population compared with a control group.

A comparative analysis of SNP frequencies in patients with urolithiasis (UL) in the Uzbek population versus controls is presented.

Table 1.
Distribution of alleles and genotypes of the UMOD rs429639 polymorphism

Allele / Genotype	ICD (n=82)	%	Control (n=178)	%	OR	Chi-square	Wald 95% CI
C	30	18.29	92	25.84	0.6424	3.564 (p=0.0590)	0.405–1.019
T	134	81.71	264	74.16	1.557	—	0.981–2.47
CC	8	9.76	20	11.24	0.8541	0.128 (p=0.7206)	0.36–2.029
CT	14	17.07	52	29.21	0.4989	4.368 (p=0.0366)	1.036–3.877
TT	60	73.17	106	59.55	1.8525	4.512 (p=0.0337)	1.045–3.285

Analysis of allele frequency distribution revealed differences between patients with urolithiasis and individuals in the control group. The frequency of the C allele in patients was 18.3%, whereas in the control group it was 25.8%. Carriage of this allele showed a tendency toward a reduced risk of urolithiasis (OR = 0.64; 95% CI: 0.41–1.02; $\chi^2 = 3.564$; $p = 0.0590$), which is close to the threshold of statistical significance and suggests a possible protective role of the C allele.

At the same time, the T allele was observed significantly more often in patients (81.7%) compared with controls (74.2%), which is reflected in the confidence interval and is consistent with the higher frequency of the TT genotype among patients (73.2% versus 59.6% in the control group). For carriers of the TT genotype, the odds ratio was OR = 1.85 (95% CI: 1.05–3.29), $\chi^2 = 4.512$ ($p = 0.0337$), indicating a significant association of the TT genotype with an increased risk of urolithiasis.

The heterozygous CT genotype was less frequent in patients (17.1%) than in controls (29.2%). For this genotype, an odds ratio of OR = 0.50 (95% CI corresponding to the inverse calculation), $\chi^2 = 4.368$ ($p = 0.0366$) was obtained, suggesting a reduced risk of the disease in heterozygous carriers compared with the TT genotype.

The frequency of the CC genotype did not differ significantly between the groups (9.8% in patients and 11.2% in controls; OR = 0.85; $p = 0.72$), indicating the absence of a pronounced association between the homozygous C variant and the risk of urolithiasis.

Overall, the obtained data suggest that the presence of the T allele and the homozygous TT genotype is associated with an increased risk of urolithiasis, whereas the C allele and the heterozygous CT genotype may play a protective role.

Hardy–Weinberg equilibrium testing for UMOD rs429639

Parameter	Value
Allele frequencies	**p(C) = 0.183; q(T) = 0.817**
Observed genotypes (O)	**CC = 8; CT = 14; TT = 60**
Expected genotypes under HWE (E)	**CC = 2.74; CT = 24.51; TT = 54.74**

χ^2 (df=1)	**15.08**
p-value	**≤ 0.001**

Parameter	Value
Allele frequencies	**p(C) = 0.258; q(T) = 0.742**
Observed genotypes (O)	**CC = 20; CT = 52; TT = 106**
Expected genotypes under HWE (E)	**CC = 11.89; CT = 68.22; TT = 97.89**
χ^2 (df = 1)	**10.07**
p-value	**≈ 0.0015**

To assess the conformity of genotype distribution with Hardy–Weinberg equilibrium (HWE), a χ^2 test was performed separately for the patient group and the control group.

In the patient group (n = 82), allele frequencies were p(C) = 0.183 and q(T) = 0.817. The observed genotype frequencies were as follows: CC – 8 cases, CT – 14, TT – 60. The expected values under Hardy–Weinberg equilibrium at the given allele frequencies were: CC – 2.74, CT – 24.51, TT – 54.74. The calculation yielded χ^2 = 15.08 with one degree of freedom, corresponding to p < 0.001, indicating a significant deviation from HWE.

In the control group (n = 178), allele frequencies were p(C) = 0.258 and q(T) = 0.742. The observed genotype frequencies were: CC – 20, CT – 52, TT – 106. The expected Hardy–Weinberg values were: CC – 11.89, CT – 68.22, TT – 97.89. The obtained value χ^2 = 10.07 (p ≈ 0.0015) also indicates a statistically significant deviation from HWE.

Distribution of alleles and genotypes of the *VDR* BsmI c.IVS7 G>A polymorphism

Allele / Genotype	Urolithiasis (MKD) n=82	%	Control n=178	%	OR	Chi-square (p-value)	Wald 95% CI
C	30	18.29	92	25.84	0.6424	3.564 (p = 0.0590)	0.405 – 1.019
T	134	81.71	264	74.16	1.557	—	0.981 – 2.47
CC	8	9.76	20	11.24	0.8541	0.128 (p = 0.7206)	0.360 – 2.029
CT	14	17.07	52	29.21	0.4989	4.368 (p = 0.0366)	1.036 – 3.877
TT	60	73.17	106	59.55	1.8525	4.512 (p = 0.0337)	1.045 – 3.285

Analysis of allele frequency distribution showed that patients with urolithiasis had a higher frequency of the G allele compared with the control group (88.4% vs. 80.3%). Carriage of this allele demonstrated a pronounced tendency toward association with the disease: the odds ratio was OR = 1.87 (95% CI: 0.99–3.56), χ^2 = 3.733, p = 0.0534, which is at the threshold of statistical significance and may reflect a moderately increased risk of urolithiasis in G-allele carriers.

In contrast, the frequency of the A allele was lower in patients (11.6% vs. 19.7% in controls), corresponding to lower OR values (0.28–1.02) and suggesting a possible protective effect of the A allele, although statistical significance for allele-level differences was not achieved.

Genotype analysis revealed more pronounced differences. The GG genotype was observed in 79.3% of patients, compared with 63.6% in the control group. This variant showed a significant association with the disease: OR = 2.18, 95% CI: 1.05–4.55; χ^2 = 4.461; p = 0.0347. Thus, the homozygous GG genotype for the G allele may be considered a risk factor for the development of urolithiasis.

The heterozygous GA genotype was identified in 18.3% of patients and 33.3% of healthy individuals. This variant, in contrast, showed a statistically significant reduction in disease risk: OR = 0.45 (95% CI: 0.21–0.96), χ^2 = 4.412; p = 0.0357. This may indicate a potential protective effect of heterozygous carriage, possibly due to a more balanced expression of the vitamin D receptor.

The frequency of the AA genotype was low in both groups (2.4% in patients and 3.0% in controls), with no statistically significant differences (OR = 0.8; p = 0.8255).

Overall, the results indicate that the G allele and the homozygous GG genotype of the VDR BsmI polymorphism are associated with an increased risk of urolithiasis in the Uzbek population, whereas the A allele and the heterozygous GA genotype may exert a protective effect. These findings are consistent with the role of VDR in regulating calcium–phosphate metabolism and calcium excretion, which is pathogenetically important in kidney stone formation.

Table 3. Distribution of alleles and genotypes of the VDR BsmI (c.IVS7 G>A) polymorphism

Allele / Genotype	Urolithiasis (n=82)	%	Control (n=66)	%	OR	Chi-square (p-value)	95% CI
G	145	88.41	106	80.30	1.8719	3.733 (p = 0.0534)	0.985 – 3.559
A	19	11.59	26	19.70	0.534	—	0.281 – 1.016
GG	65	79.27	42	63.64	2.1849	4.461 (p = 0.0347)	1.050 – 4.545
GA	15	18.29	22	33.33	0.4478	4.412 (p = 0.0357)	0.210 – 0.956
AA	2	2.44	2	3.03	0.800	0.049 (p = 0.8255)	0.110 – 5.837

Table 4. Hardy–Weinberg equilibrium test for VDR BsmI (c.IVS7 G>A) polymorphism

Group	n	Allele frequencies	Observed (O)	Expected under HWE (E)	χ^2 (df=1)	p-value
Patients	82	p(G)=0.884; q(A)=0.116	GG=65; GA=15; AA=2	GG=64.09; GA=16.80; AA=1.10	0.94	> 0.3
Control	66	p(G)=0.803; q(A)=0.197	GG=42; GA=22; AA=2	GG=42.56; GA=20.88; AA=2.56	0.19	> 0.8

4. Conclusions

As a result of the comparative analysis of UMOD rs429639 and VDR BsmI c.IVS7 G>A polymorphisms in patients with urolithiasis from the Uzbek population, it was established that the distribution of alleles and genotypes at the UMOD locus shows a pronounced association with the disease. The T allele and TT genotype were found significantly more frequently in patients, indicating an increased risk of urolithiasis, whereas carriage of the C allele and the heterozygous CT genotype was associated with a reduced probability of disease development. Testing for Hardy–Weinberg equilibrium revealed statistically significant deviations in both the patient and control groups, confirming the influence of population factors and possible locus-specific selection effects at the UMOD locus.

With regard to the VDR BsmI locus, the G allele and homozygous GG genotype were shown to predominate among patients and to be associated with an increased risk of urolithiasis, while heterozygous GA carriage exhibited a protective effect, reducing disease risk by nearly twofold. For this polymorphism, genotype frequencies in both groups conformed to Hardy–Weinberg equilibrium, confirming the validity of the samples and the absence of systematic disturbances in genotype distribution.

The identified genetic associations are consistent with the physiological roles of uromodulin and the vitamin D receptor in the regulation of electrolyte balance, calcium

reabsorption, and lithogenic processes, thereby confirming the significance of these genes in the formation of susceptibility to urolithiasis. The obtained results may be used in the future development of genetic risk panels and in further in-depth studies of the pathogenetic mechanisms of urolithiasis in different ethno-population groups.

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